Combining the kinase inhibitor ibrutinib with an investigational personalized cellular therapy known as CTL19 can lead to complete remission in patients with high-risk chronic lymphocytic leukemia (CLL), according to new research from the Perelman School of Medicine at the University of Pennsylvania and Penn's Abramson Cancer Center (ACC). The team will present the results from its pilot study of this combination therapy during the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract # 193355).

The team will present on the first 10 patients in the trial, each of whom had been taking ibrutinib for at least six months but had not achieved a complete remission. They were then infused with their own engineered “hunter” T cells. Eight of nine patients who are evaluable for response had no evidence of disease in their bone marrow at three months, and all remain in remission after a median follow-up period of six months, with a range from 0.5 to 9 months. One patient was found to have a partial response in their marrow.

The research team is led by Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine and director of Translational Research in the ACC, along with David Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in the ACC. The data will be presented by the study’s first author, Saar Gill, MD, PhD, an assistant professor of Hematology-Oncology.

“Combining ibrutinib with the CTL19 therapy achieved very powerful results for these patients, and with limited toxicity,” Gill said. “This newer, coupled approach gives us hope that personalized cell therapies could be an important option for high-risk CLL patients on these types of drugs.”

CTL19 manufacturing begins with a patient’s own T cells, some of which are removed and then re-programmed in Penn’s Clinical Cell and Vaccine Production Facility with a gene transfer technique designed to teach the T cells to target and kill tumor cells. The engineered cells contain an antibody-like protein known as a chimeric antigen receptor (CAR), which is designed to bind to a protein called CD19 found on the surface of cancerous B cells. The modified “hunter” cells are then infused back into the patient’s body, where they multiply and are believed to attack the cancer cells.

Patients in the trial had been on ibrutinib for a minimum of six months and had not achieved a complete response when they received an infusion of engineered cells split over three consecutive days. All had abnormalities of TP53 or ATM – two mutations associated with high-risk disease – and two patients had increasing BTK C481S clones, also a high-risk marker.

The new data builds off several preclinical studies supporting the use of ibrutinib with CAR therapy. In March 2016, Penn researchers published a study in Blood that showed long-term ibrutinib treatment reverses the dysfunction of T cells in CLL and that combining CAR therapy with ibrutinib enhanced engineered T cell proliferation in mice.

CAR therapy alone has led to complete remissions and responses in some CLL patients, but not all patients respond, findings that led the Penn team to seek combination therapies that might enhance efficacy of the therapy. In 2015, Penn Medicine researchers reported in Science Translational Medicine an overall response rate of 57 percent in CLL patients treated with CAR therapy, and a complete remission rate of 29 percent.

Ibrutinib is a well-tolerated, oral drug that improves symptoms and survival in high-risk CLL patients, but is not curative and requires continuous treatment for life. It rarely induces complete remissions by itself. That first year on the drug may provide an optimal window to collect T cells from patients and subsequently administer a potentially curative T cell therapy, the authors said.

“These patients had a lower disease burden and were treated earlier in the course of their disease, which distinguishes it from other studies,” Gill said. “One of the challenges in treating CLL pa-
New CTL119/Ibritinib Results for CLL

(Continued from page 1)  

tients with personalized cellular therapy is not having healthy enough cells to manufacture. The results suggest that ibrutinib restored T cell activity in the patients.

All 10 patients who received the CTL119 cells experienced mild cytokine release syndrome (CRS), a known potentially lethal type of toxicity, within a few days after receiving their infusions; however, none required treatment with tocilizumab, an immunosuppressant drug that blocks the effects of the inflammatory cytokine IL-6. All recovered from their CRS.

CRS can include varying degrees of flu-like symptoms, with high fevers, nausea, and muscle pain, and temporary neurologic symptoms, including delirium, and in more severe cases, low blood pressure and breathing difficulties which may require treatment in an intensive care unit. One patient in the study developed tumor lysis syndrome and recovered.

Longer follow-up will reveal the durability of these results, the authors said, and may support the evaluation of a first-line approach with ibrutinib and CAR therapy in an effort to remove the need for chronic therapy.

This study was supported by a grant from Novartis.

Source: Penn Medicine Communications
John Infanti, john.infanti@uphs.upenn.edu

Impact of Pictorial Warning Labels on Cigarette Packages

In recent years, smoking rates among adults in America have steadily declined; yet tobacco use remains the largest preventable cause of death and disease in the United States. Cigarette packages in most countries include a health warning label that describes the risks of using the product, but the position, size and design of the warnings may vary. In the US, health warnings with pictures have been contested through the courts by the tobacco industry. In a new study published recently in Tobacco Control, Penn researchers found that health warning labels that include images or Pictorial Warning Labels (PWLs) are more effective in gaining and holding the attention of smokers when the image and the text convey similar risks.

The study was led by Andrew A. Strasser, PhD, a research associate professor in Psychiatry, lead author Kirsten Lochbuehler, PhD, and Melissa Mercincavage, PhD, two post-doctoral researchers at the UPenn Tobacco Center of Regulatory Science (TCORS).

Strasser argues that research will help prove that images reinforce, not distract from, the important warning messages in text-only cigarette labels contrary to what some tobacco industry companies have claimed.

“It is interesting that much of the tobacco industry’s argument against PWLs is that they are mostly emotionally evocative, too graphic, or not factually true. Our study demonstrates, with non-intrusive, objective measures, that smokers engage a great deal with the images, which likely suggests they do not find them too graphic or off putting,” Strasser said.

“Adopting pictorial warning labels on tobacco products would be an improvement in communicating risk compared to the text-only versions currently on domestic packaging. This is an important and effective way to disseminate knowledge about health risks.”

In the study, Strasser and his team of researchers evaluated 112 daily cigarette smokers between the ages of 21 and 65 years old, and used eye-tracking to objectively observe how participants viewed congruent PWLs, where the images and text conveyed identical risk information, compared to incongruent PWLs, where image and text content differed. Participants were later asked to recall the image, text and risk message from each PWL. The team found that smokers who viewed congruent PWLs better recalled the information in those warnings at the end of the study. The study findings suggest that PWL formats where the image and text express similar messages or themes may be an optimal design strategy.

“The results clearly demonstrate that images in warnings get and hold viewing attention, as evidenced by the short latency to first view and the viewing duration of the images. These are important processes in attention and learning theory, and may help us to more clearly understand how to maximize ways to convey risk information,” Strasser said.

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Seminars and So Forth

Monday 6/5/17

12:00 pm

Epigenetics Institute & IDOM Joint Seminar
“Elucidating Genetic and Epigenetics Mechanisms of Endocrine Resistance in Cancer.” Myles Brown, MD, Professor of Medicine, Harvard Medical School; Director, Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute
BRB II/III Main Auditorium

Tuesday 6/6/17

12:00 pm

AFCRI/Hem-Onco Distinguished Lecture Series
“Molecular Determinants of Lung Cancer Growth and Metastasis.” Monte Winslow, PhD, Assistant Professor of Genetics and of Pathology, Stanford Cancer Institute, Stanford University
BRB II/III Auditorium

Wednesday 6/7/17

8:00 am

ACC Grand Rounds – M&M
“Treating the young adult at HUP: A case of 19M with fever and liver dysfunction,” Melina Marma-relis, Fellow, Hematology/Oncology, PSOM
“An interdisciplinary discussion about the management of low-risk neutropenic fever,” Nathan Singh, Fellow, Hematology/Oncology, PSOM
SCTR Rubenstein Auditorium

Wednesday 6/7/17

12:00 pm

Penn Epigenetics Program Meeting
“Where Chemistry and Epigenetics Hit the Road.” Jordan L. Meier, PhD, Investigator, Chemical Biology Laboratory, National Cancer Institute-Frederick, NIH/NCI
CTRB 1100A (CHOP)

Thursday 6/8/17

9:00 am

CCEB Seminar Series
“Comparison of Futility Monitoring Guidelines Using Completed Phase III Oncology Trials.” Qiang (Ed) Zhang, PhD, Senior Statistician, NRG Oncology Statistics and Data Management Center, PSOM
JMB Class of ‘62 Auditorium

Thursday 6/8/17

12:00 pm

Division of Medical Ethics Special Seminar
“Moral Problems in the Use of Human-Nonhuman Chimeras to Obtain Human Organs.” Tom L. Beauchamp, PhD, Professor Emeritus, Department of Philosophy and Kennedy Institute of Ethics, Georgetown University. RSVP to Caitlin O’Neill (caoneill@upenn.edu)
1402 Blockley Hall

Friday 6/9/17

7:00 am—4:00 pm

2017 Neuro-Oncology Symposium
“Master Class in Brain Tumor Therapy – Best Practices.” The purpose of this CME/CNE-certified activity is to provide new treatment options in neuro-oncology, including surgical techniques and intraoperative imaging that have improved patient outcomes. Register here.
Law Auditorium, Jordan Medical Education Center, PCAM

Friday 6/9/17

12:00 pm

Center for Interdisciplinary Research on Nicotine Addition
“Executive Function and Smoking Behavior.” David Evans, PhD, Assistant Member, Tobacco Research & Intervention Program, Moffitt Cancer Center; Assistant Professor, Departments of Oncologic Sciences & Psychology, University of South Florida
3535 Market St., Ste. 4100, Rm. 4123

Tuesday 6/13/17

12:00 pm

AFCRI/Hem-Onco Seminar Series
“Discovery and therapeutic genome editing of cardiovascular disease genes.” Kiran Musunuru, MD, PhD, Associate Professor of Medicine, PSOM
BRB II/III Auditorium

Thursday 6/15/17

12:00 pm

ACC Radiobiology & Imaging Program Seminar
Theresa Busch, PhD, Professor and Associate Director of Research, Department of Radiation Oncology, PSOM
SCTR 8-146AB

Thursday 6/15/17

5:30 – 9:15 pm

Updates in Oncology – a CME/CNE Course
This course is designed to efficiently discuss the most recent clinical advances in oncology. This course will address the questions that have emerged from the latest data presented at major international annual meetings. Further info and registration here.
Hilton Philadelphia City Ave., 4200 City Avenue., Philadelphia, PA

COMING SOON

Tuesday 6/20/17

9:00 am—4:30 pm

Noreen O’Neill Melanoma Research Symposium
“Melanoma: Advances in Therapy and Biology.”
Click here to learn more and to register.
Wistar Institute, 36th and Spruce Sts.

Thursday 6/22/17

8:00am—5:00 pm

18th Annual Center Retreat - Penn Center for Molecular Studies in Digestive and Liver Diseases
“Riding the innovation wave in preclinical models and therapies.” Poster abstract deadline Friday, June 9 to makent@mail.med.upenn.edu. Registration deadline Wednesday, June 14, http://www.med.upenn.edu/molecular/
Funding Opportunities

Chris4Life Research Program — Colon Cancer Alliance
DEADLINE: August 31, 2017

In honor of the late Christine Sapienza, and for all the families who are affected by colorectal cancer, the Colon Cancer Alliance established the Chris4Life Research Program in 2010. To date, they have committed over $1 million dollars to innovative and life-saving research.

In 2017 they launched their first peer-reviewed research grants program and are proud to announce that this year’s grant cycle is now open. One grant in the amount of $125,000 will be awarded over a two-year period to support the salary and benefits of the researcher while working on mentored, young-onset colorectal cancer research. Applications will be accepted from June 1-August 31, 2017. This grant will be awarded in December 2017.

To apply, please complete the online application and provide the $75 application fee. For questions, contact Stephanie Guiffre at sguifre@ccalliance.org.

Tobacco Labeling

(Continued from page 2)
In future studies, the researchers will examine how repeated exposure to PWLs affects recall as well as more complex communication constructs, such as changes in attitudes and beliefs toward tobacco products, intentions to quit smoking, changes in smoking behavior and decreases in smoke exposure using biomarker measures. Strasser’s team is also focused on examining how viewing patterns change over time when smokers are repeatedly exposed to PWLs and how accumulated exposure may be associated with more profound improvements on tobacco use and exposure.

This work was supported by the National Cancer Institute (NCI) of the National Institutes of Health (NIH) and FDA Center for Tobacco Products (CTP) (P50CA179546, R01CA180929 and P20CA095856).

Source: Penn Medicine Communications
Queen Muse, queen.muse@uphs.upenn.edu