The Clinical Cancer Letter

November 2015 • www.cancerletter.com • Vol. 38 No. 11

Melanoma

Keytruda Shows Anti-Tumor Activity in Three Combinations and Phase III Trial

Merck presented three studies investigating the use of Keytruda (pembrolizumab), an anti-PD-1 therapy, in combination with three other immunotherapies—epacadostat, Imlygic (talimogene laherparepvec), and ipilimumab—in patients with advanced melanoma.

Keytruda showed anti-tumor activity in all three combinations studied. The findings were featured in separate oral presentations at the International Congress of the Society for Melanoma Research, in San Francisco.

Additionally, updated data presented from a phase III study of Keytruda as a single agent showed superior overall response rates and progression free survival compared to ipilimumab in ipilimumab-naïve patients, with twice as many patients achieving PFS on Keytruda compared to ipilimumab.

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Drugs and Targets

FDA Approves Ninlaro and Darzalex For the Treatment of Multiple Myeloma

FDA approved Ninlaro (ixazomib), developed by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. Ixazomib is the first approved oral proteasome inhibitor.

The approval was based on an improvement in progression- free survival in a multicenter, randomized, double-blind, placebo-controlled trial enrolling 722 patients with multiple myeloma who had received one to three prior lines of therapy. Patients were randomized in a 1:1 ratio to either the combination

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Lymphoma

Lenalidomide-Rituximab Combination Shows Benefits in Mantle Cell Lymphoma

A combination therapy lacking many of the debilitating effects of traditional cancer treatment effectively manages mantle cell lymphoma, shrinking the malignancy and inducing remissions in the majority of patients, according to new research from Weill Cornell Medicine.

The phase II study demonstrated that lenalidomide, in combination with rituximab, provides an effective alternative to chemotherapy. More than 90 percent of patients in the small efficacy trial responded to the therapy, with their cancer shrinking by more than half, and two-thirds of that group had no evidence of detectable tumor growth after treatment.

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Keytruda Evaluated in Three Immunotherapy Combinations

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As previously reported, the study met its endpoint of overall survival. Patient-reported outcomes from the same study were also presented. The Keytruda clinical development program to date includes patients with more than 30 tumor types in more than 160 clinical trials, including more than 80 trials that combine Keytruda with other cancer treatments.

In the phase III study, KEYNOTE-006, patients with unresectable stage 3 or 4 advanced melanoma who were naïve to ipilimumab and had no more than one prior systemic therapy were enrolled into a global, open-label, randomized study.

Patients received Keytruda 10 mg/kg every two weeks (n=279); 10 mg/kg every three weeks (n=277); or four cycles of ipilimumab 3 mg/kg every three weeks (n=278). The findings provide data on additional endpoints of ORR and PFS based on six months of additional follow-up (median follow-up of 13.8 months), as well as the first-time presentation of patient-reported outcomes.

Findings showed PFS rates for Keytruda at 12 months were twice as high as ipilimumab—37.7 percent in the Keytruda every two week cohort and 36.3 percent in the every three week group, compared to 17.2 percent with ipilimumab (HR: 0.60 [95% CI, 0.49-0.74] and HR: 0.59 [95% CI, 0.48-0.73], respectively). Additionally, the ORR was 36.2 and 36.1 percent in patients receiving Keytruda every two weeks or every three weeks, respectively [(95% CI, 30.6-42.1) and (95% CI, 30.4-42.1), respectively], compared to 12.9 percent for ipilimumab (95% CI, 9.2-17.5).

There continued to be no treatment-related deaths in the Keytruda arm and there were no treatment-related deaths in the ipilimumab arm beyond one that was previously reported. Grade 3-5 treatment-related adverse events were lower for Keytruda than for ipilimumab – 15.1 and 12.6 percent of patients receiving Keytruda every two weeks and every three weeks had Grade 3-4 adverse events, respectively, compared to 19.9 percent of those receiving ipilimumab. Immune-mediated treatment-related adverse events were consistent with previously reported safety data for Keytruda and included hypothyroidism, hyperthyroidism, colitis, hepatitis, hypophysitis, pneumonitis, type 1 diabetes mellitus, uveitis, myositis and nephritis.

KEYNOTE-037 is an ongoing phase I/II study of Keytruda in combination with epacadostat, an investigational selective IDO1 inhibitor, in patients with advanced cancers. The trial is a collaboration between Merck and Incyte Corporation.

Data from the melanoma cohort were previously presented earlier this month at the Society for Immunotherapy of Cancer Annual Meeting as part of a presentation that included several tumor types. The SMR data includes additional safety data.

Early data from this trial showed that in 19 patients with advanced melanoma, the combination of Keytruda (2 mg/kg or 200 mg every three weeks) with epacadostat (25, 50, 100 or 300 mg twice daily) demonstrated an ORR of 53 percent (n=10/19), including three complete responses and seven partial responses. The disease control rate was 74 percent (n=14/19). Based on these findings, a phase III trial of this combination is planned.

MASTERKEY-265 is an ongoing phase Ib study evaluating the safety, efficacy, and tolerability of Keytruda in combination with Imlygic, a herpes simplex virus-1-based oncolytic immunotherapy, in patients with previously untreated, unresected advanced melanoma,

THE CLINICAL CANCER LETTER

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Editorial, Subscriptions, and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
Website: http://www.cancerletter.com

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $129 per year, by The Cancer Letter Inc.

Results from 16 evaluable patients, the first analysis of this study, showed that the combination of Keytruda (200 mg every two weeks) with Imlygic (up to 4 mL of 106 PFU/mL, then 108 PFU/mL every two weeks) resulted in an unconfirmed ORR of 56.3 percent (n=9/16) (95% CI, 19.8, 70.1), including two CRs and seven PRs. The DCR was 68.8 percent (n=11/16) (95% CI, 11, 58.7). MASTERKEY-265 is a collaboration between Merck and Amgen, and a phase III part of this trial is planned.

KEYNOTE-029 is an ongoing phase I/II study evaluating the safety, efficacy, and tolerability of Keytruda in combination with low-dose ipilimumab in patients with advanced melanoma to investigate whether lower doses of ipilimumab improve the tolerability of the combination regimen.

Early findings in 72 evaluable patients with advanced melanoma showed that Keytruda (2 mg/kg every three weeks) in combination with low-dose ipilimumab (1 mg/kg every three weeks for four doses) demonstrated an ORR of 56 percent (95% CI, 43-67), including three CRs and 37 PRs. The DCR was 79 percent (95% CI, 68-88).

Keytruda is a humanized monoclonal antibody that works by increasing the ability of the body's immune system to help detect and fight tumor cells. Keytruda blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Keytruda is indicated in the U.S. for the treatment of patients with metastatic non-small cell lung cancer whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy.

Keytruda is also indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. These indications are approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established and continued approval for these indications may depend on verification of clinical benefit.

Lymphoma

Lenalidomide-Rituximab Combo Shows Clinical Benefit in MCL

(Continued from page 1)

Investigators found that the results held steady for 85 percent of patients after two years. The study was published in the New England Journal of Medicine.

"For patients, their quality of life was preserved or improved, and that's a huge step up from regular chemotherapy," said lead author Jia Ruan, an associate professor of clinical medicine and a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine.

"With this frontline treatment, we were able to achieve a very high quality and durable response rate without needing to use chemotherapy. It's very meaningful for the patients who have always been told that their disease is without a cure."

"Conventional, intensive treatment may be out of reach or undesirable for many MCL patients, who often receive less intensive or palliative care that is of limited benefit," said Ruan, who receives clinical research funding from Celgene, the maker of lenalidomide and sponsor of the study. Ruan also served as a consultant and speaker for the company, and participated in its advisory board meetings.

The study had both induction and maintenance phases. In the induction phase, which included 38 patients who began treatment between 2011 and 2014, participants took one lenalidomide pill once a day for three weeks, omitted the fourth week, and then began the cycle again. Participants also received four weekly infusions of rituximab and received subsequent infusions every two months.

After a year, participants transitioned to a maintenance phase, the duration of which was for as long as they wanted to continue treatment while receiving benefit, up to a maximum of five years. During that time they received smaller doses of lenalidomide while their rituximab infusions remained the same. Their response was measured by CT or PET scans at pre-set intervals.

Ninety-two percent of patients' tumors shrank by more than half, and 64 percent achieved complete remission, becoming free of detectable tumors while undergoing treatment.

Two years after beginning treatment, 85 percent of patients showed no evidence of disease progression from their best response point on treatment. The most common side effect was asymptomatic low white blood cell counts that were generally reversible by adjusting

the treatment dose. Inflammatory symptoms associated with lenalidomide, such as rash, fatigue and tumor flare, commonly occurred during the initial cycle of treatment and resolved with anti-inflammatory treatment.

Patients were generally able to participate in their daily activities while undergoing treatment, as the treatment was delivered in the outpatient setting.

While further studies are needed to investigate the long-term outcomes of patients undergoing the treatment, and how it compares to more intensive chemotherapy regimens, the results suggest a potential strategy for developing less toxic anti-cancer regimens and using novel approaches early in the course of treatment, according to researchers at Weill Cornell.

The study was funded by Celgene, and led by Weill Cornell Medicine and NewYork-Presbyterian Hospital, with participation by three additional institutions: Moffit Cancer Center, University of Pennsylvania Abramson Cancer Center, and University of Chicago Medical Center.

Glioblastoma

ICT-107 Boosts Overall Survival by 10 Percent In Phase II Trial

Updated overall survival results and immune response data a phase II trial of ICT-107 in patients with newly diagnosed glioblastoma demonstrated a survival advantage compared to the control group.

ICT-107, developed by ImmunoCellular Therapeutics Ltd., is a dendritic cell-based immunotherapy targeting multiple tumor-associated antigens on glioblastoma stem cells. The study data also show a significant association between immune response and survival, especially in HLA-A2 positive patients, the target patient population for a phase III registration trial.

The data were presented at the annual Scientific Meeting and Education Day of the Society for Neuro-Oncology in San Antonio.

The trial was a randomized, double-blind, placebo-controlled study of the safety and efficacy of ICT-107 in patients with newly diagnosed glioblastoma multiforme following resection and chemoradiation.

ICT-107 is an intradermally administered autologous immunotherapy consisting of the patient's own dendritic cells pulsed with six synthetic tumor-associated antigens: AIM-2, MAGE-1, TRP-2, gp100, HER-2, IL-13R 2. The placebo control consisted of the patient's unpulsed dendritic cells. All patients in the trial received standard-of-care temozolomide.

Overall survival results were analyzed at three years after the last patient enrolled. For the 124-patient intent-to-treat population, median OS was 1.6 months or 10 percent better for ICT-107 patients than control. The difference in the Kaplan-Meier survival curves for this patient population was not statistically significant.

Updated OS results for the pre-specified subgroup of HLA-A2+ patients continue to support selecting this patient population alone for a well-powered phase III trial. For the MGMT methylated, HLA-A2+ PP population, OS was 13.8 months, or 58 percent better for ICT-107 treated patients. For the MGMT unmethylated, HLA-A2+ per-protocol population, median OS was 4.0 months or 34 percent better.

The differences in the KM survival curves for these two pre-specified phase II sub-populations were not powered for and did not achieve statistical significance.

ELISPOT evaluation of antigen-specific immune response demonstrated a more frequent immune response in HLA-A2+ patients compared with HLA-A1 patients, and this difference was statistically significant. This increased immune response in HLA-A2+ patients further supports the selection of HLA-A2+ patients exclusively for inclusion in the phase 3 trial, according to ImmunoCellular.

In HLA-A2+ patients, immune response was shown to be associated with survival: 60 percent of ICT-107 treated patients demonstrated a statistically significant immune response compared to only 36 percent of control patients. In a KM comparison of OS for immune responders versus non-responders, the responder curve showed a statistically significant survival benefit with a log-rank p-value of 0.0084.

For ICT-107 treated patients, the KM comparison of OS for responders versus non-responders showed a significant survival benefit with a log-rank p-value of 0.0147.

Immune response did not differ statistically for MGMT methylated compared to unmethylated patients. This result supports including both MGMT types of patients in phase III testing.

There was an unexpected finding of increased immune response in some control patients post-treatment. One potential explanation is that the phase II control (activated dendritic cells without peptide loading) was immunologically active. The phase III design employs a different control comprising the patients' own monocytes, which are less immunologically active than dendritic cells. This control could help clarify a potential survival difference between ICT-107 and control treated patients, according to ImmunoCellular.

"The final data from the phase II trial continue

to demonstrate the therapeutic value of ICT-107 as a potential treatment for patients with newly diagnosed glioblastoma, and strongly support advancing to phase III testing," said John Yu, founder of ImmunoCellular. "The clear association between immune response and survival is an important finding that we believe validates the immunotherapeutic mechanism of ICT-107 and strengthens our optimism for the phase III trial."

The phase III trial is designed as a randomized, double-blind, placebo-controlled study of over 400 HLA-A2+ subjects, which will be conducted at about 120 sites in the U.S., Canada and the European Union. The primary endpoint in the trial is overall survival. Secondary endpoints include progression-free survival and safety, as well as overall survival in the two pre-specified MGMT subgroups.

ImmunoCellular reached an agreement with FDA on a Special Protocol Assessment on the primary and secondary endpoints, as well as the statistical plan, for the phase III trial. ImmunoCellular has also been awarded a $19.9 million grant from the governing board of the California Institute for Regenerative Medicine to implement the trial.

Childhood Cancer

Researchers: All Pediatric Patients, Regardless of Family History, Could Benefit from Genomic Screening

According to investigators at St. Jude Children's Research Hospital, comprehensive genomic screening may be warranted for all pediatric cancer patients, not just those with a family history of cancer, based on a detailed analysis of the role of germline mutations in genes associated with cancer predisposition.

Ultimately, researchers anticipate that systematic monitoring of patients and family members who have germline mutations in cancer predisposition genes will allow the detection of cancers at their earliest and most curable stage.

The study from the St. Jude and the Washington University Pediatric Cancer Genome Project was published in the New England Journal of Medicine.

Researchers conducted next-generation DNA sequencing of both the tumor and normal tissues from 1,120 pediatric cancer patients and found that 8.5 percent of patients had pathogenic or likely pathogenic mutations of genes within their normal tissue that increase their risk of developing cancer.

Prior to this study, the presence of such germline mutations in pediatric cancer patients was thought to be extremely rare and restricted to children in families with strong histories of cancer. This study revealed that more than half of the children with germline mutations lacked any family history of cancer.

"This paper marks an important turning point in our understanding of pediatric cancer risk and will likely change how patients are evaluated," said corresponding author James Downing, St. Jude president and chief executive officer. "For many pediatric cancer patients, comprehensive next-generation DNA sequencing of both their tumor and normal tissue may provide valuable information that will not only influence their clinical management but also lead to genetic counseling and testing of their parents and siblings who may be at risk and would benefit from ongoing surveillance.

"The frequency of 8.5 percent represents our current estimate of the number of pediatric patients with a hereditary cancer predisposition," Downing said. "This number will likely increase as we learn more about mutations in this class of genes in young cancer patients."

St. Jude launched the Genomes for Kids clinical research study, which incorporates next-generation sequencing into the medical workup of every eligible pediatric cancer patient who enters the hospital for treatment.

Any child found to have a germline mutation in a cancer predisposition gene will be referred to the new St. Jude Hereditary Cancer Predisposition Clinic.

"We've suspected for some time that many pediatric cancers could be traced to an inherited genetic predisposition," said co-author Richard Wilson, director of the McDonnell Genome Institute at Washington University School of Medicine in St. Louis. "Now, using genome sequencing, we can see the contribution of germline mutations to pediatric cancer risk. Our results explain why children, who have not lived long enough to accumulate a critical number of cancer-causing mutations can still develop cancer."

This study involved sequencing the whole genome, whole exome, or both, of patients enrolled in the Pediatric Cancer Genome Project to check for germline mutations in 565 genes associated with cancer. Data analysis was done on 60 of these genes that are associated with autosomal dominant hereditary cancer predisposition syndromes. Mutations in these genes are known to increase cancer risk when one of the two copies of the gene is altered.

In this study, 95 patients, or 8.5 percent, had germline mutations in 21 of the 60 genes. Investigators checked whole-exome sequencing data of a comparison

group without cancer and found that only 1.1 percent of 966 adults enrolled in the 1000 Genomes Project, an international collaboration to map human genetic variation, had alterations in the same genes. The genes selected for detailed analysis were chosen based on a review of available cancer and genetic databases, the medical literature and other information.

In this study, the frequency of germline mutations in cancer predisposition genes varied by the type of cancer the child had. The highest frequency, 16.7 percent, was found in children with non-central nervous system solid tumors, followed by CNS tumors, 9 percent, and leukemia, 4.4 percent.

The most commonly mutated genes in the affected patients were TP53, APC, BRCA2, NF1, PMS2 and RB1. Many of these genes have been previously associated with rare families with multiple children who develop cancer.

An unexpected finding was the identification of mutations in the breast and ovarian cancer genes BRCA1 and BRCA2 in a number of the pediatric cancer patients. These genes are not currently included in pediatric cancer genetic screening. The prevalence of mutations in these genes in this pediatric cancer cohort suggests that the role of these genes in pediatric cancer needs to be further studied, according to researchers.

The research was funded in part by the Pediatric Cancer Genome Project, including Kay Jewelers, a lead sponsor; an NCI grant (CA021765); and ALSAC.

Cancer Genomics

TCGA Researchers Identify 7 Subtypes of Prostate Cancer And 2 Drivers of Papillary RCC

Researchers from The Cancer Genome Atlas Network recently published two studies—one identifying seven distinct molecular subtypes of prostate cancer, and one exploring the genetic drivers of papillary renal cell carcinoma.

A comprehensive analysis of 333 prostate cancers identified key genetic alterations that may help improve classification and treatment of the disease, revealing seven new molecular subtypes of prostate cancer based on known and novel genetic drivers of the disease. These subtypes may therefore have prognostic and therapeutic implications, according to researchers.

Of the seven subtypes, four are characterized by gene fusions (in which parts of two separate genes are linked to form a hybrid gene) involving members of the ETS family of transcription factors (ERG, ETV1, ETV4, and FLI1), and the other three are defined by mutations of the SPOP, FOXA1, and IDH1 genes.

Notably, the IDH1 mutation was identified as a driver of prostate cancers that occur at younger ages. Although 74 percent of the analyzed tumors could be categorized into one of the seven molecular subtypes, the remaining 26 percent of prostate tumors in this analysis could not be categorized because molecular alterations driving their growth were not identified.

Another finding from the analysis was that gene expression profiles differed based on whether the tumors were driven by gene fusions or by mutations.

Within the mutation-driven tumors, the SPOP and FOXA1 gene subtypes shared similar patterns of DNA methylation, a chemical modification of DNA that inhibits gene expression; somatic copy-number alteration and messenger RNA expression. These genomic commonalities suggest that mutations in SPOP and FOXA1 genes cause similar disruptions in the cell to bring about cancer.

Additionally, the SPOP and FOXA1 subtypes showed the highest levels of androgen receptor-mediated gene expression, suggesting potential preventive and therapeutic possibilities targeting androgens, which are male sex hormones that can stimulate the growth of prostate cancer.

The researchers, led by Chris Sander, of Memorial Sloan-Kettering Cancer Center, published their results online in the journal Cell.

In the second study, a comprehensive genomic analysis of 161 tumors from people with papillary renal cell carcinoma provided insights into the molecular basis of this cancer and may inform its classification and treatment.

PRCCs are divided into two main subtypes, Type 1 and Type 2, which are traditionally defined by how the tumor tissue appears under a microscope. Findings from this genomic analysis, carried out by investigators from The Cancer Genome Atlas Research Network, have confirmed that these subtypes are distinct diseases distinguished by certain genomic characteristics.

Researchers found that Type 1 PRCC is characterized by alterations in cell signaling involving the MET gene that are known to drive cancer cell growth, the growth of tumor blood vessels, and cancer metastasis or spread. MET gene mutations or other alterations that affect its activity were identified in 81 percent of Type 1 PRCCs examined. This finding suggests that it may be possible to treat Type 1 PRCCs with specific inhibitors of the MET cell signaling pathway, including the MET/VEGFR inhibitor foretinib, which is currently being

tested in phase II clinical trials in PRCC and other cancer types.

Type 2 PRCC was found to be more genomically heterogeneous. A specific characteristic, referred to as the CpG island methylation phenotype, was found almost exclusively in Type 2 PRCC and defined a distinct Type 2 subgroup that was associated with the least favorable outcome.

CIMP is marked by increased DNA methylation, which is a chemical modification of DNA that inhibits gene expression. Across all Type 2 PRCCs examined, 25 percent demonstrated decreased expression of CDKN2A, a tumor suppressor gene that helps regulate the cell cycle. Loss of CDKN2A expression was also associated with a less favorable outcome.

The researchers in this study were led by Paul Spellman, of Oregon Health and Science University, and Marston Linehan, of NCI. Their findings were published in the New England Journal of Medicine. TCGA is a collaboration jointly supported and managed by NCI and the National Human Genome Research Institute.

Lung Cancer

FDA Requests Data from Clovis For Rociletinib NDA in NSCLC

FDA has requested additional clinical data from Clovis Oncology Inc., for the agency's efficacy analysis of the 500mg and 625mg BID dose patient groups for rociletinib. Clovis said it would provide the information in a major amendment to the FDA.

The agency said that its efficacy analysis would focus solely on confirmed responses. The company's New Drug Application contained immature data sets based on both unconfirmed response rates and confirmed response rates, according to Clovis.

The updated results contain a lower-than-expected rate of confirmed responses to the drug.

Rociletinib is a novel, oral, targeted covalent mutant-selective inhibitor of EGFR in development for the treatment of NSCLC in patients with initial activating EGFR mutations, as well as the dominant resistance mutation T790M. Data from both the single-arm TIGER-X and TIGER-2 clinical trials served as the basis for the U.S. and E.U. regulatory submissions for the treatment of advanced mutant EGFR T790M-positive lung cancer.

As the rociletinib clinical trials were enrolling, Clovis presented interim data publicly and at medical meetings, and these data included a dataset based primarily on unconfirmed responses. This was also true of the company's Breakthrough Therapy designation submission, according to Clovis. In the NDA submission, both immature confirmed and unconfirmed response analyses were submitted. Rociletinib was given Breakthrough Therapy designation by the FDA in May 2014.

"As the efficacy data have matured, the number of patients with an unconfirmed response who converted to a confirmed response was lower than expected," the company said in a statement.

"In the intent to treat analysis of the 79 patients in the 500mg dose group, the current confirmed response rate is 28 percent, and 34 percent in the 170 patients in the 625mg dose group, with an encouraging duration of response in both doses.

"The most frequent reasons that patients' responses were not confirmed in a subsequent scan were due to progression, often due to brain metastasis, and due to subsequent scans not demonstrating tumor shrinkage greater than 30 percent."

The company said it believes that this could lead to an extension of the expected March 30, 2016, Prescription Drug User Fee Act review completion date.

"We remain confident in rociletinib and its potential to treat patients with mutant EGFR T790M-positive lung cancer," said Patrick Mahaffy, president and CEO of Clovis Oncology. "We will continue to work diligently with the FDA on our NDA submission."

Following the release of the FDA's decision Nov. 16, Clovis' stock price dropped nearly 70 percent, down to $30.24 from $99.43, and has remained around $30 since.

"The decimation of Clovis Oncology on Monday reminds investors—and not in a good way—of ImClone Systems minus Martha Stewart, the 2001 insider trading scandal that grabbed headlines for a while. As with ImClone, the Clovis mess could have a long-lasting, negative effect on the entire biotech sector," wrote Adam Feuerstein, in his Biotech Blog for The Street.

"Like ImClone, Clovis kept the bad news about its lung cancer drug hidden from investors until FDA action compelled the company to make the information public," Feuerstein wrote.

NCI CTEP-Approved Studies For the Month of November

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

CITN-12: Phase I Study of MK-3475 (Pembrolizumab) in Patients with Human Immunodeficiency Virus (HIV) and Relapsed/ Refractory or Disseminated Malignant Neoplasm. Cancer Immunotherapy Trials Network; Uldrick, Thomas S. (301) 402-6296

PBTC-047: Phase I Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma. Pediatric Brain Tumor Consortium; Monje, Michelle. (650) 736-0885

Phase II

ADVL1522: A Phase 2 Study of IMGN901 (Lorvotuzumab Mertansine; IND#: 126953, NSC#: 783609) in Children with Relapsed or Refractory Wilms Tumor, Rhabdomyosarcoma, Neuroblastoma, Pleuropulmonary Blastoma, Malignant Peripheral Nerve Sheath Tumor (MPNST) and Synovial Sarcoma. Children's Oncology Group; Geller, James Ian. (513) 636-6312 X 6312

AOST1321: Phase 2 Study of Denosumab (IND# 127430, NSC# 744010), a RANK Ligand Antibody, for Recurrent or Refractory Osteosarcoma. Children's Oncology Group; Janeway, Katherine Anne. (617) 632-4994

AOST1421: A Phase II Study of Human-Mouse Chimeric Anti-Disialoganglioside Monoclonal Antibody ch14.18 (Dinutuximab, NSC# 764038, IND# 4308) in Combination with Sargramostim (GM-CSF) in Patients with Recurrent Osteosarcoma. Children's Oncology Group; Hingorani, Pooja. (602) 546-0920

Other Phases

AALL14B7-Q: Screening Low-Hypodiploid B-ALL for Pro-B Phenotypes. Children's Oncology Group; Carlson, Christopher. (206) 667-7034

AAML15B5-Q: The Role of Id1 in Leukemogenesis. Children's Oncology Group; Wang, Lan. (305) 243-8920

AEWS15B1-Q: Development of Specific and Reversible LSD1 Inhibitors for Ewing's Sarcoma. Children's Oncology Group; Lessnick, Stephen L. (415) 476-3831

AEWS15B1-Q: Development of Specific and Reversible LSD1 Inhibitors for Ewing's Sarcoma. Children's Oncology Group; Lessnick, Stephen L. (415) 476-3831

ANHL14B1-Q: Genomic Analysis of Pediatric Anaplastic Large Cell Lymphoma ALCL. Children's Oncology Group; Leventaki, Vasiliki. (901) 595 7531

APEC14B1: The Project: EveryChild Protocol: A Registry, Eligibility Screening, Biology and Outcome Study. Children's Oncology Group; Adamson, Peter C. (215) 590-6359

E1608T2: Inherited Markers as Predictors of Adverse Events and Survival Among Melanoma Patients Treated with Ipilimumab. ECOG-ACRIN Cancer Research Group; Nathanson, Katherine Leah. (215) 573-9840

S1417CD: Implementation of a Prospective Financial Impact Assessment Tool in Patients with Metastatic Colorectal Cancer. SWOG; Shankaran, Veena (206) 288-7456

Drugs and Targets

FDA Approves Ninlaro and Darzalex in Multiple Myeloma

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of ixazomib, lenalidomide and dexamethasone (n=360) or the combination of placebo, lenalidomide and dexamethasone (n=362). Patients continued treatment until disease progression or unacceptable toxicity.

The trial showed a statistically significant improvement in PFS. The median PFS on the combination arm of ixazomib, lenalidomide and dexamethasone was 20.6 months (95% CI: 17.0, NE) compared to a median PFS of 14.7 months (95% CI: 12.9, 17.6) on the combination arm of placebo, lenalidomide and dexamethasone (PFS HR 0.74, 95% CI: 0.59, 0.94; p=0.012).

The more common adverse reactions associated with an increased rate on the ixazomib combination arm compared to the placebo combination arm were diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain.

This application was approved before its Prescription Drug User Fee Act date of March 10, 2016 and was previously granted Priority Review.

"The field of cancer treatment, and multiple myeloma in particular, has never seen a watershed moment like this," said Walter Capone, president and CEO of the Multiple Myeloma Research Foundation. "With two breakthrough designation drug approvals in the treatment of multiple myeloma in the last week, including today's approval of ixazomib, the transformation in the treatment of myeloma is clearly underway."

FDA granted accelerated approval for Darzalex (daratumumab) to treat patients with multiple myeloma who have received at least three prior treatments. Darzalex is the first monoclonal antibody approved for treating multiple myeloma.

"Targeting proteins that are found on the surface of cancer cells has led to the development of important oncology treatments," said Richard Pazdur, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research. "Darzalex provides another treatment option for patients with multiple myeloma who have become resistant to other therapies."

Darzalex, marketed by Janssen Biotech, is a monoclonal antibody that works by helping certain cells in the immune system attack cancer cells. The safety and efficacy of Darzalex were demonstrated in two open-label studies.

In one study of 106 participants receiving Darzalex, 29 percent of patients experienced a complete or partial reduction in their tumor burden, which lasted for an average of 7.4 months. In the second study of 42 participants receiving Darzalex, 36 percent had a complete or partial reduction in their tumor burden.

The most common side effects of Darzalex were infusion-related reactions, fatigue, nausea, back pain, fever and cough. Darzalex may also result in lymphopenia, neutropenia, leukopenia or anemia and low levels of blood platelets.

The FDA granted breakthrough designation for this application based on preliminary clinical evidence suggesting that if approved, Darzalex may offer a substantial improvement over available therapies. Darzalex also received priority review and orphan drug designations.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

FDA approved Empliciti (elotuzumab) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

Empliciti, sponsored by Bristol-Myers Squibb, is a monoclonal antibody directed against Signaling Lymphocyte Activation Molecule Family 7. SLAMF7 is present on myeloma cells and is also present on natural killer cells.

The approval was based on a multicenter, randomized, open-label, controlled trial evaluating progression-free survival and overall response rate in patients with relapsed or refractory multiple myeloma who had received one to three prior lines of therapy. A total of 646 patients were randomized to receive Empliciti in combination with lenalidomide and dexamethasone (n=321) or lenalidomide plus dexamethasone alone (n=325). Patients continued treatment until disease progression or the development of unacceptable toxicity.

The trial demonstrated a statistically significant

improvement in both PFS and ORR. The median PFS in the Empliciti-containing arm was 19.4 months and 14.9 months in the lenalidomide plus dexamethasone alone arm (HR: 0.70, 95% CI: 0.57, 0.85; p=0.0004).

The ORR in the Empliciti-containing arm was 78.5 percent (95% CI: 73.6, 82.9) compared to 65.5 percent (95% CI: 60.1, 70.7) in the lenalidomide and dexamethasone arm (p=0.0002).

The safety data reflect exposure in 318 patients to Empliciti in combination with lenalidomide and dexamethasone and 317 patients to lenalidomide plus dexamethasone. The most common adverse reactions, with an increased rate in the Empliciti arm compared to the control arm, were fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite, and pneumonia.

Other important adverse reactions include infusion reactions, infections, second primary malignancies, hepatotoxicity, and interference with determination of complete response. As Empliciti is an IgG kappa monoclonal antibody, it can be detected in the serum protein electrophoresis and immunofixation assays used to assess response.

Serious adverse events occurred in 65.4 percent of patients in the Empliciti-containing arm compared to 56.5 percent in the lenalidomide plus dexamethasone alone arm. The most common serious adverse reactions were pneumonia, pyrexia, respiratory tract infection, anemia, pulmonary embolism, and acute renal failure.

The recommended dose and schedule for Empliciti is 10 mg/kg intravenously every week for the first two cycles and every two weeks, thereafter, until disease progression or unacceptable toxicity with lenalidomide 25 mg daily orally on days 1 through 21.

Elotuzumab is being approved prior to its Prescription Drug User Fee Act goal date of Feb. 29, 2016, and was previously granted Priority Review and a Breakthrough Therapy Designation.

FDA granted accelerated approval to Tagrisso (osimertinib) tablets for the treatment of patients with metastatic epidermal growth factor receptor T790M mutation-positive non-small cell lung cancer, as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

The approval was based on two multicenter, single-arm, open-label clinical trials in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. All patients were required to have EGFR T790M mutation-positive NSCLC as detected by the cobas EGFR mutation test and received osimertinib 80 mg once daily.

The major efficacy outcome measure was objective response rate according to RECIST v1.1 as evaluated by a Blinded Independent Central Review. Duration of response was an additional outcome measure.

The first study (n=201) showed an ORR of 57 percent (95% CI: 50%, 64%). The second study (n=210) demonstrated an ORR of 61 percent (95% CI: 54%, 68%). The majority, 96 percent, of patients in both trials had ongoing responses at the time of primary analysis, and the median DOR had not been reached, with duration of ongoing responses ranging from 1.1 to 5.6 months after a median duration of follow-up of 4.2 months in Study 1 and 4.0 months in Study 2. The dose finding phase of Study 1 (n=63) showed an ORR of 51 percent and median DOR of 12.4 months.

Safety data was evaluated in 411 patients who received osimertinib at a dose of 80 mg daily. The most common adverse events were diarrhea, rash, dry skin, nail toxicity, eye disorders, nausea, decreased appetite, and constipation.

Osimertinib, sponsored by AstraZeneca Pharmaceuticals LP, previously received a Breakthrough Therapy Designation, and the application was granted a Priority Review. The application was approved before the Prescription Drug User Fee Act goal date of Feb. 6, 2016.

FDA approved Cotellic tablets (cobimetinib) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Cobimetinib is not indicated for treatment of patients with wild-type BRAF melanoma.

The approval was based on the demonstration of improved progression-free survival and overall survival

in a double-blind, randomized, active-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic melanoma as detected using the cobas 4800 BRAF V600 mutation test. Cobimetinib is sponsored by Genentech.

All patients received vemurafenib 960 mg orally twice daily and were randomized (1:1) to receive cobimetinib 60 mg (n=247) or matching placebo (n=248) orally once daily on days 1-21 of an every 28-day cycle. The median age of the study population was 55 years (range 23 to 88 years), 60 percent had stage M1c disease, 72 percent had a baseline ECOG performance status of 0, 45 percent had an elevated baseline serum lactate dehydrogenase, 10 percent had received prior adjuvant therapy, and less than 1 percent had previously treated brain metastases.

The trial demonstrated a statistically significant improvement in PFS [HR: 0.56 (95% CI: 0.45, 0.70), $p < 0.001$]; the median PFS was 12.3 months (95% CI: 9.5, 13.4) and 7.2 months (95% CI: 5.6, 7.5) on the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively.

The trial also demonstrated a statistically significant improvement in OS based on an interim analysis [HR: 0.63 (95% CI: 0.47, 0.85); stratified log-rank p-value=0.0019]. The median OS was not reached (95% CI: 20.7, NR) and was 17 months (95% CI: 15.0, NR) on the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively.

The confirmed objective response rates were 70 percent (95% CI: 64, 75) and 50 percent (95% CI: 44, 56) on the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively ($p < 0.001$).

Safety data was evaluated in 247 patients who received at least one dose of cobimetinib. The most common adverse reactions were diarrhea, photosensitivity reaction, nausea, pyrexia, and vomiting. The most serious risks in patients receiving cobimetinib were new primary malignancies, hemorrhage, cardiomyopathy, severe dermatologic reactions, serous retinopathy and retinal vein occlusion, hepatotoxicity, rhabdomyolysis, and severe photosensitivity reactions.

FDA approved Portrazza (necitumumab) in combination with two forms of chemotherapy to treat patients with metastatic squamous non-small cell lung cancer who have not previously received medication specifically for treating their advanced lung cancer. Portrazza is a monoclonal antibody that blocks activity of EGFR.

The safety and efficacy of Portrazza were evaluated in a multicenter, randomized, open-label clinical study of 1,093 participants with advanced squamous NSCLC who received the chemotherapies gemcitabine and cisplatin with or without Portrazza. Those taking Portrazza plus gemcitabine and cisplatin lived longer on average, 11.5 months, compared to those only taking gemcitabine and cisplatin, at 9.9 months. Portrazza was not found to be an effective treatment in patients with non-squamous NSCLC.

Portrazza includes a boxed warning to alert health care providers of serious risks of treatment with Portrazza, including cardiac arrest and sudden death. The most common side effects of Portrazza are skin rash and magnesium deficiency, which can cause muscular weakness, seizure, irregular heartbeats and can be fatal. Portrazza is marketed by Eli Lilly & Co.

FDA granted Breakthrough Therapy Designation to pexidartinib (formerly PLX3397) for the treatment of tenosynovial giant cell tumor where surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity.

Currently, there is no FDA-approved systemic therapy for the treatment of TGCT. The designation was granted based on results from an extension cohort of a single-arm, multi-center phase I study that assessed the safety and efficacy of pexidartinib. Results of this study were published in The New England Journal of Medicine.

A pivotal phase III trial of pexidartinib called ENLIVEN is currently enrolling patients with symptomatic TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity.

Pexidartinib is an oral small molecule that potently and selectively inhibits colony stimulating factor-1 receptor, which is a primary growth driver of abnormal cells in the synovium that causes TGCT. Pexidartinib has not been approved by FDA or any other regulatory authority for uses under investigation.

In addition to Breakthrough Therapy Designation, pexidartinib has been granted Orphan Drug Designation by FDA for the treatment of PVNS and GCT-TS. Pexidartinib also has received Orphan Designation from the European Commission for the treatment of TGCT. Pexidartinib is sponsored by Daiichi Sankyo Inc. and Plexxikon Inc., a member of the Daiichi Sankyo Group.