The Clinical Cancer Letter

July 2015 • www.cancerletter.com • Vol. 38 No. 7

Lymphoma

Phase II Trial Shows Benefit with Imbruvica In Activated B-cell-like Subtype of DLBCL

A phase II clinical trial identified patients with a specific molecular subtype of diffuse large B-cell lymphoma that are more likely to respond to Imbruvica (ibrutinib) treatment.

In the trial, patients with the activated B-cell-like subtype of DLBCL were more likely to respond to Imbruvica than patients with the germinal center B-cell-like subtype. The trial was jointly conducted by NCI and Pharmacyclics Inc., and was published in Nature Medicine.

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Drugs and Targets

FDA Approves Odomzo in Advanced BCC, Kyprolis Combination in Multiple Myeloma

FDA approved Odomzo (sonidegib) capsules for the treatment of patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. Odomzo is marketed by Novartis Pharmaceuticals Corp.

The approval was based on demonstration of a durable objective response rate in an international, multi-center, double-blind, randomized, two-arm, non-comparative trial in patients with locally advanced basal cell carcinoma not amenable to local therapy or metastatic basal cell carcinoma.

The trial enrolled 230 patients who were randomized to receive Odomzo 800 mg (n=151) or 200 mg (n=79) daily until disease progression or unacceptable toxicity.

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Prostate Cancer

Researchers: As Many as 40% of Patients Could be Receiving Overtreatment

As many as 40 percent of patients with lower-risk prostate cancers may be currently receiving overtreatment, according to researchers that examined common treatment practices.

Monitoring men with very low- and low-risk prostate cancers using watchful waiting or active surveillance, or expectant management, is a useful approach for a large number of men with localized tumors and could spare them the debilitating side effects of aggressive treatments that are too often unnecessarily used in this patient population, according to a study led by researchers at UCLA.

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Phase II Trial Identifies Subgroup That Benefits from Imbruvica

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The trial enrolled 80 patients with DLBCL that had relapsed or had not responded to prior treatment. All patients received Imbruvica. Tumor responses were seen in 25 percent of patients overall, including eight patients with complete responses and 12 with partial responses.

For the study population as a whole, after a median follow-up of 11.5 months, the median progression-free survival and overall survival were 1.6 and 6.4 months, respectively.

An analysis based on disease subtype showed that Imbruvica produced complete or partial responses in 37 percent (14 of 38) of patients with ABC DLBCL but only 5 percent of patients with GCB DLBCL.

The target for Imbruvica, Bruton's tyrosine kinase, is a key component of B-cell receptor signaling. The new study provides the first clinical evidence that ABC but not GBC tumors may produce abnormal B-cell receptor signals that promote the survival of cancer cells by activating BTK, thereby accounting for the sensitivity of ABC tumors to Imbruvica.

"Clinical trials such as this are critical for translating basic molecular findings into effective therapies," said Louis Staudt, of the NCI Center for Cancer Genomics, who co-led the study and discovered the role of B-cell receptor signaling in ABC DLBCL.

Study co-leader Wyndham Wilson, of the NCI Center for Cancer Research, added, "This is the first clinical study to demonstrate the importance of precision medicine in lymphomas."

Based on this study's results, an international phase III trial of standard chemotherapy with or without Imbruvica in patients with DLBCL, excluding the GCB subtype, is being conducted by Janssen Pharmaceuticals in collaboration with Wilson and Staudt. This is the first time a phase III trial has been designed to selectively enroll patients with a particular molecular subtype of DLBCL.

Ibrutinib has been approved by the U.S. Food and Drug Administration for the treatment of certain patients with several other cancers, including mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia.

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.

Prostate Cancer

Researchers: As Many as 40% Of Patients Could be Overtreated

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Since the initiation of PSA screening tests, most men with prostate cancer are now diagnosed with localized, low-risk prostate tumors that are unlikely to kill them. However, nearly all of these men undergo surgery or radiation, putting them at risk for ongoing side effects such as erectile dysfunction and impaired urinary function.

"This study is the most up-to-date and comprehensive review of expectant management of prostate cancer patients worldwide," said review senior author Mark Litwin, professor and chair of UCLA Urology.

"Active surveillance and other observational strategies have produced excellent, long-term disease-specific survival and minimal morbidity for men with prostate cancer. Despite this, expectant management remains underused for men with localized prostate cancer."

The study was published in the journal CA: A Cancer Journal for Clinicians. The study was funded in part by the American Cancer Society.

First, researchers clarified the definitions of types of surveillance. Active surveillance uses repeated PSA testing and prostate biopsies to monitor for development of more aggressive disease in younger, healthier patients who might benefit from delaying treatment.

Watchful waiting avoids aggressive testing and watches for any physical symptoms of progressive disease. It is generally reserved for avoiding treatment altogether for older, sicker patients.

The review described the current surveillance protocols, and reviewed the outcomes for each of these strategies in terms of cancer survival and quality of life. Additionally, the review covered technologies such as prostate MRI and fusion biopsies.

"Considerable questions remain regarding both the identification of optimal candidates for surveillance, as well as understanding the ideal monitoring strategy after the initiation of observational protocols," said Leonard Marks, study co-author and a professor of urology.

"Using strict inclusion criteria for very low-risk or low-risk prostates cancer can select a group of prostate cancer patients for active surveillance who would avoid the side effects of therapy while experiencing comparable survival and quality of life."

More work is required to optimize the delivery of these expectant management strategies for patients treated in certain settings that may not have incorporated active surveillance into their treatment repertoire, researchers said.

"Ultimately, the decision-making process surrounding treatment for a man with localized prostate cancer must take an individualized approach. The risks and benefits of expectant management vis-a-vis active treatment should be reviewed with the patient in light of existing knowledge, potentially with the use of decision aids to help enable a truly shared decision-making process," the review states.

"Active surveillance is a viable approach for most men with low-risk prostate cancer, and its broader adoption has the potential to stop the overtreatment of men with indolent lesions and redirect resources to men with more serious cancers."

Colorectal Cancer

Vectibix Improves OS In Phase III Trial of mCRC

A phase III study of Vectibix (panitumumab) in metastatic colorectal cancer met its primary endpoint of improving overall survival.

The trial evaluated Vectibix and best supporting care in patients with chemorefractory wild-type KRAS (exon 2) metastatic disease compared to treatment with best supporting care alone. Full results will be submitted to a future medical congress and for publication, according to the trial's sponsor, Amgen.

The Vectibix treatment arm further showed statistical significance for all secondary endpoints including OS and PFS in patients with wild-type RAS (absence of mutations in exons 2, 3 and 4 of KRAS and NRAS) mCRC. Observed adverse events were consistent with the known Vectibix safety profile.

In the global, randomized, open-label study, patients were randomized 1:1 to receive 6 mg/kg of Vectibix every 14 days and BSC, or BSC alone (as defined by the investigator).

Vectibix is the first fully human anti-EGFR antibody approved by the FDA for the treatment of metastatic colorectal cancer. Vectibix was approved in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC after disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

In May 2014, the FDA approved Vectibix for use in combination with FOLFOX, as first-line treatment in patients with wild-type KRAS (exon 2) mCRC. With this approval, Vectibix became the first-and-only biologic therapy indicated for use with FOLFOX, one of the most commonly used chemotherapy regimens, in the first-line treatment of mCRC for patients with wild-type KRAS mCRC.

Liver Cancer

Cyramza Trial Fails OS Endpoint; Subgroup Data to Form New Study

A phase III trial of Cyramza (ramucirumab) as a second-line treatment for hepatocellular carcinoma failed to meet its primary endpoint of overall survival.

However, encouraging single-agent activity was observed, according to the drug's sponsor, Eli Lilly & Co., with meaningful improvements in key secondary endpoints as well as within certain patient subgroups.

Those findings will help form the basis for a new phase III trial.

While the trial's primary endpoint of overall survival favored the Cyramza arm, it was not statistically significant. The trial results were published in The Lancet Oncology.

The global, randomized, double-blind trial, named REACH, compared Cyramza plus best supportive care to placebo plus best supportive care as a second-line treatment in patients with HCC after being treated with sorafenib in the first-line setting.

Median overall survival was 9.2 months on the ramucirumab arm compared to 7.6 months on the placebo arm (HR 0.866; 95% CI: 0.717-1.046; p=0.1391).

While the median OS was not statistically significant, a prespecified subgroup of patients with an elevated baseline of alpha-fetoprotein ≥ 400 ng/mL showed a greater survival improvement with ramucirumab treatment. Median OS in this subgroup of patients was 7.8 months in the ramucirumab arm compared to 4.2 months in the placebo arm (HR 0.674; 95% CI 0.508-0.895; p=0.0059).

The REACH study analyses presented at the Gastrointestinal Cancers Symposium earlier this year concluded that a greater reduction in the risk of death in patients with progressively higher baseline AFP values warrants further investigation. Based on these findings, Lilly will soon begin enrollment in REACH-2, a new phase III trial to evaluate the benefit of ramucirumab treatment in advanced liver cancer patients with an elevated baseline AFP.

Alpha-fetoprotein is a glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including hepatocellular carcinoma, hepatoblastoma, and nonseminomatous germ cell tumors of the ovary and testis.

Initiated in 2010, REACH enrolled 565 patients across 27 countries. The primary analyses were focused on patients with a Child-Pugh score of <7 (Child-Pugh Class A only). Key secondary endpoints included progression-free survival, overall response rate, time to progression, and safety.

The safety data in the REACH study were consistent with results from previous single-agent ramucirumab studies and the safety information included in the U.S. Prescribing Information for ramucirumab.

The most common clinical grade 3 or higher adverse events occurring more frequently in patients on the ramucirumab arm compared to the control arm were hypertension, fatigue, and malignant neoplasm progression. The safety profile of ramucirumab in patients with elevated baseline AFP >400 ng/mL was consistent with that observed in the overall safety population.

Cyramza has been granted Orphan Drug Designation for treatment of hepatocellular carcinoma in the U.S. and EU.

In the U.S., Cyramza is approved for use as a single agent or in combination with paclitaxel as a treatment for people with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

It is also approved in combination with docetaxel as a treatment for people with metastatic non-small cell lung cancer whose cancer has progressed on or after platinum-based chemotherapy. Additionally, it is approved with FOLFIRI as a treatment for people with metastatic colorectal cancer whose cancer has progressed on or after therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Leukemia

Pracinostat/Vidaza Combination Shows Response in Phase II Trial

Updated results from a phase II study of elderly patients with newly diagnosed acute myeloid leukemia showed that to date, in 50 patients treated with Pracinostat in combination with azacitidine (Vidaza), 27 patients achieved complete response, plus complete response with incomplete blood count recovery plus morphologic leukemia-free state, including 16 patients who achieved a CR.

The response rate from this study compares favorably with previous studies of azacitidine alone in this population. The trial data was presented at the European Hematology Association Annual Congress in Vienna.

Median overall survival has not yet been reached, with 32 patients still being followed (range, 6-15 months). Survival of patients with intermediate-risk cytogenetic abnormalities appears greater than that for patients with high-risk cytogenetics, though neither subset of patients has reached median survival. The 60-day mortality rate was 10 percent.

Pracinostat in combination with azacitidine was well tolerated in this population of elderly AML patients. The most common treatment-emergent adverse events included febrile neutropenia, thrombocytopenia, nausea and fatigue. AEs resulting in dose reductions were

frequently due to disease under study. Nearly half of the patients (22 of 50) to date have received study drug beyond six months.

"The combination of Pracinostat and azacitidine continues to demonstrate compelling clinical activity in these elderly patients with newly diagnosed AML," said Daniel Gold, president and CEO of the drug's sponsor, MEI Pharma.

"While the overall survival trend in this study is encouraging, we believe that longer follow-up is needed to gain an accurate survival estimate. Ultimately, this survival estimate will be critical in determining the development path forward for this combination. We look forward to providing an update when these data mature, which we expect to occur later this year."

Pracinostat is an oral inhibitor of histone deacetylases, which belong to a larger set of epigenetic regulator proteins. Pracinostat has been tested in multiple phase I and phase II clinical studies in advanced hematologic diseases and solid tumor indications with side effects often associated with drugs of this class, the most frequent of which is fatigue.

Bladder Cancer

Study: Robotic Surgery Shows Long-term Results Similar to Traditional Open Surgery

In the largest multi-institutional study to date, patients diagnosed with bladder cancer and treated with robot-assisted surgery experienced similar results to those who underwent a traditional open operation, according to research led by scientists at Roswell Park Cancer Institute.

The study is a retrospective review of long-term patient outcomes for cystectomies that currently populate the International Robotic Cystectomy Consortium, which represents 11 institutions in 6 countries. Data from 702 patients with clinically localized bladder cancer from 2003 to date were analyzed for five-year recurrence-free survival (67%), cancer-specific survival (75%) and overall survival (50%). When compared with traditional open surgery, patients treated with robot-assisted surgery experienced similar long-term survival outcomes.

The study results were published in the journal of the European Association of Urology.

"We found that robot-assisted radical cystectomy, an advanced surgical procedure used to treat bladder cancer that has spread to the bladder wall or recurred, despite local treatment in the bladder, provides similar early oncological outcomes while reducing operative blood loss," says Khurshid Guru, director of robotic surgery in the Department of Urology at RPCI.

This research was conducted in collaboration with City of Hope and Beckman Research Institute; Henry Ford Health System; Karolinska University Hospital, Stockholm; Weill Cornell Medical College; Guy's and St Thomas's Hospital, London; Onze-Lieve-Vrouw Ziekenhuis, Aalst, Belgium; Arthur Smith Institute for Urology; University Clinics of Saarland, Homburg, Germany; Cleveland Clinic Foundation; Yonsei University Health Systems Severance Hospital, Seoul, South Korea.

NCI CTEP-Approved Trials For the Month of July

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

9681: A Phase 1 Study of (Cabozantinib) Plus Nivolumab (CaboNivo) Alone or in Combination with Ipilimumab (CaboNivoIpi) in Patients with Advanced/Metastatic Urothelial Carcinoma and Other Genitourinary Tumors. National Cancer Institute LAO; Apolo, Andrea Borghese (301) 451-1984

AMC-095: A Phase I Study of Ipilimumab and Nivolumab in Advanced HIV Associated Solid Tumors with an Expansion Cohort in HIV Associated Solid Tumors. AIDS-Associated Malignancies Clinical Trials Consortium; Rajdev, Lakshmi (718) 904-2754

Phase II

A021302: Impact of Early FDG-PET Directed Intervention on Preoperative Therapy for Locally Advanced Gastric Cancer: A Random Assignment Phase II Study. Alliance for Clinical Trials in Oncology; Shah, Manish Arvind (646) 962-6200

EA2133: InterAACT - An International Multicentre Open Label Randomised Phase II Advanced Anal Cancer Trial Comparing Cisplatin Plus 5-Fluorouracil Versus Carboplatin Plus Weekly Paclitaxel in Patients with Inoperable Locally Recurrent or Metastatic Disease. ECOG-ACRIN Cancer Research Group; Eng, Cathy (713) 792-2828

EAI141: Early Assessment of Treatment Response in AML Using FLT PET/CT Imaging. ECOG-ACRIN Cancer Research Group; Jeraj, Robert (608) 263-8619

NRG-GY003: Phase II Randomized Trial of Nivolumab with or Without Ipilimumab in Patients with Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer. NRG Oncology; Burger, Robert Allen (215) 662-3318

Pilot Phase

ABTC-1403: The Effect of IL-7 (CYT107) on CD4 Counts in Patients with High Grade Gliomas and Severe Treatment-Related CD4 Lymphopenia After Concurrent Radiation and Temozolomide. Adult Brain Tumor Consortium; Campian, Jian Li (314) 747-4241

Other Phases

9937: Association of Genetic Variants with Cardiotoxicity in Patients Treated for HER2+ Breast Cancer in the N9831 Clinical Trial. Mayo Clinic in Florida; Perez, Edith A. (904) 953-7283

AALL15B3-Q: The Role of PreB Cell Receptor in Acute Lymphocytic Leukemia. Children's Oncology Group; Schroeder, Harry W. (205) 394-4769

ANBL15B2-Q: Serial Sequencing of Neuroblastoma. Children's Oncology Group; Roberts, Stephen S. (212) 639-4034

MC1432: Analysis of the Predictive Potential of Gene Expression Panels in Early Stage HER2+ Breast Cancer Samples From NCCTG (Alliance) N9831. Mayo Clinic; Perez, Edith A. (904) 953-7283

Drugs and Targets

FDA Approves Odomzo, Kyprolis; EU Approves Opdivo, Imbruvica

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Randomization was stratified by disease stage (locally advanced or metastatic), histologic subtype (aggressive or nonaggressive) and geographic region. Eighty-four percent of those enrolled had locally advanced disease.

Approval was based on demonstration of durable objective responses in patients with laBCC as determined by central independent review according to a modification of RECIST. The ORR for the 66 patients with laBCC randomized to the Odomzo 200 mg arm was 58 percent (95% CI: 45, 70), consisting of three complete responses and 35 partial responses.

A pre-specified sensitivity analysis using an alternative definition for complete response, defined as at least a PR according to MRI and/or photography and no evidence of tumor on biopsy of the residual lesion, yielded a CR rate of 20 percent. A similar response rate was noted in the 128 patients with laBCC randomized to the Odomzo 800 mg arm [44 percent (95% CI: 35, 53)]. Among the 38 responding patients with laBCC in the 200 mg arm, seven patients experienced subsequent disease progression, and four of these seven patients had maintained a response of six months or longer.

The remaining 31 patients continue to respond with ongoing responses ranging from 1.9+ to 18.6+ months; 16 patients have ongoing responses of six months or longer, and the median duration of response has not been reached.

Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said: "Thanks

to a better understanding of the Hedgehog pathway, the FDA has now approved two drugs for the treatment of basal cell carcinoma just in the last three years." In 2012, Genentech's Erivedge (vismodegib) was the first drug approved to treat locally advanced and metastatic basal cell carcinoma.

Odomzo carries a Boxed Warning alerting healthcare professionals that Odomzo may cause death or severe birth defects in a developing fetus when administered to a pregnant woman. Pregnancy status should be verified prior to the start of Odomzo treatment, and both male and female patients should be warned about these risks and advised to use effective contraception.

FDA approved Kyprolis (carfilzomib) in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy. Kyprolis is sponsored by Onyx Pharmaceuticals Inc., an Amgen subsidiary.

The approval was based on a demonstration of improved progression-free survival in a multicenter, open-label trial (PX-171-009 ASPIRE). The trial enrolled 792 patients with relapsed or refractory multiple myeloma after one to three lines of prior therapies. The patients were randomized to receive lenalidomide and dexamethasone with or without Kyprolis for 18 cycles. Lenalidomide and dexamethasone were continued thereafter until disease progression. There was no planned cross-over from the control arm to treatment with Kyprolis.

A statistically significant prolongation of PFS, as determined by an independent review committee, was demonstrated [HR 0.69 (95% CI: 0.57, 0.83); p = 0.0001, stratified log-rank test].

Median PFS was 26.3 months in the Kyprolis arm and 17.6 months in the two-drug arm. A treatment effect was observed across all subgroups tested, but the magnitude of the treatment effect was reduced in patients with higher tumor burden at study baseline (improvement in median PFS: 11 months for ISS Stage I, 8 months for ISS Stage II and 2 months for ISS Stage III).

An interim analysis of overall survival was conducted at the same time. The difference in OS did not reach the prespecified boundary for statistical significance. A partial response or better was achieved by 87 percent of patients on the Kyprolis arm and 67 percent on the two-drug arm.

The safety profile of Kyprolis in the 3-drug combination was similar to that described in the current label. Cardiovascular events, venous thromboembolic events, and thrombocytopenia occurred more frequently in the Kyprolis arm than in the Kyprolis arm.

In Cycles 1-12 of therapy, the VTE rate was 13 vs 6 percent, respectively, despite protocol-mandated use of thromboprophylaxis.

The revised labeling includes new Warnings and Precautions for VTE, cardiac toxicities, acute renal failure, pulmonary toxicities, and hypertension.

The European Medicines Agency granted accelerated approval to Opdivo (nivolumab) for the treatment of metastatic melanoma.

Opdivo is a monoclonal antibody that targets the programmed cell death 1 receptor expressed on T cells. PD-1 functions to suppress T cell activity and Opdivo blocks this suppression releasing the T cells to mediate tumor regression. Two PD-1 targeted agents, Opdivo and pembrolizumab, were approved by FDA for the treatment of advanced melanoma in 2014.

The accelerated EMA approval is based on the results of CheckMate-066 and CheckMate-037 trials, which involved treatment-naïve and pre-treated melanoma patients, respectively. Opdivo is sponsored by Bristol-Myers Squibb.

CheckMate-066 revealed 73 percent one-year survival rate in patients treated with Opdivo, compared to 42 percent in those treated with comparator drug, dacarbazine.

In CheckMate-037, the combination of Opdivo and Yervoy (ipilimumab)—plus a BRAF inhibitor in patients who were BRAF-positive—achieved an objective response rate of 32 percent, compared to 11 percent among patients treated with conventional chemotherapy alone.

The European Commission approved Imbruvica capsules (ibrutinib) for adult patients with Waldenstrom's macroglobulinemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

Imbruvica is co-developed by Cilag GmbH International, a member of the Janssen Pharmaceutical Companies, and Pharmacyclics LLC, an AbbVie company. Janssen affiliates market ibrutinib in Europe, the Middle East and Africa, as well as the rest of the world, except for the U.S., where it is co-marketed by Janssen Biotech Inc. and Pharmacyclics.

Imbruvica has already been approved in Europe for the treatment of adult patients with relapsed or refractory mantle cell lymphoma, or adult patients with

chronic lymphocytic leukemia who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Imbruvica has also been recently approved for the treatment of WM by the U.S. FDA, which granted it Breakthrough Therapy Designation in 2013.

Genome sequencing of patients with WM has revealed a common mutation in the MYD88 gene. This mutation triggers the activation of a number of targets, including Bruton's tyrosine kinase, which is a key component needed to regulate immune cell proliferation and cell survival which plays a part in B-cell malignancies, such as WM. Imbruvica forms a strong covalent bond with BTK, thereby inhibiting the enzyme and blocking the transmission of cell survival signals within the malignant B cells.

The phase II multi-center study on which the approval was based evaluated the efficacy and tolerability of Imbruvica 420 mg once daily in 63 patients with previously treated WM (median age of 63; range, 44-86 years old).

Updated results from the study were published in April in The New England Journal of Medicine. The overall response rate using criteria adopted from the International Workshop on WM was 90.5 percent, 57 out of 63 patients (95 percent CI 80.4-96.4).

Eleven patients (17 percent) achieved a minor response, 36 patients (57 percent) achieved a partial response (PR) and 10 patients (16 percent) achieved a very good PR. The median times to at least minor and partial responses were four weeks and eight weeks respectively.

Secondary endpoints of the registration trial included progression free survival and the safety and tolerability of Imbruvica in symptomatic patients with previously treated WM. The estimated two-year PFS and overall survival rates among all patients were 69.1 percent (95% CI 53.2-80.5) and 95.2 percent (95% CI 86.0-98.4) respectively.

FDA granted Priority Review to MM-398 for the treatment of metastatic adenocarcinoma of the pancreas following a gemcitabine-based therapy.

The FDA has set a goal of October 24 to take action under the Prescription Drug User Fee Act.

Sponsored by Merrimack Pharmaceuticals Inc. and Baxalta Incorporated, the new drug application is based upon the results of an international phase III study, NAPOLI-1, conducted in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy. MM-398 in combination with 5-fluorouracil and leucovorin achieved its primary and secondary endpoints by demonstrating a statistically significant improvement in overall survival, progression free survival and overall response rate compared to the control group of patients who received a combination of 5-FU and leucovorin.

Data for the study were presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer in June 2014 and the American Society of Clinical Oncology 2015 Gastrointestinal Cancers Symposium in January.

MM-398 (irinotecan liposome injection) is a novel encapsulation of irinotecan in a long-circulating liposomal formulation. The activated form of irinotecan is SN-38, which functions by inhibiting topoisomerase I and promoting cell death.

The European Medicines Agency has also accepted a Marketing Authorization Application for MM-398 for the treatment of patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy. The acceptance of the MAA marks the beginning of the review process in the European Union for MM-398 in this indication.

The FDA and EMA have granted MM-398 orphan drug designation for patients with metastatic pancreatic cancer. MM-398 was granted Fast Track designation by the FDA in November 2014.

Merrimack and Baxalta have entered into an exclusive licensing agreement to develop and commercialize MM-398 outside of the United States.

FDA granted an Orphan Drug Designation to ImMucin for the treatment of multiple myeloma, developed by Vaxil Bio.

ImMucin trains the patient's immune system to identify and destroy cells which display a short specific 21-mer portion (signal peptide domain) of the cancer-associated expression of MUC1, which appears on 90% of all cancer cells but not in patient blood.

Vaxil completed a phase I/II clinical study with ImMucin in MM patients, which showed strong diversified T/B-cell immunity in all 15 patients across MHC repertoires and initial indications of clinical efficacy; 11 out of the 15 treated patients demonstrated stable disease or clinical improvement which did not require any further treatment.

An ongoing follow-up study in patients who responded clinically to ImMucin has shown that some patients haven't required any further treatment for their disease in the four years since ImMucin treatment.

FDA granted an Orphan Drug Designation to Cleave Biosciences' lead drug candidate, CB-5083, for treatment of multiple myeloma.

CB-5083 is a first-in-class, oral inhibitor of p97, an enzyme that controls various aspects of protein homeostasis.

Cleave's ongoing studies include an open-label, phase I dose escalation/dose expansion trial to evaluate the safety, pharmacokinetics, pharmacodynamics and anti-tumor activity of CB-5083 in multiple myeloma patients who have relapsed/refractory or refractory disease after receiving two or more lines of therapy, including an immunomodulatory agent and a proteasome inhibitor.

Cleave expects to enroll up to 60 patients at multiple U.S. cancer centers that are part of the Multiple Myeloma Research Consortium. A second phase I study of CB-5083 is focused in patients with solid tumor malignancies.

FDA granted Fast Track designation to immuno-oncology products Toca 511 and Toca FC, developed by Tocagen Inc., for the treatment of recurrent high grade glioma, including glioblastoma and anaplastic astrocytoma. A study in this indication is planned for later this year, according to Tocagen.

Toca 511 and Toca FC are designed to selectively transform cancer cells so they produce a chemotherapy drug within the tumor while also activating the immune system against the tumor with local and systemic benefits.

Toca 511 is a retroviral replicating vector that selectively delivers a gene for the enzyme cytosine deaminase to the cancer cells. The patient then takes oral cycles of Toca FC, a novel formulation of an antifungal drug, which is converted into the FDA-approved chemotherapy drug, 5-fluorouracil.

FDA granted an Orphan Drug Designation to Anisina (ATM-3507) for neuroblastoma. Anisina is developed by Novogen Ltd.

The designation was based on data from preclinical studies which were done as part of the Children's Oncology Drug Alliance involving Australian charity, The Kids' Cancer Project, The University of New South Wales, The Nationwide Children's Hospital of Columbus, Ohio, and Novogen.

The key findings from these studies showed that Anisina significantly improved the effectiveness of the standard of care microtubule targeting compound, vincristine, in an animal model of neuroblastoma. The data from these studies were recently announced and presented at Eighth Annual Cancer Molecular Therapeutics Research Association meeting in Boston.

Novogen is now conducting pre-clinical studies to further validate the combinatorial effect of Anisina with a range of microtubule-targeting compounds in animal models of adult cancer. Once the company has completed its pre-clinical toxicology program for Anisina, the drug is expected to enter the clinic for adults in mid-2016 with clinical trials in childhood cancer in Australia and the U.S. to follow in early 2017.

FDA granted a Breakthrough Therapy Designation to Lenvima (lenvatinib) in patients with advanced or metastatic renal cell carcinoma who were previously treated with a vascular endothelial growth factor-targeted therapy.

Lenvima is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Lenvima is not indicated for patients with metastatic renal cell carcinoma.

Lenvima received the designation based on results of a phase II open-label, multicenter study involving 153 patients who were previously treated with a VEGF-targeted therapy and randomized 1:1:1 to receive Lenvima and everolimus (18+5 mg once a day), Lenvima (24 mg once a day) or everolimus (10 mg once a day).

Nearly all patients (99 percent) had received one prior VEGF-targeted therapy, 1 percent had received two prior VEGF-targeted therapies, and 18 percent had received prior immunotherapy treatment. The results of this study were presented in an oral presentation at the 2015 annual meeting of the American Society of Clinical Oncology.

Lenvima, sponsored by Eisai, inhibits the kinase activities of vascular endothelial growth factor receptors VEGFR1-3. Lenvima also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor receptors FGFR1-4; the platelet derived growth factor receptor alpha, KIT, and RET.

Lenvima was approved under the Priority Review designation for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer by the FDA in February 2015.

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Cigna Corp. issued a positive coverage decision for VeriStrat serum proteomic testing developed by Biodesix Inc. Cigna published its position to extend coverage for the VeriStrat blood-based test, stating the test is "…medically necessary for an individual with advanced non-small cell lung cancer (NSCLC)…"

VeriStrat testing is considered standard of care by nationally recognized clinical guidelines, and is clinically proven for use in patients with NSCLC, according to Biodesix. The test now covered for more than 115 million people in the U.S.

Amgen submitted a supplemental New Drug Application to the FDA for Kyprolis (carfilzomib) for Injection to seek an expanded indication for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy.

The sNDA is based on data from the global ENDEAVOR trial. ENDEAVOR is the first of two head-to-head phase III trials of Kyprolis versus Velcade (bortezomib).

Relapsed multiple myeloma patients treated with Kyprolis and dexamethasone in the ENDEAVOR study lived twice as long without their disease worsening, demonstrating statistically and clinically significant superiority over Velcade (median progression-free survival of 18.7 months versus 9.4 months, HR=0.53, 95% CI, 0.44 - 0.65; $p<0.0001$).

The Kyprolis combination demonstrated superiority over the Velcade combination for secondary objectives of higher overall response rate and lower neuropathy events. Overall survival data are not yet mature and continue to be monitored.

Kyprolis is also being evaluated in the CLARION study, a head-to-head Phase 3 multicenter, open-label, randomized study in transplant-ineligible patients with newly diagnosed multiple myeloma. The study is evaluating the safety and efficacy of Kyprolis, melphalan and prednisone versus Velcade, melphalan and prednisone.

Sanofi and Regeneron Pharmaceuticals Inc. entered into a five-year, global collaboration to develop and commercialize new antibody cancer treatments, with Sanofi committing to an initial investment of up to $2.17 billion.

The two companies plan to jointly develop a programmed cell death protein 1 inhibitor currently in phase I testing, with clinical trials beginning in 2016 with therapeutic candidates based on ongoing preclinical programs.

Sanofi will make an upfront payment to Regeneron of $640 million. Together, the companies will invest a total of $1 billion for discovery through proof of concept development of monotherapy and novel combinations of immuno-oncology antibody candidates—funded 25 percent by Regeneron and 75 percent by Sanofi. The companies have also committed to equally fund an additional $650 million for development of REGN2810, a PD-1 inhibitor.

In addition, Sanofi will pay Regeneron a one-time milestone of $375 million in the event that sales of a PD-1 product and any other collaboration antibody sold for use in combination with a PD-1 product exceed, in the aggregate, $2 billion in any consecutive 12-month period.

Finally, the two companies have agreed to re-allocate $75 million over three years for immuno-oncology antibodies from Sanofi's $160 million annual contribution to their existing antibody collaboration formed in late 2009.

Regeneron will be responsible for discovery, antibody generation and development through proof of concept, at which time Sanofi will have the ability to opt-in to further development and commercialization. In the existing antibody collaboration, Sanofi has the opportunity to opt-in at the time of an Investigational New Drug application.

The agreement covers both monoclonal antibodies and bi-specific antibodies, a variation of standard antibody therapeutics in which two distinct targets within the body can be bound by the same molecule, usually the cancer cell and an immune cell. Regeneron has developed a novel and flexible manufacturing platform that enables efficient production of bi-specific antibodies that are otherwise similar to natural antibodies.

Beyond PD-1, other programs in preclinical development include antibodies to lymphocyte-activation gene 3, glucocorticoid-induced tumor-necrosis-factor-receptor-related protein and a programmed death ligand inhibitor. Finally, the collaboration is advancing bi-specific antibodies that target hematologic and solid cancers, either as monotherapies or in combination regimens with other immune modulating treatments.

Additional terms, including potential therapeutic targets or mechanisms, were not disclosed.