The Clinical Cancer Letter

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Drugs and Targets

FDA Approves Imlygic as First Oncolytic Viral Therapy in the U.S., for Melanoma

FDA approved Imlygic (talimogene laherparepvec) as the first oncolytic viral therapy in the U.S.

Imlygic, developed by Amgen, is indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery. Imlygic has not been shown to improve overall survival or have an effect on visceral metastases.

Imlygic is a genetically modified herpes simplex virus type 1 designed to replicate within tumors and produce granulocyte-macrophage colony-stimulating factor, an immunostimulatory protein. Imlygic causes cell lysis rupturing tumors and releasing tumor-derived antigens, which along with GM-CSF, may promote an anti-tumor immune response. However, the exact mechanism of action is unknown, according to Amgen.

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Breast Cancer

Phase III Trial Finds Equivalent OS Rates Between APBI Brachytherapy and Whole Breast Irradiation Therapy

A prospective, randomized, multicenter phase III study comparing accelerated partial breast irradiation with interstitial multicatheter brachytherapy to whole breast irradiation showed that APBI brachytherapy lead to equivalent overall survival and local and regional cancer control rates, as compared to WBI after breast conserving surgery for selected patients with early stage breast cancers.

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Non-Small Cell Lung Cancer

Patients Receiving IMRT Had Less Toxicity Compared to 3D CRT, Study Finds

Patients with locally advanced non-small cell lung cancer that received intensity modulated radiation therapy had less severe lung toxicity and were able to better tolerate their chemotherapy compared to patients who received 3D conformal radiation therapy, according to a secondary analysis of a large phase III trial.

The study, NRG/RTOG 0617, originally enrolled patients from 2007 to 2011, and compared a high dose of 74 Gy to the standard dose of 60 Gy. All underwent concurrent chemotherapy (carboplatin/paclitaxel, with or without cetuximab) and either 3D CRT or IMRT. In the study, 482 patients were treated with radiation—53 percent with IMRT and 47 percent with 3-D CRT.

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Imlygic Approved as First U.S. Oncolytic Viral Therapy

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"Imlygic is the first clinical and regulatory validation of an oncolytic virus as a therapy, which Amgen is proud to bring to patients with a serious form of skin cancer. Not all melanoma patients currently benefit from available therapies, and Imlygic represents an important new option that can provide meaningful durable responses for patients with this aggressive and complex disease," said Sean Harper, executive vice president of research and development at Amgen.

"Immunotherapy is an exciting area for cancer research, and we are currently studying Imlygic in combination with other immunotherapies in advanced melanoma and other solid tumors."

The approval of Imlygic is based on data from Study 005/05, or OPTiM. OPTiM was a phase III, multicenter, open-label, randomized clinical trial comparing Imlygic to GM-CSF in patients with advanced melanoma (Stage IIIB, IIIC, or IV) that was not surgically resectable.

The primary endpoint of the study was durable response rate, defined as the percent of patients with complete response or partial response maintained continuously for a minimum of six months.

OPTiM enrolled 436 patients. In the study, 16.3 percent of patients treated with Imlygic achieved a durable response compared to 2.1 percent of patients treated with GM-CSF ($p < 0.0001$). Of the patients who experienced a durable response, 29.1 percent had a durable CR and 70.8 percent had a durable PR. In the study, the median time to response was 4.1 (range: 1.2 to 16.7) months in the IMLYGIC arm.

The most common adverse drug reactions in IMLYGIC treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness and injection site pain. Most adverse reactions reported were mild or moderate in severity and generally resolved within 72 hours. The most common grade 3 or higher adverse reaction was cellulitis.

Imlygic recently received a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency, for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease.

Amgen anticipates the average cost of Imlygic therapy to be approximately $65,000. Given that Imlygic represents a novel and first-in-class oncolytic viral therapy, the company expects variability of Imlygic dosing from patient to patient, and intends to work with the healthcare community to implement a program that helps limit the average cost of Imlygic therapy to $65,000 for eligible participating institutions.

FDA granted accelerated approval for Keytruda (pembrolizumab) to treat patients with advanced non-small cell lung cancer whose disease has progressed after other treatments and with tumors that express the protein PD-L1.

Keytruda is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors.

In 2014, Keytruda was approved to treat patients with advanced melanoma following treatment with immunotherapy ipilimumab. Another drug, Opdivo (nivolumab), manufactured by Bristol-Meyers Squibb, also targets the PD-1/PD-L1 pathway and was approved to treat squamous non-small cell lung cancer (a certain kind of NSCLC) in 2015.

The effectiveness of Keytruda for this use was demonstrated in a subgroup of 61 patients enrolled within a larger multicenter, open-label, multi-part study.

The subgroup consisted of patients with advanced NSCLC that progressed following platinum-based chemotherapy or, if appropriate, targeted therapy for certain genetic mutations (ALK or EGFR). This subgroup also had PD-L1 positive tumors based on the results of the 22C3 pharmDx diagnostic test.

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Editor and Publisher: Paul Goldberg
Associate Editor: Conor Hale

Editorial, Subscriptions, and Customer Service:
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Study participants received 10 mg/kg of Keytruda every two or three weeks. The major outcome measure was overall response rate: tumors shrank in 41 percent of patients treated with Keytruda and the effect lasted between 2.1 and 9.1 months.

FDA had previously granted Keytruda breakthrough therapy designation for this indication. The drug also received priority review status. Approved under the agency's accelerated approval program, an improvement in survival or disease-related symptoms in patients being treated with Keytruda has not yet been established.

Keytruda is marketed by Merck & Co., and the PD-L1 IHC 22C3 pharmDx diagnostic test is marketed by Dako North America Inc.

FDA approved Onivyde (irinotecan liposome injection), in combination with fluorouracil and leucovorin, to treat patients with metastatic pancreatic cancer who have been previously treated with gemcitabine-based chemotherapy. The agency previously granted Priority Review and orphan drug designations for Onivyde.

The effectiveness of Onivyde was demonstrated in a phase III, three-arm, randomized, open label study of 417 patients (NAPOLI-1) with metastatic pancreatic adenocarcinoma whose cancer had grown after receiving gemcitabine or a gemcitabine-based therapy. The study was designed to determine whether patients receiving Onivyde plus fluorouracil/leucovorin or Onivyde alone lived longer than those receiving fluorouracil/leucovorin. The monotherapy regimen in this study did not achieve its primary endpoint and, therefore, Onivyde is not indicated as a single agent.

Patients treated with Onivyde plus fluorouracil/leucovorin lived an average of 6.1 months, compared to 4.2 months for those treated with only fluorouracil/leucovorin ($p=0.014$, unstratified HR=0.68, 95% CI: [0.50-0.93]). There was no survival improvement for those who received only Onivyde compared to those who received fluorouracil/leucovorin.

In addition, patients receiving Onivyde plus fluorouracil/leucovorin had a delay in the amount of time to tumor growth compared to those who received fluorouracil/leucovorin. The average time for those receiving Onivyde plus fluorouracil/leucovorin was 3.1 months compared to 1.5 months for those receiving fluorouracil/leucovorin.

The safety of Onivyde was evaluated in 398 patients who received either Onivyde with fluorouracil/leucovorin, Onivyde alone or fluorouracil/leucovorin. The most common side effects of treatment with Onivyde included diarrhea, fatigue, vomiting, nausea, decreased appetite, inflammation in the mouth and fever. Onivyde was also found to result in lymphopenia and neutropenia. Death due to sepsis following neutropenia has been reported in patients treated with Onivyde.

The labeling for Onivyde includes a boxed warning to alert health care professionals about the risks of severe neutropenia and diarrhea. Onivyde is not approved for use as a single agent for the treatment of patients with metastatic pancreatic cancer.

Onivyde is marketed by Merrimack Pharmaceuticals Inc.

FDA approved Yondelis (trabectedin) for the treatment of liposarcoma and leiomyosarcoma that cannot be removed by surgery or is metastatic. This treatment is approved for patients who previously received chemotherapy that contained anthracycline.

The effectiveness of Yondelis, marketed by Janssen Products, was demonstrated in 518 clinical trial participants with metastatic or recurrent leiomyosarcoma or liposarcoma. Participants were randomly assigned to receive either Yondelis (345 patients) or dacarbazine (173 patients), another chemotherapy drug. Participants who received Yondelis experienced a delay in the growth of their tumor (progression-free survival), which occurred on average about 4.2 months after starting treatment, compared to participants assigned to dacarbazine, whose disease progressed an average of 1.5 months after starting treatment.

The most common side effects among participants who received Yondelis were nausea, fatigue, vomiting, diarrhea, constipation, decreased appetite, shortness of breath, headache, tissue swelling, a decrease in infection-fighting white blood cells, low blood platelet counts, low red blood cell count, elevated liver enzymes and decreases in albumin, a protein found in blood.

Yondelis carries a warning alerting health care providers of the risk of severe and fatal blood infections, muscle tissue breakdown, liver damage, leakage around the vein or catheter, tissue necrosis and heart failure. Patients with known hypersensitivity to trabectedin, a drug used to treat cancer, should not take Yondelis.

Health care providers are also encouraged to advise women of potential risks to a developing fetus when taking Yondelis. Women who are taking Yondelis should not breastfeed.

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FDA approved Opdivo (nivolumab) to treat patients with non-squamous, advanced non-small cell lung cancer whose disease progressed during or after platinum-based chemotherapy.

The FDA also approved the PD-L1 IHC 28-8 pharmDx companion diagnostic to detect PD-L1 protein expression levels and help physicians determine which patients may benefit most from treatment with Opdivo.

Earlier this year, the FDA approved Opdivo to treat patients with advanced squamous NSCLC whose disease progressed during or after platinum-based chemotherapy. Opdivo targets the PD-1/PD-L1 cellular pathway to help the immune system fight cancer cells.

The safety and effectiveness of Opdivo for this use was demonstrated in an international, open-label, randomized study of 582 participants with advanced NSCLC. Participants were treated with Opdivo or docetaxel. Those treated with Opdivo lived an average of 12.2 months compared to 9.4 months in the docetaxel arm.

Additionally, 19 percent of those treated with Opdivo experienced a complete or partial shrinkage of their tumors, an effect that lasted an average of 17 months, compared to 12 percent among those taking docetaxel, which lasted an average of 6 months.

The most common side effects of Opdivo are fatigue, musculoskeletal pain, decreased appetite, cough and constipation. Opdivo also has the potential to cause serious side effects that result from the immune system effect of Opdivo.

The FDA granted Opdivo breakthrough therapy designation for this indication. It also received priority review status—the approval of Opdivo occurred approximately three months ahead of the goal date of Jan. 2, 2016.

Opdivo is marketed by Bristol-Myers Squibb. ThePD-L1 IHC 28-8 pharmDx test is marketed by Dako North America Inc.

FDA granted Priority Review for defibrotide for the treatment of patients with hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome, with evidence of multi-organ dysfunction following hematopoietic stem-cell transplantation.

FDA review of the new drug application is expected to be completed by March 31, 2016.

The application, submitted by Jazz Pharmaceuticals plc, includes safety and efficacy data from three clinical studies of defibrotide for the treatment of hepatic VOD with MOD following HSCT, as well as a retrospective review of registry data from the Center for International Blood and Marrow Transplant Research. The safety database includes over 900 patients exposed to defibrotide in the clinical development program for the treatment of hepatic VOD.

Defibrotide was granted Orphan Drug Designation by the FDA in May 2003 and has Fast Track designation. Defibrotide is being made available as an investigational new drug free of charge through an expanded access Treatment Protocol that is currently enrolling patients diagnosed with VOD in the U.S. In Europe, defibrotide is marketed under the name Defitelio.

FDA granted a Breakthrough Therapy designation to abemaciclib, a cyclin-dependent kinase 4 and 6 inhibitor, for patients with refractory hormone-receptor-positive advanced or metastatic breast cancer.

This designation is based on data from the breast cancer cohort expansion of a phase I trial, JPBA, sponsored by Eli Lilly & Co., which studied the efficacy and safety of abemaciclib in women with advanced or metastatic breast cancer.

Patients in this cohort had received a median of seven prior systemic treatments. These data were presented at the San Antonio Breast Cancer Symposium in 2014.

Lilly has an active clinical development program studying abemaciclib in breast cancer. MONARCH 1 is a phase II trial evaluating the use of abemaciclib as monotherapy in women with hormone-receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer.

In addition, Lilly is evaluating abemaciclib in two phase III clinical trials: MONARCH 2 to evaluate the combination of abemaciclib and fulvestrant in postmenopausal patients with HR+, HER2- advanced or metastatic breast cancer, and MONARCH 3 to evaluate the combination of abemaciclib and a nonsteroidal aromatase inhibitor in patients with HR+, HER2- locoregionally recurrent or metastatic breast cancer.

FDA granted orphan drug designation to drug candidate BLU-554 for the treatment of hepatocellular carcinoma.

BLU-554, a selective inhibitor of fibroblast growth factor receptor 4, is currently being evaluated in a phase I clinical trial in patients with advanced HCC and cholangiocarcinoma.

Aberrantly activated signaling of FGFR4 may be a key driver in up to 30 percent of HCC patients, according to an analysis by Blueprint Medicines, the drug's sponsor. BLU-554 has been shown to have

significant anti-tumor activity in preclinical models of HCC driven by aberrant FGFR4 signaling.

The European Medicines Agency Committee for Medicinal Products for Human Use delivered two positive opinions, recommending marketing authorization for Kyprolis and Blincyto.

Kyprolis (carfilzomib) received a recommendation for a combination with lenalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Blincyto (blinatumomab) was recommended a conditional marketing authorization for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukemia.

"The results of the ASPIRE study demonstrate that Kyprolis extended the time patients live without their disease progressing. Additionally, there is a critical need for new therapies for patients with relapsed or refractory B-cell precursor ALL," said Sean Harper, executive vice president of Research and Development at Amgen.

Kyprolis is a proteasome inhibitor for use in the treatment of patients with relapsed multiple myeloma. Blincyto is the first clinical validation of the bispecific T cell engager immunotherapy platform.

The CHMP positive opinions will now be reviewed by the European Commission, and if granted, the two products will have marketing authorization in the 28 member countries of the European Union (EU), as well as Iceland, Lichtenstein and Norway.

Kyprolis was granted orphan drug designation by the EMA in 2008, and in February, its marketing authorization application was granted accelerated assessment by the EMA. Kyprolis (carfilzomib) for Injection was approved as a monotherapy in the U.S. in July 2012, and in combination with lenalidomide and dexamethasone in July 2015.

Kyprolis is a product of Onyx Pharmaceuticals Inc. Onyx Pharmaceuticals is a subsidiary of Amgen and holds development and commercialization rights to Kyprolis globally, excluding Japan.

Blincyto is a bispecific CD19-directed CD3 T cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells.

Blincyto was granted breakthrough therapy and priority review designations by FDA, and received accelerated approval in the U.S. for the treatment of Ph- relapsed or refractory B-cell precursor ALL.

The European Medicines Agency granted an Orphan Drug Designation to CF102, developed by Can-Fite BioPharma Ltd., for hepatocellular carcinoma.

CF102 will benefit from protocol assistance and a 10-year market exclusivity following market authorization in the 28 European Union member states, as well as three additional European Economic Area countries.

In the U.S., CF102 has received Fast Track Designation as a second line for the treatment of HCC of patients who have previously received Nexavar (sorafenib) and Orphan Drug Designation for the treatment of HCC.

Can-Fite is conducting a phase II study with CF102 in patients with advanced HCC in the U.S., Europe and Israel. The randomized, double blind, placebo controlled study is expected to complete enrollment by the end of the first half of 2016 in 78 patients with Child-Pugh Class B cirrhosis.

The European Medicines Agency granted an Orphan Drug Designation to ENMD-2076, developed by CASI Pharmaceuticals Inc., for the treatment of hepatocellular carcinoma, including fibrolamellar carcinoma, a rare type of HCC.

FDA granted the drug Orphan Drug Designation for the treatment of HCC in 2014.

ENMD-2076 is an orally-active, Aurora A/ angiogenic kinase inhibitor with a unique kinase selectivity profile and multiple mechanisms of action. ENMD-2076 has been shown to inhibit a distinct profile of angiogenic tyrosine kinase targets in addition to the Aurora A kinase. Aurora kinases are key regulators of mitosis. ENMD-2076 also targets the VEGFR, Flt-3 and FGFR3 kinases.

ENMD-2076 is currently in phase II clinical trials in multiple indications, including triple-negative breast cancer, soft tissue sarcoma, ovarian clear cell carcinomas and fibrolamellar carcinoma. ENMD-2076 has received orphan drug designation from the U.S. FDA for the treatment of ovarian cancer, multiple myeloma, acute myeloid leukemia, and hepatocellular carcinoma.

Imbruvica was awarded the Prix Galien 2015 Award for Best Pharmaceutical Agent.

Imbruvica won this distinction out of 24 category nominees, all of which were deemed innovative in the field of medicine and were approved by the FDA within the past five years. Imbruvica is jointly developed and commercialized by Pharmacyclics LLC, an AbbVie Company, and Janssen Biotech Inc.

"We are honored that Imbruvica, a first-in-class, oral therapy has been recognized by the Prix Galien USA Committee for the role it continues to play in treating patients with certain blood cancers," said Erik von Borcke, president of Pharmacyclics. "Our goal is to continue developing clinically meaningful, scientifically sound therapies that offer healthcare professionals and their patients the opportunity at the best possible outcome, allowing them to resume as normal a life as possible."

Imbruvica (ibrutinib) is currently approved for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy, all CLL patients who have del 17p and patients with Waldenstrom's macroglobulinemia.

Imbruvica is also approved for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Accelerated approval was granted for the MCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Imbruvica is a first-in-class, oral, once-daily therapy that inhibits Bruton's tyrosine kinase. Imbruvica was one of the first medicines to receive FDA approval via the new Breakthrough Therapy Designation pathway, and is currently the only product to have received three Breakthrough Therapy Designations.

Imbruvica is being studied alone and in combination with other treatments in several blood cancers. More than 6,100 patients have been treated in clinical trials of Imbruvica conducted in 35 countries by more than 800 investigators. Currently, 13 phase III trials have been initiated with Imbruvica and 67 trials are registered on www.clinicaltrials.gov.

Breast Cancer

Equivalent OS Rates Found Between APBI and WBI Therapy

(Continued from page 1)

The primary objective of the trial was to assess the role of APBI brachytherapy alone compared to whole breast irradiation with boost in a defined group of patients with invasive (stage I-IIA) breast cancer or ductal carcinoma in situ (stage 0) who underwent breast-conserving surgery.

Researchers evaluated a total of 1,184 patients aged 40 years and above who were randomized to a standardized treatment arm involving whole breast irradiation (n=551) or the APBI treatment arm (n=633).

The median age of enrolled patients was 62 years. Patients received follow-up examinations every three months initially and annually after 60 months, with the median follow up being 6.6 years.

The study was conducted by The Groupe Europeen de Curietherapie European Society for Therapeutic Radiology and Oncology, and the results were presented at the annual meeting of the American Society for Radiation Oncology in San Antonio.

Study results confirm that adjuvant APBI with brachytherapy after breast conserving surgery is not inferior to adjuvant WBI with boost for selected patients with early breast cancer, with equivalent local recurrence observed with both treatment modalities, according to GEC-ESTRO.

At five-year follow-up, nine patients treated with APBI and five patients treated with WBI had a local recurrence, equating to cumulative recurrence rates of 1.44 and 0.92 percent, respectively (p=0.42). No significant difference in regional recurrence was observed between groups.

The incidence of salvage surgery was low with mastectomy being performed in one APBI patient and zero WBI patients, and lumpectomy being performed in two APBI patients and four WBI patients.

Five-year overall survival was 95.55 percent with WBI versus 97.27 percemt for APBI, with no observed difference in breast cancer related mortality between treatment arms. Efficacy of APBI at five years was independent of age and tumor characteristics.

The multicenter study was conducted at 16 medical centers in Austria, the Czech Republic, Germany, Hungary, Poland, Spain and Switzerland.

"GEC-ESTRO is the most comprehensive clinical study to date evaluating the efficacy of APBI brachytherapy alone versus traditional external whole

breast irradiation," said Vratislav Strnad, chair of the GEC-ESTRO Brachytherapy Working Group and radiation oncologist at the Department of Radiation Oncology of University Hospital in Erlangen, Germany.

"APBI brachytherapy is an attractive treatment approach with a high level of precision, versatility and flexibility. The benefits of APBI brachytherapy include an at least four-fold reduction in total radiation exposure to healthy surrounding tissue and nearby structures including the chest wall, heart, lungs or skin; preservation of future treatment options; and a notably shorter course of therapy—four or five days, compared to three or up to seven weeks for whole breast irradiation."

Non-Small Cell Lung Cancer

Study Finds Less Toxicity with IMRT Compared to 3D CRT

(Continued from page 1)

The study found 44 percent fewer cases of severe pneumonitis (defined by the researchers as lung iammation that required oxygen, steroids or mechanical ventilation, and/or led to death) in patients who received IMRT—3.5 percent of patients, despite having larger tumors, compared to 7.9 percent of the 3D CRT group.

While the benefit of IMRT was seen in all tumor sizes, the reduction of severe pneumonitis was more pronounced in larger tumors, according to Stephen Chun, a fellow in radiation oncology at MD Anderson Cancer Center, who presented the research at the American Society for Radiation Oncology's annual meeting. Additionally, those who received IMRT were more likely to complete consolidative chemotherapy—37 percent, compared to 29 percent in those treated with 3D CRT.

"IMRT was developed more than a decade ago and because it's been shown to reduce toxicity, it has been accepted to treat prostate, brain, and head & neck cancers," said Chun, the lead author of the study.

"This the first analysis of a prospective clinical trial to show a reduction of toxicity associated with IMRT in locally advanced lung cancer and could lead to a major change in the way radiation therapy is delivered for the disease."

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Prostate Cancer

Phase III Trial Demonstrates Shorter, Hypofractionated RT Can Deliver Similar Results Compared to Conventional RT

Hypofractionated radiation therapy, which is delivered in larger doses over a shorter time period than conventional RT, can result in similar rates of cure and side effects compared to a longer treatment schedule for some men with low-risk prostate cancer, according to research presented at the American Society for Radiation Oncology's annual meeting.

A phase III study, RTOG 0415, was conducted from April 2006 to December 2009 across the U.S. and Canada and compared the five-year disease-free survival rate in men with low-risk prostate cancer.

Baseline characteristics were similar between the two treatment arms, including the patients' median age of 65 and pretreatment prostate specific antigen scores, with median PSA equal to 5.4 ng/mL. The study also looked at overall survival rates and patients' biochemical recurrence.

A total of 1,105 patients qualified for the study protocol and were randomized to two groups: conventional RT, consisting of 73.8 Gy in 41 fractions delivered over 8.2 weeks was administered to 547 of the men, while 554 men received hypofractionated RT, consisting of 70 Gy in 28 fractions delivered over 5.6 weeks.

At a median follow-up of 5.9 years, the results demonstrated that hypofractionated treatment results in similar disease-free survival, as compared to conventional RT for men with low-risk prostate cancer, It is estimated that seven-year disease-free survival rates is 76 percent for patients assigned to conventional RT, and 82 percent for patients assigned to hypofractionated RT.

Comparison of biochemical recurrence and overall survival also met protocol non-inferiority criteria, and both groups reported a similar rate of Grade 3 side effects.

Of the patients who received conventional RT, 3 percent had gastrointestinal side effects and 5 percent had genitourinary side effects, compared to 5 percent of the patients in the hypofractionated RT group who had gastrointestinal side effects and 6 percent who reported genitourinary side effects.

Mesothelioma

WT1 Vaccine Doubles PFS In MPM Patients in Phase II Trial

A phase II clinical study of the WT1 cancer vaccine, developed by SELLAS Life Sciences Group, showed increased median overall survival in patients with malignant pleural mesothelioma.

Patients that received WT1 demonstrated an OS of 39 months compared to 18 months in the control arm. In addition, WT1 treatment resulted in a median progression-free survival of 11.5 months, more than double that of the control arm's 5.5 months.

The double-blinded, randomized study compared WT1 analog peptides vaccine in combination with Montanide-adjuvant plus granulocyte-macrophage colony-stimulating factor, versus Montanide-adjuvant plus GM-CSF in patients with MPM who had previously completed combined modality therapy.

Thirty-nine patients were to be enrolled in each arm at Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center. However, in May 2015, the trial's independent data monitoring committee requested discontinuation of the control arm due to futility while leaving open the WT1 cancer vaccine arm. This change led to unblinding the study earlier than planned: total enrollment has reached 40 patients, with 19 patients in WT1 cancer vaccine arm and 21 in the control arm.

During the trial, the WT1 vaccine was shown to have a favorable safety and tolerability profile. The investigators are continuing to track patient outcomes, according to SELLAS. SELLAS plans to begin phase III studies in acute myeloid leukemia and mesothelioma early next year.

The WT1 vaccine is an immunotherapy being developed to target hematologic cancers and solid tumors, including AML, mesothelioma, multiple myeloma, ovarian cancer, and multiple other cancers. The WT1 antigen is a transcription factor that is not generally expressed in normal adult cells, but appears in a large number of cancers, as well as in certain cancer stem cells.

WT1 has been ranked by the NCI as the Number 1 target for cancer immunotherapy. While WT1 has not been druggable by traditional approaches, it can be targeted by the immune system. Specifically, a number of different peptide sequences from the WT1 antigen have been identified as immunogenic and capable of stimulating cytotoxic T-cells that can target and kill WT1-expressing cancer cells. Studies also have shown that WT1 does not provoke tolerization, and that patients' T-cells can remain reactive to the antigen over time.

The WT1 vaccine, originally developed by Memorial Sloan Kettering and licensed to SELLAS, has been further modified and engineered by SELLAS to comprise four modified peptide chains that induce a strong innate immune response (CD4+/CD8+ T-cells) against the WT1 antigen.

Renal Cell Carcinoma

Study: Lenvatinib-Everolimus Combination Can Improve PFS

Lenvatinib, used in combination with everolimus, demonstrated significantly improved progression-free survival compared everolimus alone in people with metastatic renal cell carcinoma following prior VEGF-targeted therapy in a phase II trial.

PFS was 14.6 months when treated with the lenvatinib-everolimus combination, compared to 5.5 months in the control arm (HR=0.40; 95% CI: 0.24-0.68; $p<0.001$).

Results from the study, published in The Lancet Oncology, showed significant improvements in objective response rates for the lenvatinib-everolimus combination compared to everolimus alone—43 vs. 6 percent, respectively ($p<0.0001$)—and for lenvatinib compared to everolimus alone, at 27 vs. 6 percent, respectively. ($p=0.0067$).

In an updated analysis, lenvatinib plus everolimus extended overall survival compared to everolimus alone—with a median OS of 25.5 months and 15.4 months, respectively (HR 0.51, 95% CI: 0.30 to 0.88; P=0.024).

For lenvatinib in combination with everolimus, the most common treatment-emergent adverse events reported were diarrhea, fatigue and decreased appetite. The most common Grade 3 or higher events included diarrhea, fatigue and hypertension.

Patients in the study were previously treated with a VEGF-targeted therapy and randomized 1:1:1 to receive lenvatinib (24 mg once a day); everolimus (10 mg once a day); or a combination of lenvatinib (18 mg once a day) and everolimus (5 mg once a day).

Nearly all patients, 99 percent, had received one prior VEGF-targeted therapy, 1 percent had received two prior VEGF-targeted therapies, and 18 percent had received prior immunotherapy treatment.

Lenvatinib is currently indicated for the treatment of adult patients with progressive locally advanced or metastatic, differentiated thyroid carcinoma refractory to radioactive iodine.

Lenvatinib, discovered and developed by Eisai,

is an oral molecular tri-specific targeted therapy that possesses a potent selectivity and a binding mode different to other tyrosine kinase inhibitors. Lenvatinib simultaneously inhibits the activities of several different molecules including vascular endothelial growth factor receptors, fibroblast growth factor receptors, RET, KIT and platelet-derived growth factor receptors.

Carcinoid Syndrome

Telotristat Etiprate Demonstrates Clinical Benefit in Phase III Study

Telotristat etiprate showed clinical benefit in treating carcinoid syndrome in cancer patients not adequately controlled by long-acting somatostatin analog therapy, the current standard of care, according to data from the phase III TELESTAR study.

The study was presented at the European Cancer Congress in Vienna, Austria.

Telotristat etiprate, developed by Lexicon Pharmaceuticals Inc., met the study's primary endpoint with clinically meaningful reductions in bowel movement frequency in patients whose condition was not adequately controlled by SSA therapy. Carcinoid syndrome is characterized by frequent and debilitating diarrhea, as well as by facial flushing, abdominal pain, and heart valve damage.

Telotristat etiprate targets tryptophan hydroxylase, an enzyme that triggers excess serotonin production within mNET cells.

TELESTAR enrolled 135 patients in three arms, and evaluated two doses of oral telotristat etiprate—250 mg and 500 mg, each taken three times daily—against placebo, over a 12-week period and measured the reduction from baseline in the average number of daily bowel movements. Patients in both the treatment and placebo arms continued their SSA therapy throughout the study.

Data show that patients who added telotristat etiprate to SSA therapy at both the 250 mg and 500 mg doses experienced a statistically significant reduction from baseline compared to placebo in the average number of daily bowel movements over the 12-week study period ($p<0.001$), meeting the study's primary endpoint.

Patients who received 250 mg of telotristat etiprate experienced a reduction of 1.71 bowel movements (29 percent) in the average number of daily bowel movements during the final week of the study compared to baseline, and those in the 500 mg arm experienced a reduction of 2.11 bowel movements (35 percent); the placebo group showed a reduction of 0.87 bowel movements (17 percent).

A substantially greater proportion of patients on telotristat etiprate achieved a durable response (44 percent and 42 percent in the 250 mg and 500 mg arms, respectively), defined as at least a 30 percent reduction in daily bowel movements over at least half the days of the study period, as compared to 20 percent response on placebo ($p<=0.02$).

The mean change in urinary 5-HIAA, the main metabolite of serotonin, from baseline to week 12 was a reduction of 40 mg/24 hours in the 250 mg arm and 58 mg/24 hours in the 500 mg arm versus an increase of 11 mg/24 hours in the placebo group ($p<0.001$).

Baseline urinary 5-HIAA levels were 93 mg/24 hours in the 250 mg arm, 90 mg/24 hours in the 500 mg arm, and 81 mg/24 hours in the placebo group.

Treatment with telotristat etiprate was generally well tolerated during the double-blind treatment period. The proportions of patients with treatment-emergent adverse events were 82 percent in the 250 mg arm, 93 percent in the 500 mg arm and 87 percent in the placebo group during the 12-week study period.

The tolerability profile of the telotristat etiprate 250 mg dose appeared similar to placebo and somewhat better than the 500 mg dose in terms of gastrointestinal discomfort and mood. There were six events of patients experiencing mild to moderate nausea in the 250 mg arm, 13 in the 500 mg arm and five in the placebo group. There were two events of depression or depressed mood in the 250 mg arm, eight in the 500 mg arm and three in the placebo group. There were no discontinuations of treatment due to nausea, depression or depressed mood in the 250 mg and 500 mg arms during the 12-week study period.

Telotristat etiprate has previously received Fast Track and Orphan Drug designation from FDA.

Cervical Cancer

Outreach Program Boosts HPV Three-Dose Series Completion

A multicomponent outreach program increased completion of the three-dose human papillomavirus vaccination series that reduces the risk of cervical cancer, according to a joint study by UT Southwestern Medical Center and Parkland Health & Hospital System.

The study was the first to compare effectiveness in safety-net hospital populations of HPV-specific information and follow-up calls to those overdue for later doses of the vaccine, versus more traditional general vaccine information. The study was published

in the journal Pediatrics, and was funded by the Cancer Prevention and Research Institute of Texas.

The study was conducted at Parkland, the public health system for Dallas County, the ninth largest county by population and one of the most ethnically diverse counties in the U.S. From Parkland's system of 10 neighborhood-based pediatric clinics, researchers identified four clinics with the largest volume of patients aged 11 to 18. All of the clinics use electronic health records. At the time of this study (2010-2011), the vaccine was only recommended for girls. Since then, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has recommended that boys also receive the vaccine.

The 814 girls in the study were randomly assigned to one of two groups. Those in one group received a general adolescent vaccine brochure. Members of the other group received an HPV vaccine-specific brochure, plus telephone calls to parents who declined, and reminder calls to patients overdue for the second and third doses of the vaccine. One year later, HPV one-dose and three-dose coverage rates were assessed via electronic health records. Study participants were diverse – 68 percent Hispanic and 28 percent African-American.

The HPV vaccine-specific educational brochure, designed to motivate parents to start the series, had mixed results by race/ethnicity. Developed with feedback from Parkland parents to explain the value of the cancer-fighting HPV vaccine in a culturally sensitive manner, the brochure was effective for Hispanic parents only.

The study authors recommended that future research test mechanisms that may mediate intervention effects for different racial/ethnic groups, such as different informational needs, experiences, norms, or cultural beliefs.

NCI CTEP-Approved Trials For the Month of October

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

Pilot Phase

9664: Pilot Study for the Treatment of Steroid-Refractory Sclerodermatous Chronic Graft-Versus-Host Disease (GVHD) with GDC-0449 (GDC-0449). Huntsman Cancer Institute/University of Utah; Kovacsovics, Tibor J. (503) 494-1877

Phase II

9855: A Phase 2 Study of CDX-011 (Glembatumumab Vedotin) for Metastatic Uveal Melanoma. University of Texas M D Anderson Cancer Center P2C; Patel, Sapna Pradyuman. (713) 792-2921

9880: A Phase 2 Study of Subcutaneous Recombinant Human IL-15 and Haploidentical Donor Natural Killer Cell Infusion in Adults with Refractory or Relapsed Acute Myelogenous Leukemia. University of Minnesota/Masonic Cancer Center; Miller, Jeffrey Steven. (612) 624-0123

S1505: A Randomized Phase II Study of Perioperative mFOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel as Therapy for Resectable Pancreatic Adenocarcinoma. SWOG; Sohal, Davendra Pratap Singh. (216) 444-8258

Phase II/III

NRG-CC003: Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer. NRG Oncology; Gondi, Vinai. (630) 352-5350

Other Phases

AAML14B8-Q: Minimal Residual Disease Surveillance of Pediatric Normal Karyotype AML Via Error-Corrected Next-Generation Sequencing. Children's Oncology Group; Druley, Todd E. (314) 286-2124

AAML15B4-Q: Tumor Immunity in Children with Cancer. Children's Oncology Group; Dhodapkar, Kavita M. (203) 785-4640

AMC-S004: Clinical and Genomic Factors for Prognosis of AIDS Primary Effusion Lymphoma. AIDS Malignancy Consortium; Reid, Erin Gourley. (858) 822-6276

AOST15B1-Q: Descriptive Study of Genome-Wide DNA Methylation Patterns in Osteosarcoma Tissues and Their Potential Role as Predictive Biomarkers for Chemotherapy Response. Children's Oncology Group; Cherry, Mohamad. (405) 271-8777

AREN14B1-Q: Analysis of 1q Gain in Subsets of Favorable Histology Wilms Tumor. Children's Oncology Group; Mullen, Elizabeth Anne. (617) 632-1938