The Clinical Cancer Letter

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Non-Small Cell Lung Cancer:

Tecentriq Demonstrates Increase In Overall NSCLC Survival in Phase III Study

Genentech announced positive results for Tecentriq (atezolizumab) from the Phase III study OAK. The study met its co-primary endpoints and showed a statistically significant and clinically meaningful improvement in overall survival compared with docetaxel chemotherapy in people with locally advanced or metastatic non-small cell lung cancer whose disease progressed on or after treatment with platinum-based chemotherapy.

Adverse events were consistent with what has been previously observed for Tecentriq. Genentech, a member of the Roche Group, will present full results at an upcoming medical meeting in 2016.

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Lymphoma:

Adcetris Improves ORR4 in Phase III Trial

Takeda Pharmaceutical Co. Ltd. and Seattle Genetics Inc. said that the phase III ALCANZA clinical trial evaluating Adcetris (brentuximab vedotin) in cutaneous T-cell lymphoma met its primary endpoint, demonstrating a highly statistically significant improvement in the rate of objective response lasting at least four months (ORR4).

This randomized trial, which received a Special Protocol Assessment from FDA and scientific advice from the European Medicines Agency, compared the use of single-agent Adcetris to a control arm of investigator's choice of standard therapies, methotrexate or bexarotene, in 131 patients with CD30-expressing CTCL who received prior systemic or radiation therapy.

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Breast Cancer:

Abemaciclib Phase III Trial Continues After Interim Efficacy Criteria Not Met

Eli Lilly and Co. said that following a pre-planned interim analysis of the MONARCH 2 trial, an independent data monitoring committee provided the recommendation to continue the study without modification as the interim efficacy criteria were not met.

The phase III trial compares abemaciclib plus fulvestrant versus placebo with fulvestrant in women with hormone-receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer.

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Tecentriq Demonstrates Increase In Overall Survival

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The FDA granted Breakthrough Therapy Designation for Tecentriq for the treatment of people with PD-L1 (programmed death-ligand 1) positive NSCLC whose disease has progressed during or after platinum-based chemotherapy (and appropriate targeted therapy for those with an EGFR mutation-positive or ALK-positive tumor). Genentech's Biologics License Application for NSCLC was granted Priority Review with an action date of Oct. 19, 2016.

Tecentriq is a monoclonal antibody designed to bind with a protein called PD-L1. Tecentriq is designed to bind to PD-L1 expressed on tumor cells and tumor-infiltrating immune cells, blocking its interactions with both PD-1 and B7.1 receptors. By inhibiting PD-L1, Tecentriq may enable the activation of T cells. Tecentriq may also affect normal cells.

Tecentriq is the first and only anti-PD-L1 cancer immunotherapy approved by the FDA, and is indicated for the treatment of people with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based adjuvant or neoadjuvant chemotherapy.

This indication for Tecentriq is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Genentech has eight phase III lung studies underway evaluating Tecentriq alone or in combination with other treatments in people with early and advanced stages of lung cancer.

OAK is a phase III, global, multicenter, open-label, randomized, controlled study evaluating the efficacy and safety of Tecentriq compared with docetaxel in people with locally advanced or metastatic NSCLC whose disease progressed on or after treatment with platinum-containing chemotherapy.

The study's co-primary endpoints were overall survival in all people randomized to treatment in the study (intention-to-treat or ITT population) and in a PD-L1 selected subgroup of people.

PD-L1 expression was assessed on both tumor cells and tumor-infiltrating cells with an investigational immunohistochemistry (IHC) test based on the SP142 antibody being developed by Roche Tissue Diagnostics, and was defined as people whose tumors were determined to express PD-L1 with an IHC score of TC1/2/3 or IC1/2/3.

Secondary endpoints included objective response rate, progression-free survival, duration of response and safety.

A total of 1,225 patients were enrolled and randomized 1:1 to receive either docetaxel (75 mg/m2 intravenous infusion) or Tecentriq (1200 mg intravenous infusion) every three weeks. Treatment on Tecentriq continued as long as patients experienced clinical benefit as assessed by the investigator or until unacceptable toxicity. The primary efficacy analysis was based on the first 850 randomized patients, and the secondary efficacy analysis will include all 1,225 randomized patients.

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Selumetinib Shows No Significant Effect In Study

AstraZeneca announced the results from the Phase III SELECT-1 trial of the MEK 1/2 inhibitor, selumetinib, in combination with docetaxel chemotherapy as 2nd-line treatment in patients with KRAS mutation-positive (KRASm) locally-advanced or metastatic non-small cell lung cancer. Array BioPharma was informed of these results on Monday, August 8, 2016.

The results showed that the trial did not meet its primary endpoint of progression-free survival, and selumetinib did not have a significant effect on overall survival. The adverse event profiles for selumetinib and docetaxel were consistent with those seen previously.

SELECT-1 is an international trial with 510 randomized patients in over 200 centers. Patients received either selumetinib (75mg, orally, twice daily) or placebo in combination with docetaxel (intravenously, 75mg/m2, on day one of every 21-day cycle).

Selumetinib is being explored as a treatment option in registration-enabling studies in patients with differentiated thyroid cancer where the treatment received Orphan Drug Designation, and patients with neurofibromatosis type 1, a genetic disorder that causes tumors to grow along nerve tissue.

AstraZeneca acquired exclusive worldwide rights to selumetinib from Array. To date, Array received $26.5 million in up-front and milestone payments and is entitled to potential additional development milestone payments of approximately $70 million (with $30 million specific for selumetinib) and royalties on product sales.

Selumetinib is an oral highly selective MEK 1/2 inhibitor. MEK 1/2 are critical components of the RAS-ERK pathway, activation of which is implicated in driving cancer growth and progression, including in patients with KRASm NSCLC.

In May 2016, selumetinib was granted Orphan Drug Designation by FDA for adjuvant treatment of patients with stage III or IV differentiated thyroid cancer, and AstraZeneca said it's committed to exploring its full potential, including in phase III trials in patients with DTC and in an NCI-sponsored phase II registration trial in patients with pediatric neurofibromatosis type 1.

SELECT-1 (NCT01933932) is a phase III, double-blind, randomized, placebo-controlled trial. It is designed to assess the efficacy and safety of selumetinib (75 mg twice daily, given orally on a continuous schedule) in combination with docetaxel (75 mg/m2 intravenously on day 1 of every 21-day cycle), compared with matched placebo in combination with docetaxel (same schedule) in 510 patients receiving 2nd-line treatment for KRASm locally advanced or metastatic NSCLC (stage IIIB-IV), confirmed by central testing of tumor tissue using the cobas KRAS Mutation Test (Roche Molecular Systems)

The primary endpoint is PFS, and secondary endpoints include OS, objective response rate, duration of response, and safety and tolerability.

Lymphoma

Adcetris Improves ORR4 in Phase III Trial

(Continued from page 1)

Adcetris is an antibody-drug conjugate directed to CD30 which is expressed on skin lesions in approximately 50 percent of patients with CTCL. Adcetris is currently not approved for the treatment of CTCL.

The results of the ALCANZA trial demonstrated that treatment with Adcetris resulted in a highly statistically significant improvement in the ORR4 versus the control arm as assessed by an independent review committee (p-value <0.0001). The ORR4 was 56.3 percent in the Adcetris arm compared to 12.5 percent in the control arm. The key secondary endpoints specified in the protocol, including complete response rate, progression-free survival and reduction in the burden of symptoms during treatment, were all highly statistically significant in favor of the Adcetris arm. The safety profile associated with Adcetris from the ALCANZA trial was generally consistent with the existing prescribing information.

The ALCANZA trial is a randomized, open-label phase III study designed to evaluate single-agent Adcetris versus a control arm of investigator's choice of standard therapies, methotrexate or bexarotene, in patients with CD30-expressing CTCL, including those with primary cutaneous anaplastic large cell lymphoma or mycosis fungoides. The primary endpoint is ORR4 as assessed by Global Response Score in the Adcetris arm compared to the control arm. Key secondary endpoints are complete response rate, progression-free survival and reduction in the burden of symptoms during treatment.

The clinical trial enrolled 131 patients at 50 sites globally. Patients with pcALCL must have received at least one prior systemic or radiation therapy and patients with MF must have received at least one prior systemic therapy. Patients received Adcetris every three weeks versus investigator's choice for up to approximately one year. This international multi-center trial has been conducted in North and South America, Europe and Australia under operational responsibility of Takeda Pharmaceuticals.

Adcetris received orphan drug designation from the FDA for the treatment of MF, which is the most common type of CTCL. It also received orphan drug designation from the European Commission for CTCL, including subtypes pcALCL and MF.

Adcetris is being evaluated broadly in more than 70 ongoing clinical trials, including two phase III studies, ECHELON-1 in frontline classical Hodgkin lymphoma and ECHELON-2 in frontline mature T-cell lymphomas, as well as trials in many additional types of CD30-expressing malignancies, including B-cell lymphomas.

Adcetris is an ADC comprising an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E. The ADC employs a linker system that is designed to be stable in the bloodstream but to release MMAE upon internalization into CD30-expressing tumor cells.

Adcetris for intravenous injection has received FDA approval for three indications: (1) regular approval for the treatment of patients with classical Hodgkin lymphoma after failure of autologous hematopoietic stem cell transplantation or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, (2) regular approval for the treatment of classical Hodgkin lymphoma patients at high risk of relapse or progression as post-auto-HSCT consolidation, and (3) accelerated approval for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for the sALCL indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Health Canada granted Adcetris approval with conditions for relapsed or refractory Hodgkin lymphoma and sALCL.

Adcetris was granted conditional marketing authorization by the European Commission in October 2012 for two indications: (1) for the treatment of adult patients with relapsed or refractory CD30-positive Hodgkin lymphoma following autologous stem cell transplant, or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and (2) the treatment of adult patients with relapsed or refractory sALCL.

Adcetris has received marketing authorization by regulatory authorities in more than 60 countries for relapsed or refractory Hodgkin lymphoma and sALCL. In June 2016, the European Commission extended the current conditional marketing authorization of Adcetris and approved Adcetris for the treatment of adult patients with CD30+ Hodgkin lymphoma at increased risk of relapse or progression following ASCT.

Breast Cancer

Abemaciclib Trial Continues After Interim Criteria Not Met

(Continued from page 1)

"We had stringent criteria set for this interim analysis and we look forward to receiving the final MONARCH 2 results in the first half of 2017," Richard Gaynor, senior vice president, product development and medical affairs for Lilly Oncology, said in a statement. "We remain optimistic that treatment with abemaciclib, in combination with fulvestrant could offer improved outcomes for patients."

The double-blind study, designed to evaluate the safety and efficacy of abemaciclib in combination with fulvestrant, was conducted across 142 sites worldwide. The intent-to-treat population of 669 patients was randomized to receive abemaciclib or placebo orally every 12 hours on a continuous dosing schedule, given in combination with fulvestrant at the approved dose and schedule, until disease progression. Patients enrolled in the study had experienced disease progression on or within 12 months of receiving endocrine treatment in the neoadjuvant or adjuvant setting or while receiving first-line endocrine therapy for metastatic disease. Patients who had received chemotherapy in the metastatic setting were not eligible for the study. The primary endpoint for MONARCH 2 is progression-free survival (PFS).

The trial will continue into the first half of 2017 and will include a final analysis of PFS, overall survival and safety data.

Lilly will await further data and continue to work with the FDA to inform its submission plan for single-agent abemaciclib, based on the MONARCH 1 study. This phase II study evaluated the single-agent activity and safety of abemaciclib in patients with refractory metastatic breast cancer, whose disease had progressed following multiple prior treatments, including chemotherapy.

Along with MONARCH 1 and MONARCH 2, Lilly currently has three additional MONARCH trials evaluating abemaciclib in breast cancer. MONARCH 3 is a phase III trial of abemaciclib in combination with a nonsteroidal aromatase inhibitor in patients with HR+, HER2- locoregionally recurrent or metastatic breast cancer. Additionally, there are two phase II MONARCH trials: neoMONARCH, which is evaluating abemaciclib in combination with a nonsteroidal aromatase inhibitor in the neoadjuvant setting, and monarcHER, which is evaluating abemaciclib plus trastuzumab (with or without fulvestrant) in women with HR+, HER2+

locally advanced or metastatic breast cancer.

Abemaciclib (LY2835219) is an investigational, oral cell cycle inhibitor, designed to block the growth of cancer cells by specifically inhibiting cyclin-dependent kinases, CDK 4 and CDK 6. In many cancers, uncontrolled cell growth arises from a loss of cell cycle regulation due to increased signaling from CDK 4 and CDK 6. Abemaciclib inhibits both CDK 4 and CDK 6, and was shown in cell-free enzymatic assays to be most active against Cyclin D 1 and CDK 4.

FDA granted abemaciclib Breakthrough Therapy Designation in 2015 based on data from the breast cancer cohort expansion of the company's phase I trial, JPBA, which studied the efficacy and safety of abemaciclib in women with advanced or metastatic breast cancer. In addition to its current MONARCH clinical trials evaluating abemaciclib in breast cancer, a phase III trial of abemaciclib in lung cancer is also underway.

Prostate Cancer

Custirsen Trial Fails to Show Improvement in Survival

The phase III AFFINITY study failed to show a statistically significant improvement in overall survival for patients treated with custirsen in combination with cabazitaxel/prednisone compared to cabazitaxel/prednisone alone.

The trial studied custirsen in men with metastatic castrate resistant prostate cancer whose disease had progressed after treatment with docetaxel. The results were consistent with those observed in previous trials of custirsen in metastatic CPRC.

Custirsen is sponsored by OncoGenex Pharmaceuticals Inc.

The company said that as a result of these data and previous custirsen findings it will initiate discussions with FDA to evaluate options related to an early analysis of the phase III ENSPIRIT trial investigating custirsen in combination with docetaxel as second-line chemotherapy in patients with non-small cell lung cancer (NSCLC).

"Given that the ENSPIRIT trial has nearly completed enrollment and we believe there are likely a sufficient number of events to determine the effect of custirsen in NSCLC, we are eager to expedite the final data analysis, which would allow us to conserve resources and fully understand the value of the asset as we evaluate our alternatives to maximize shareholder value," Scott Cormack, president and CEO of OncoGenex, said in a statement.

Non-Small Cell Lung Cancer

Post-Hoc Analysis: Gilotrif Dose Adjustments Improve Safety, Preserve Efficacy

Results from a post-hoc analysis of two large phase III trials (LUX-Lung 3 and LUX-Lung 6) assessing the impact of dose adjustments for Gilotrif (afatinib) in patients with advanced non-small cell lung cancer were published in Annals of Oncology. The analysis suggests specific dose reductions, as described in the prescribing information, led to decreases in the incidence and severity of treatment-related adverse events in afatinib-treated patients without any apparent compromise in efficacy.

"Afatinib's efficacy and safety profile in the first-line treatment of patients with EGFR mutation-positive NSCLC has been well established in multiple large trials. This further analysis suggests that dosing of afatinib can be adjusted to help manage a patient's treatment-related adverse events, without any apparent reduction in efficacy. This may provide physicians and their patients with confidence and allows physicians to help address adverse events," principal investigator and lead author James Chih-Hsin Yang, director of the Department of Oncology, National Taiwan University Hospital, and director of the Graduate Institute of Oncology, National Taiwan University Cancer Center, Taiwan, said in a statement.

Afatinib-treated patients from the LUX-Lung 3 [NCT00949650] (n=229) and LUX-Lung 6 [NCT01121393] (n=239) trials were included in the analysis. Dose reductions took place in 53.3% (n=122) and 28% (n=67) of patients in each study, respectively, most within the first six months of treatment. Dose reductions were associated with decreases in the incidence and severity of treatment-related AEs, while median progression-free survival (PFS) was similar in patients who dose-reduced within the first six months of treatment versus those who did not (LUX-Lung 3, 11.3 vs 11 months; LUX-Lung 6, 12.3 vs 11 months).

LUX-Lung 3 and LUX-Lung 6 are multicenter, randomized, open-label, phase III trials of afatinib versus chemotherapy (pemetrexed / cisplatin and gemcitabine / cisplatin, respectively) as first-line treatment for patients with EGFR mutation-positive, advanced and metastatic NSCLC. Both trials met their primary endpoint of PFS with afatinib significantly delaying tumor growth when compared to standard chemotherapy. In addition, afatinib is the first

treatment to have shown an overall survival (OS) benefit for patients with the most common EGFR mutation (exon 19 deletions; del19) compared to chemotherapy.

Afatinib is approved in over 70 countries for the first-line treatment of EGFR mutation-positive NSCLC. Approval of afatinib in this indication was based on the primary endpoint of PFS from the LUX-Lung 3 clinical trial. Afatinib should be initiated at the approved dose of 40 mg/day; tolerability-guided dose adjustments can then be made to reduce afatinib-related AEs without an apparent impact on therapeutic efficacy.

Melanoma

Two-drug Immunotherapy May Produce Better Survival in Advanced Melanoma

Combining two immunotherapy drugs upfront for advanced melanoma appears to increase the two-year survival rate over that achieved with a single agent, according to an analysis of results from a multi-center phase II clinical trial, scientists report.

In a group of patients who received both nivolumab (Opdivo) and ipilimumab (Yervoy), the two-year survival rate was 63.8 percent compared to 53.6 percent treated with ipilimumab alone, reported researchers from Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center.

The difference wasn't statistically significant.

In a paper in *The Lancet Oncology,* the authors of the said the results suggest that the combination "might lead to improved outcomes compared with ipilimumab alone in patients with advanced melanoma." Thus far, the median survival rate has not been reached in either treatment group.

The report represents the longest follow-up to date of patients with advanced melanoma who received the nivolumab-ipilimumab combination in a randomized clinical trial, say the authors. First author is F. Stephen Hodi, director of Dana-Farber's Melanoma Center and its Center for Immuno-Oncology. The analysis of results from the CheckMate 069 phase II trial is based on results in 140 patients treated at 19 centers in the United States and France.

Both drugs target checkpoint molecules--protein switches that cancer cells can exploit to avoid recognition and attack by defender T cells of the immune system. Drugs that disable the checkpoint switches are designed to allow immune system T cells to home in on cancer cells and destroy them. Ipilimumab targets as checkpoint called CTLA-4, while nivolumab blocks the PD-1 checkpoint.

Until the advent of new immunotherapy drugs, advanced metastatic melanoma had a median overall survival of about 8 months, with a five-year survival rate of only 10 percent. Ipilimumab was the first agent to improve survival, achieving a two-year survival of 25 percent and a three-year survival rate of 22 percent in pooled clinical trials.

In the study, patients were randomized to receive ipilimumab plus nivolumab, or ipilimumab plus a placebo. Treatment continued as long as the drugs were having clinical benefit until unacceptable side effects occurred or the patient asked to stop treatment. Patients whose disease began to progress while being treated with ipilimumab alone were allowed to "cross over" and receive nivolumab as well.

Along with improved survival, patients who received the two-drug combination had a higher proportion of responses – tumor shrinkage or disappearance – as well as longer time until the disease worsened.

Patients who underwent combined treatment had a higher rate of side effects, including those classified as more severe (grade 3 or 4). Three patients in the combination group died from treatment-related side effects. The investigators said these results reflect an acceptable risk-benefit profile and noted that further research will be done to reduce the most severe side effects of combination immunotherapy treatment.

The trial is funded by Bristol-Myers Squibb, which manufactures nivolumab.

Hepatocellular Carcinoma

Study Confirms Association Between RFA Burn Time, OS In Patients Receiving ThermoDox

Celsion Corp. said NIH has conducted an independent retrospective analysis of data from the intent-to-treat population of the Company's HEAT Study, a 701-patient study investigating ThermoDox, Celsion's proprietary heat-activated liposomal encapsulation of doxorubicin in combination with radiofrequency ablation in primary hepatocellular carcinoma.

The findings will be presented at an oral session Nov. 28, at the 102nd Scientific Assembly and Annual Meeting of the Radiological Society of North America in Chicago.

Celsion is studying the use of RFA as a heat source both for tumor ablation and to activate ThermoDox as a means of treating the area surrounding the tumor, where untreated tumor may be present.

The NIH analysis, which sought to evaluate the correlation between RFA burn time per tumor volume (min/ml) and clinical outcome in patients treated with ThermoDox, concluded that increased burn time per tumor volume substantially improved survival in patients treated with RFA + ThermoDox compared to patients treated with RFA alone.

These findings are consistent with Celsion's analysis of the HEAT Study data showing that in patients treated with RFA for more than 45 minutes, standardized RFA plus ThermoDox resulted in a statistically significant improvement in overall survival, compared to standardized RFA alone.

"Findings from the NIH's independent analysis provide additional strong confirmatory support indicating that the use of RFA for more than 45 minutes in patients treated with ThermoDox can have a correlative impact on reductions in tumor size and overall survival in patients with primary liver cancer," Michael Tardugno, Celsion chairman, president and CEO said in a statement. "Our latest 285 patient subgroup OS readout from the HEAT Study demonstrates that over a 3.5 year period, there was a consistent two year survival benefit for ThermoDox plus optimized RFA over the optimized RFA only group."

"Additionally, these results provide further validation for our ongoing global phase III OPTIMA study, which is evaluating ThermoDox in combination with optimized RFA standardized to a minimum of 45 minutes versus standardized RFA alone in the treatment of primary liver cancer."

The phase III OPTIMA Study is expected to enroll up to 550 patients in up to 75 clinical sites in the United States, Europe, China and Asia Pacific, and will evaluate ThermoDox in combination with optimized RFA, which will be standardized to a minimum of 45 minutes across all investigators and clinical sites for treating lesions three to seven centimeters, versus standardized RFA alone.

The primary endpoint for the trial is Overall Survival, which is supported by post-hoc analysis of data from the Company's 701 patient HEAT Study, where optimized RFA has demonstrated the potential to significantly improve survival when combined with ThermoDox. The statistical plan calls for two interim efficacy analyses by an independent Data Monitoring Committee.

Kidney Cancer

Study Finds HIF-2 Inhibitors More Effective Than Sunitinib

A new class of drugs called HIF-2 inhibitors is more effective and better tolerated than the standard of care drug sunitinib in treating kidney cancer, researchers with the Kidney Cancer Program at Harold C. Simmons Comprehensive Cancer Center have found.

HIF-2 inhibitors, which grew out of research begun more than 20 years ago at UT Southwestern Medical Center, work by interfering with processes that fuel the growth of cells.

Investigators conducted a pre-clinical trial in mice transplanted with kidney cancer from over 20 patients and showed that the HIF-2 inhibitor PT2399 controlled cancer in half of the tumors, according to a study published in the journal Nature.

"This is a completely new treatment for kidney cancer. We want to make HIF-2 inhibitors available to patients and are currently carrying out clinical trials," said James Brugarolas, Director of the Kidney Cancer Program, who is leading an $11 million SPORE grant from the National Cancer Institute seeking to translate new discoveries into novel therapies for kidney cancer patients. Part of the SPORE grant, one of just two directly related to kidney cancer in the nation, is focused on further researching HIF-2 inhibitors.

Kevin Courtney, Assistant Professor of Internal Medicine and a coauthor of the current study, previously reported at the American Association of Clinical Oncology annual meeting that HIF-2 inhibitors were safe in patients and had activity even in heavily pretreated patients. In the Nature study, investigators show that HIF-2 inhibition was able to control metastatic kidney cancer even after 7 lines of prior therapy.

The findings show that HIF-2 is a promising target to combat kidney cancer, said Brugarolas, senior author and a Virginia Murchison Linthicum Scholar in Medical Research at UT Southwestern.

HIFs or hypoxia-inducible factors, like HIF-2, allow the body's cells to adjust to low-oxygen environments. HIFs activate programs that promote the development of blood vessels, facilitate oxygen delivery and promote efficient nutrient utilization. Kidney cancer cells hijack the same system to fuel their growth.

HIF-2 inhibitors work by suppressing the effects of HIF-2 which include downregulating an important

protein called VEGF that promotes the formation of blood vessels needed for tumors to grow.

"Unlike existing VEGF inhibitors, the HIF-2 inhibitor blocks VEGF only in the cancer and therefore does not cause cardiac toxicity or hypertension," Brugarolas explained.

In the Nature study, researchers compared the two drugs head to head and found that the HIF-2 inhibitor was more active than sunitinib and that it was active against tumors progressing on sunitinib.

"Furthermore, it was also better tolerated. As sometimes happens in patients, mice on sunitinib were sickly and lost weight, whereas mice on the HIF-2 inhibitor gained weight while on the study," he said.

Researchers surprisingly found a subset of tumors that do not respond to the drug, but were able to identify biomarkers that, once verified, would help determine which patients are more likely to benefit from HIF-2 therapies.

"HIF-2 is believed to be the most important driver of kidney cancer. Traditionally, proteins like HIF-2 were disregarded as drug targets because their shape made it nearly impossible to design drugs against them," Brugarolas said. "The approaches we have taken pave the way for identifying drug candidates for other proteins that have traditionally been considered undruggable."

HIF-2 also appears significant in other types of cancer, including deadly brain cancers called glioblastomas and non-small cell lung cancer, the most common type of lung malignancy.

NCI CTEP-Approved Trials for the Month of August

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

Phase I

9914: A Phase I Study of a Combination of MM-398 and Veliparib in Solid Tumors. National Cancer Institute LAO; Thomas, Anish. (301) 451-8418

9952: Phase 1 Trial to Determine the Recommended Phase 2 Dose (RP2D) of VX-970 When Combined with Whole Brain Radiotherapy (WBRT) in Patients with Brain Metastases from Non-Small Cell Lung Cancer (NSCLC). Mayo Clinic Cancer Center LAO; Mohindra, Pranshu. (410) 328-6080

Phase II

A021501: Preoperative Extended Chemotherapy Vs. Chemotherapy Plus Hypofractionated Radiation Therapy for Borderline Resectable Adenocarcinoma of the Head of the Pancreas. Alliance for Clinical Trials in Oncology; Katz, Matthew Harold G. (713) 794-4660

S1416: Phase II Randomized Placebo-Controlled Trial of Cisplatin with or Without ABT-888 (Veliparib) in Metastatic Triple-Negative Breast Cancer and/or BRCA Mutation-Associated Breast Cancer. SWOG; Rodler, Eve Therese. (916) 734-5959

S1507: A Phase II Trial of Trametinib with Docetaxel in Patients with KRAS Mutation Positive Non-Small Cell Lung Cancer (NSCLC) and Progressive Disease Following One or Two Prior Systemic Therapies. SWOG; Gadgeel, Shirish M. (313) 576-8753

Phase III

A051301: A Randomized Double-Blind Phase III Study of Ibrutinib During and Following Autologous Stem Cell Transplantation Versus Placebo in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma of the Activated B-cell Subtype. Alliance for Clinical Trials in Oncology; Andreadis, Charalambos Babis. (415) 353-8363

A211401: Reducing Surgical Complications in Newly Diagnosed Lung Cancer Patients Who Smoke Cigarettes. Alliance for Clinical Trials in Oncology; Croghan, Ivana Tallerico. (507) 284-7313

A221502: Pulmonary Rehabilitation Before Lung Cancer Resection. Alliance for Clinical Trials in Oncology; Benzo, Roberto P. (507) 284-0561

Other

AALL15B11-Q: Mechanism of DLX5 in Promoting T-Cell Lymphoma/Leukemia. Children's Oncology Group; Testa, Joseph. (617) 636-7651

AALL16B3-Q: Effects of PI3K/AKT/mTOR Pathway Inhibition on Efficacy of Standard Chemotherapy in B-ALL. Children's Oncology Group; Fruman, David A. (949) 824-1947

AALL16B4-Q: Mutations in Inherited Pediatric ALL. Children's Oncology Group; Rao, Sridhar. (414) 955-4170

AAML16B3-Q: Investigating Microenvironment Required by AML Cells. Children's Oncology Group; Frenette, Paul S. (718) 678-1256

ANBL16B1-Q: The Role of Stroma-Derived HBEGF in Neuroblastoma. Children's Oncology Group; Armstrong, Michael Brannon. (919) 684-3401

ANBL16B2-Q: Pilot Study: The Metabolic Landscape of Neuroblastoma. Children's Oncology Group; Rabinowitz, Joshua. (609) 258-8985

AREN16B1-Q: Urine Proteomics of Wilms Tumors. Children's Oncology Group; Kentsis, Alex. (646) 888-2593

ARST15B3-Q: Identifying and Characterizing Actionable Kinase Fusions in Inflammatory Myofibroblastic Tumors. Children's Oncology Group; Lovly, Christine Marie. (615) 936-3457

NCI CTEP-Approved Trials for the Month of September

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

Phase I

ADVL1515: A Phase 1 Study of LY2606368, a CHK1/2 Inhibitor, in Pediatric Patients with Recurrent or Refractory Solid Tumors, Including CNS Tumors. COG Phase 1 Consortium; Wetmore, Cynthia Jean. (404) 727-1180

Phase II

9922: A Phase 2 Study of Ibrutinib (PCI-32765) in Refractory Distant Metastatic Cutaneous Melanoma: Correlation of Biomarkers with Response and Resistance. Duke University - Duke Cancer Institute LAO; Moschos, Stergios J. (919) 843-7713

9944: Phase 2 Study of VX-970 (NSC# 780162) in Combination with Gemcitabine Versus Gemcitabine Alone in Subjects with Platinum-Resistant Recurrent Ovarian or Primary Peritoneal Fallopian Tube Cancer. Dana-Farber - Harvard Cancer Center LAO; Konstantinopoulos, Panagiotis A. (617) 632-5269

9947: A Randomized Phase 2 Trial of Cisplatin/Gemcitabine with or Without VX-970 in Metastatic Urothelial Carcinoma. City of Hope Comprehensive Cancer Center LAO; Pal, Sumanta Kumar. (626) 256-4673 X 69200

NRG-GI002: A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer. NRG Oncology; George, Thomas J. (412) 339-5300

Phase III

AMC-099: A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions Among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT). AIDS Malignancy Consortium; Chibwesha, Carla Joan. (919) 966-8935

Other

9980: Enhancing Minority Participation in Clinical Trials (EMPaCT). Enhancing Minority Participation in Clinical Trials; Durant, Raegan Winston. (205) 558-4234

AALL16B5-Q: Prognostic miRNA Biomarkers for Childhood Acute Lymphoblastic Leukemia: A Pilot Study. Children's Oncology Group; Amankwah, Ernest. (727) 767-2944

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Regulatory Actions

Novartis, MEI Pharma. Receive Breakthrough Therapy Designations

FDA granted Breakthrough Therapy designation to LEE011 (ribociclib), in combination with letrozole, for the treatment of hormone receptor positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer. LEE011 is a selective cyclin dependent kinase (CDK4/6) inhibitor.

The designation is based primarily on results of the phase III MONALEESA-2 trial in postmenopausal women who had received no prior therapy for their advanced disease. The trial met its primary endpoint of progression free survival at a pre-planned interim analysis.

Results of this study will be presented at an upcoming medical congress and will form the basis of regulatory discussions in the US, Europe and other countries for use in this indication, according to the drug's sponsor, Novartis.

LEE011 has been studied in non-clinical models and is currently being evaluated in combination with additional endocrine agents as part of the MONALEESA (Mammary ONcology Assessment of LEE011's Efficacy and SAfety) clinical trial program. LEE011 is not approved for any indication in any market at this time. LEE011 was developed by Novartis Institutes for BioMedical Research under a research collaboration with Astex Pharmaceuticals.

FDA and the Centers for Medicare and Medicaid Services accepted the FoundationOne comprehensive genomic profiling assay for parallel review. FDA also accepted Foundation Medicine's request for review as part of its Expedited Access Pathway for breakthrough devices.

If approved, the assay would be the first to incorporate multiple companion diagnostics to support precision medicine in oncology, including an indication for use as a companion diagnostic across a diverse range of solid tumors, according to Foundation Medicine.

Obtaining a Medicare National Coverage Determination from CMS concurrently will allow FoundationOne to be offered as a covered benefit under Medicare. Foundation Medicine expects the review will conclude in the second half of 2017.

MEI PHARMA Inc. said FDA granted **Breakthrough Therapy Designation** for the investigational drug Pracinostat in combination with azacitidine for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are >=75 years of age or unfit for intensive chemotherapy. In addition, the FDA has agreed to the Company's proposed phase III study design.

The Breakthrough Therapy Designation is supported by data from a phase II study of Pracinostat plus azacitidine in elderly patients with newly diagnosed AML, not candidates for induction chemotherapy, which showed a median overall survival of 19.1 months and a complete response (CR) rate of 42% (21 of 50 patients). These data compare favorably to a phase III study of azacitidine (AZA-AML-001(1)), which showed a median overall survival of 10.4 months with azacitidine alone and a CR rate of 19.5% in a similar patient population. The combination of Pracinostat and azacitidine was generally well tolerated, with no unexpected toxicities. The most common grade 3/4 treatment-emergent adverse events included febrile neutropenia, thrombocytopenia, anemia and fatigue.

ARRAY BIOPHARMA said FDA accepted its New Drug Application for **binimetinib** with a target action date under the Prescription Drug User Fee Act of June 30, 2017. Array completed its NDA submission of binimetinib in late Jun. 2016 based on findings from the phase III NEMO trial in patients with NRAS-mutant melanoma.

CUMBERLAND PHARMACEUTICALS INC. will begin distributing **Ethyol (amifostine) for injection** to U.S. wholesalers. Ethyol is an FDA approved cytoprotective drug indicated to reduce the incidence of xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer. It also reduces the cumulative renal toxicity associated with the repeated administration of cisplatin in patients with advanced ovarian cancer.

Earlier this year, Cumberland signed an exclusive agreement with Clinigen Group plc, a global pharmaceutical, and services company, to commercialize Ethyol in the United States. Clinigen acquired the worldwide rights to Ethyol from AstraZeneca in 2014.

JANSSEN BIOTECH Inc. submitted a supplemental Biologics License Application for **daratumumab (Darzalex)** to FDA.

The application seeks to expand the current indication, using daratumumab in combination with lenalidomide (an immunomodulatory agent) and dexamethasone, or bortezomib (a proteasome inhibitor [PI]) and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Daratumumab received Breakthrough Therapy Designation from the FDA for this pending indication on July 25, 2016.

Janssen has also submitted a request for Priority Review of this sBLA. The FDA will inform Janssen whether a Priority Review has been granted within the next 60 days. If the FDA grants Priority Review, the review should be completed within six months from Aug. 17.

The regulatory submission for daratumumab is supported by data from two phase III studies:

• **The CASTOR (MMY3004)** clinical study, which showed daratumumab in combination with bortezomib and dexamethasone reduced the risk of disease progression or death by 61 percent, compared to bortezomib and dexamethasone alone, in patients with multiple myeloma who received at least one prior therapy (Hazard Ratio [HR] = 0.39; 95 percent CI [0.28-0.53], p<0.0001). Overall, the safety of the daratumumab combination therapy was consistent with the known safety profile of daratumumab monotherapy and bortezomib plus dexamethasone, respectively.

• **The POLLUX (MMY3003)** clinical study which showed daratumumab in combination with lenalidomide and dexamethasone reduced the risk of disease progression or death by 63 percent, compared to lenalidomide and dexamethasone alone, in patients with multiple myeloma who received at least one prior therapy (HR=0.37; 95 percent CI [0.27-0.52], p<0.0001). Overall, the safety of the daratumumab combination therapy was consistent with the known safety profile of daratumumab monotherapy and lenalidomide plus dexamethasone, respectively.

The submission also included data from the phase I study of daratumumab in combination with pomalidomide and dexamethasone in patients who received at least two prior lines of therapy.

MYLAN N.V. and **Biocon LTD** said the European Medicines Agency accepted for review Mylan's Marketing Authorization Application for a proposed biosimilar **trastuzumab**, which is used to treat certain HER2-positive breast and gastric cancers.

This filing includes analytical, functional and pre-clinical data, as well as results from the pharmacokinetics and confirmatory efficacy/safety global clinical trials for Trastuzumab. The PK study had demonstrated measured bioequivalence of Mylan's and Biocon's proposed Trastuzumab biosimilar relative to that of the reference drug. The second study, the HERITAGE, evaluated the efficacy, safety and immunogenicity of the proposed biosimilar Trastuzumab in comparison to branded Trastuzumab.

BTG INTERNATIONAL CANADA INC., part of the global specialist healthcare company BTG, said that it received approval from Health Canada for DC Bead LUMI a radiopaque drug-eluting bead called DC Bead that can be loaded with doxorubicin or irinotecan for the local treatment of tumours in patients with hepatocellular carcinoma (HCC) and malignant colorectal cancer metastasized to the liver (mCRC).

DC Bead enables real-time visible confirmation of bead location during embolization. The technology has the potential to provide interventional radiologists increased control, enabling real-time adjustments to optimize patient treatment. DC Bead LUMI will also be visible in follow-up scans, allowing continued evaluation of the completeness of tumor treatment.

The Committee for Medicinal Products for Human Use of the **European Medicines Agency** issued a positive opinion recommending **marketing authorization of Onivyde (irinotecan liposome injection, nal-IRI)**, in combination with 5-fluorouracil and leucovorin, for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine based therapy.

The opinion will now be reviewed by the European Commission for marketing authorization in the European Union, with a final decision expected this year.

The CHMP recommended a dose of 70 mg/m(2) irinotecan free base (equivalent to 80 mg/m(2) irinotecan hydrochloride salt), every two weeks, which is also the FDA-approved dose regimen for pancreatic cancer. Data supporting the opinion were based on findings from the phase III NAPOLI-1 study.

The Onivyde combination extended overall survival and progression-free survival and increased tumor response rate without compromising quality of life compared to 5-FU/LV in metastatic pancreatic cancer patients who have progressed after gemcitabine-based therapy.

NAPOLI-1 patients were enrolled at 76 sites

in 14 countries across North America, Europe, Asia, South America, and Australia. The study evaluated Onivyde (80mg/m2) in combination with 5-FU and LV administered intravenously every two weeks and as a monotherapy (120 mg/m2) administered every three weeks. Each Onivyde arm was compared to a control arm of 5-FU and LV.

Onivyde demonstrated a median overall survival of 6.1 months compared to 4.2 months in the control (HR=0.67; 95% CI 0.49-0.92, p=0.012).

Onivyde is a registered trademark of Merrimack Pharmaceuticals Inc. Shire is responsible for the development and commercialization of Onivyde outside of the U.S. and Taiwan. Onivyde received FDA approval in October 2015 for the treatment of patients with metastatic adenocarcinoma of the pancreas who have progressed following treatment with gemcitabine-based therapy. Onivyde was also approved in Taiwan in in October 2015, where PharmaEngine holds commercialization rights.

The European Medicines Agency granted a PRIority MEdicines, or PRIME, designation for **DNX-2401** as a treatment for recurrent glioblastoma.

The PRIME designation was launched by the EMA in March to accelerate the regulatory approval of breakthrough therapies that target an unmet medical need. The objective is to provide patients who have few treatment options with early access to priority medicines that could provide significant benefit.

DNX-2401 is an oncolytic adenovirus; multiple clinical studies in patients with recurrent glioblastoma and gynecologic cancer have shown that DNX-2401 has a favorable safety profile, strong tumor-killing potential and can trigger an antitumor immune response, according to DNAtrix, the drug's sponsor.

Ongoing studies include a multicenter phase II clinical study evaluating DNX-2401 with the checkpoint inhibitor pembrolizumab in patients with recurrent glioblastoma.

MYLAN N.V. and **Biocon Ltd.** said the **European Medicines Agency** accepted a **Marketing Authorization Application for Pegfilgrastim**, a proposed biosimilar for the reduction of the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy, with the exception of chronic myeloid leukaemia and myelodysplastic syndromes.

In addition to analytical, functional and pre-clinical data, the application includes clinical data from pivotal pharmacokinetic and pharmacodynamics and confirmatory efficacy, safety and immunogenicity studies completed earlier in 2016. The results from these studies are expected to be presented at the European Society of Medical Oncology Annual Congress to be held in Copenhagen in October.

Mylan has exclusive commercialization rights for the proposed biosimilar Pegfilgrastim in the U.S., Canada, Japan, Australia, New Zealand and in the European Union and European Free Trade Association countries. Biocon has co-exclusive commercialization rights with Mylan for the product in the rest of the world.

Screening

FDA Warns Against Ovarian Cancer Screening

By Laura Brawley

FDA has recommended against the use of ovarian cancer screening tests, regardless of risk level.

In a safety communication published Sept. 7, the agency warned women and their physicians against relying on "unproven" technology. No study published to date has provided reliable evidence that ovarian cancer screening saves lives, the agency said.

"FDA is concerned that women and their physicians may be misled by such claims and rely on inaccurate results to make treatment decisions," FDA said in a statement. "Available data do not demonstrate that currently available ovarian cancer screening tests are accurate and reliable in screening asymptomatic women for early ovarian cancer."

FDA's recommendation echoes previous statements from other organizations. The U.S. Preventive Services Task Forcerecommends against screening for ovarian cancer: the screening tests received a "D" score.

"The USPSTF concludes that there is at least moderate certainty that the harms of screening for ovarian cancer outweigh the benefits," the task force wrote.

The American Cancer Society, Memorial Sloan Kettering Cancer Center, and Mayo Clinic recommend against ovarian cancer screening. The CDC recommends patients consult their doctor on whether they should be screened if they have certain risk factors or show symptoms of ovarian cancer.

According to NCI, ovarian cancer is the fifth leading cause of cancer death in women in the United States. Two tests are used to screen for ovarian cancer:

transvaginal ultrasound (TVU) and the CA-125 blood test. A manual pelvic exam can also be used to look for ovarian cancer.

"There are no ovarian cancer screening tests that have been cleared or approved by the FDA," the agency said.

FDA specifically expressed concerns that patients could be misled by product advertisements. The agency cited the example of the Risk of Ovarian Cancer Algorithm (ROCA) test, a type of CA-125 test that takes into account other patient risk factors like age and family history of ovarian and breast cancer through an algorithm. Abcodia, a British company, owns ROCA.

"Over the years, numerous companies have marketed tests that claim to screen for and detect ovarian cancer," FDA said. "For example, recently, Abcodia Incorporated began marketing the Risk of Ovarian Cancer Algorithm (ROCA) test in the United States, with claims that the ROCA test can screen for and detect ovarian cancer before symptoms appear and increase the chance for survival. Yet, available data do not support its claims."

In statements on the ROCA test website, Abcodia recommends that women should consider being screened annually for ovarian cancer. The company attempts to minimize the risk of false positives and negatives, claiming that ROCA is 99.8 percent effective at identifying women who do not have ovarian cancer. The company does admit, however, that the ROCA test may miss 14.2 percent of women with ovarian cancer.

ROCA tests are processed at Abcodia's lab in Tennessee. Companies offering LDTs must process all specimens in one laboratory. Under federal law, laboratory tests are classified as medical devices and can fall under the regulatory purview of the FDA. In the past, the FDA has not regulated laboratory-developed tests, also called "home brew" tests, which include ROCA. The agency proposed a regulatory framework for LDTs in 2014, but the tests do not currently have to be approved by the FDA.

"The FDA has generally not enforced premarket review and other applicable FDA requirements because LDTs were relatively simple lab tests and generally available on a limited basis," the agency wrote in a statement. "But, due to advances in technology and business models, LDTs have evolved and proliferated significantly since the FDA first obtained comprehensive authority to regulate all in vitro diagnostics as devices in 1976. Some LDTs are now more complex, have a nation-wide reach and present higher risks, such as detection of risk for breast cancer and Alzheimer's disease, which are similar to those of other IVDs that have undergone premarket review."

"We all wish there were an effective screening test for ovarian cancer. Unfortunately, we haven't yet found a test proven to save women's lives," Audra Moran, president and CEO of Ovarian Cancer Research Fund Alliance, said in a statement. "We share the FDA's concern that the ROCA Test, which is being marketed directly to women in 47 states, may do more harm than good. The money spent marketing tests of questionable benefit would be much better spent on research to find an effective test, better treatments and a cure."

The Ovarian Cancer Research Fund Alliance and Banbury Conference Writing Group recently wrote an editorial published in American Family Physician advocating for women to forgo ovarian cancer screening.

FDA said that available studies provide no evidence of benefit.

"Information in the medical literature, including published clinical trial data, do not demonstrate that currently available ovarian cancer screening tests are accurate and reliable, particularly for asymptomatic women," the agency wrote.

In a 2011 study published in JAMA, Effects of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial, investigators found that death from ovarian cancer did not decrease when women were screened with annual CA-125 tests and transvaginal ultrasound. Investigators observed that, of the 3285 women with false positive results, 1,080 had surgery to follow-up on their diagnosis, and 15 percent had at least one serious complication.

Another study, Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening, shows that CA-125 testing using ROCA had a nonsignificant reduction of mortality over fifteen years (95% confidence interval, -3 to 30; P=.10). According to the study, during years 7-14, the group receiving ROCA testing had a decrease in mortality in comparison to those who were not screened. No decrease in mortality was found in the group screened with transvaginal ultrasound.

"Further follow-up is needed before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening," the study's authors wrote in their conclusion.