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Neupogen's New Indication: Nuke Mishaps and Terrorism

By Paul Goldberg

Neupogen, a drug widely used in oncology, recently received an FDA approval for boosting survival in people acutely exposed to myelosuppressive doses of radiation, also known as hematopoietic syndrome or acute radiation syndrome.

Neupogen (filgrastim)—a myeloid growth factor, a class of drugs that includes GM-CSF and Neulasta—as well as other similar drugs have been used to treat victims of radiation and nuclear accidents since Chernobyl.

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Robert Peter Gale: Two Chernobyl Doctors Were First Humans to Get GM-CSF

By Robert Peter Gale

By 1986, there were substantial data in animals that molecularly-clone human haematopoietic growth factors, such as granulocyte-macrophage colony stimulating factor (GM-CSF), could accelerate bone marrow recovery and increase survival after exposure to high-dose ionizing radiations given under controlled experimental conditions.

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FBI Probes Who Knew What and When In Power Morcellation Imbroglio

By Matthew Bin Han Ong

The Federal Bureau of Investigation is reportedly trying to establish whether Johnson & Johnson—one of the largest manufacturers of power morcellators—knew as early as nine years ago that the gynecological device can disseminate uterine cancers.

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Neupogen's New Indication: Nuke Mishaps and Terrorism

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"Based on my experience treating victims of many nuclear and radiation accidents worldwide, I think drugs like G- and GM-CSF may be useful in accelerating bone marrow recovery in persons exposed to moderate doses of ionizing radiations in whom sufficient numbers of undamaged bone marrow cells remain to respond and who have no irreversible damage to other tissues and organs such as the skin and lungs," said Robert Peter Gale, an American physician who was the first physician to use these drugs in the aftermath of a nuclear accident.

"These drugs may make a difference in some radiological or nuclear events, but, as in all of medicine, prevention is better than cure," said Gale. "Stopping terrorists from gaining access to radioactive materials, radiological devices and nuclear weapons and preventing the spread of nuclear weapons are better strategies. And don't count on G-CSF or GM-CSF to bail us out of nuclear war; there won't be physicians left to give them to survivors or hospital to treat them in—and, maybe, no one to treat."

In order to administer GM-CSF to Chernobyl victims, Gale and his Soviet counterpart became the first humans to get the drug. His account of this action appears on page 1. This is the first time the story is being told in its entirety.

Since human trials would be neither ethical nor feasible, approval of Neupogen was based on animal studies conducted under the criteria of the FDA 2002 "animal rule."

Amgen Inc. wasn't the initial principal sponsor of the animal study, done in monkeys, that ultimately led to the drug's approval. That work, conducted at the University of Maryland, was sponsored by the National Institute of Allergy and Infectious Diseases.

The approval likely positions Neupogen's sponsor, Amgen, as the leading contender for the market for drugs that may be used for mitigation of the bone marrow suppression resulting from a terrorist attack or radiological or nuclear accident.

The government is building up an inventory of these drugs to keep on hand in case such events occur. The supply of Neupogen will remain in Amgen's rotating inventory, and would be sold and administered for other indications.

The value of Neupogen's new indication to Amgen—or any other company—is unclear.

In 2013, an FDA Medical Imaging Drugs Advisory Committee and Oncologic Drugs Advisory Committee, meeting in a joint session, recommended that the entire class of drugs, leucocyte growth factors (LGF)—including Amgen's Neulasta, the Sanofi-Aventis drug Leukine and any approved biosimilars—would be appropriate for use in this indication.

The committees voted overwhelmingly that animal survival data were reasonably likely to predict benefit in humans.

In discussion, committee members said that they were not in favor of repeated animal studies to look at alternative LGFs for this indication. Neupogen's safety and efficacy in the radiological/nuclear incident setting can be generalized to the use of other LGFs in this setting.

However, further animal studies to examine variable radiation doses and variable timing of LGF administration may be warranted, the committee said.

"The only drug that has gone through GLP-compliant pivotal trial in non-human primates to show efficacy for lethality has been Neupogen," by Thomas MacVittie, a professor of radiation oncology and pathology at the University of Maryland School of Medicine and a member of the Molecular and Structural Biology Program at the University of Maryland Marlene and Stewart Greenebaum Cancer Center, who conducted the clinical trial in monkeys.

"It took from May of 2013, when the advisory committee recommended approval to March 2015 before the FDA finally approved Neupogen [for the indication]. They have approved only Neupogen at this point, so Neulasta, Leukine and the bio-similars are sitting on the outside looking in, because they have yet to do a pivotal trial."

Sources say that marketing authorization is FDA's

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and BARDA's ultimate goal for products that may be used in these indications. However, the agency can purchase any drug by seeking the FDA emergency use authority, called the Emergency Use Authorization.

In fact, in September of 2013—months after the FDA advisory committee made its recommendations, but before approval—the federal government's Project BioShield, administered by Biomedical Advanced Research and Development Authority in the HHS Office of the Assistant Secretary for Preparedness and Response, awarded a $36.5 million contract to Sanofi-Aventis for late stage development and procurement of Leukine. At the same time, Amgen received a $157.5 million contract for the purchase of Neupogen.

"If you read the literature on EUA, it's not easy there, either. You have to have a substantial, consistent database in relevant studies for the government to be convinced that they should buy some of the countermeasure and stockpile it. The government can say to the [biosimilars manufacturers], Yes, the medical countermeasure (drug) works in the clinic, but we don't know whether it works for people exposed to relatively high doses of radiation. This may require a pivotal trial performed similar to that for neupogen under the FDA Animal Rule."

"In the U.S., until recently, there were no licensed products available for the treatment of underlying injuries associated with hematopoietic syndrome of Acute Radiation Syndrome," Amgen officials said in a statement.

"Amgen decided to submit an sBLA for this indication because based on the underlying biology, clinical data associated with reduction of duration and severity of neutropenia in both cancer and severe chronic neutropenia patients, and supportive animal studies, Amgen believed that filgrastim may provide clinical benefit as treatment for radiation-induced myelosuppression resulting from radiation exposure."

At this time, BARDA doesn't have an outstanding RFP for more purchases of these drugs.

Two Chernobyl Doctors Were The First Humans to Get GM-CSF

(Continued from page 1)

On April 26, 1986, my Soviet colleagues and I were suddenly faced with treating about 200 firefighters, emergency personnel and technicians exposed to very high doses of ionizing radiations from an accident at the Chernobyl nuclear power facility in Ukraine. The most severely affected persons receiving >2 Gray (Gy; for reference the average dose of the A-bomb survivors was 10 times less and there were no survivors of doses >1 Gy)[1] were flown to Moscow where we set up operations at Clinical Hospital 6, a high security facility attached to the Institute of Biophysics.[2]

We used diverse physical, biological and modeling techniques to arbitrarily divide victims into low-, moderate-, high- and very-high dose radiation exposure cohorts. Persons in the low-dose cohort received supportive care, many in the high-dose cohort received bone marrow transplants and those in the very high-dose cohort (unlikely to survive because of irreversible damage to other tissues and organs such as the lungs) again received supportive care. The question we faced was whether to try GM-CSF in persons in the moderate-dose cohort and those in the high-dose cohort lacking an appropriate bone marrow donor.

GM-CSF had never been given to humans and the Soviet leadership, although wishing to do *everything possible,* was reluctant to see its citizens become the first humans to receive. We developed a plan.

First, Prof. Andrei Vorobiov, member of the USSR Academy of Medical Sciences and then head of the USSR Hematology Center, presented our strategy to a special Soviet Government Commission on Chernobyl reporting to the Politburo and General Secretary Mikhail Gorbachev who tentatively agreed.

Next, the late Prof. David Golde and I convinced Dr. Angelika Stern at Sandoz in Basel to send us GMP-compliant GM-CSF developed for clinical trials, which were scheduled to begin soon. To avoid difficulties with customs officials in Moscow the drug was placed into the checked luggage of a Swiss businessman and removed at Sheremetyevo airport before it was returned to him.

The next step was for Prof. Vorobiov to inject me with 10 times the maximum-tolerated-dose in monkeys.

We would wait an hour and if I were OK I would inject him with the same dose (I objected, he insisted). This went well and I left for dinner at Spaso House with US Ambassador Arthur Hartman.

Midway through dinner I received a telephone call

Robert Peter Gale (left) with Anatoly Dobrynin, Soviet ambassador to the U.S., and industrialist Armand Hammer at a Moscow art exhibit in 1986.

from the hospital: Prof. Vorobiov is dying. I returned quickly and found Vorobiov in the coronary care unit, white as a sheet, diaphoretic, on oxygen and cardiac monitors and clutching his chest. A first thought: "Lubyanka prison here I come."

My exam of him showed nothing special; his ECG was normal. I realized Vorobiov's pain was in his sternum reminding me of the bone pain one sometimes sees in children with acute lymphoblastic leukemia when their bone marrow is packed with leukemia cells. Might his pain be from large numbers of granulocytes in the sternum caused by giving him GM-CSF? I had no bone pain and there was no evidence of pain in monkeys (how would be know?). Vorobiov and I spent an anxious night together.

By morning he improved, I was fine and our blood tests showed a huge increase in granulocytes. With these encouraging outcomes, and under Vorobiov's special authority, Profs. Alexander Baranov, the late Angelina Guskova and I began treating several victims in the moderate radiation dose cohort. Results are published.[3] Of course, we lacked controls but what seemed encouraging outcomes led us to use GM-CSF after a large radiation accident in Goiania, Brazil the following year[4] and in several subsequent nuclear accidents such as Tokaimura in Japan.

Vorobiov and I are fine (as far as we know). Some people have asked whether I though it dangerous for us to be the first normals (an ascertainment no doubt open to question) to receive GM-CSF. I don't think so. As someone who skydives in Mohave, bicycles in New York and goes to war zones in Beirut, the former Yugoslavia and Azerbaijan, it seemed only a modest risk. Recently FDA approved a similar drug, granulocyte-colony-stimulating factor (G-CSF) for use after radiation accident.

Based on my experience treating victims of many nuclear and radiation accidents worldwide, I think drugs like G- and GM-CSF may be useful in accelerating bone marrow recovery in persons exposed to moderate doses of ionizing radiations in whom sufficient numbers of undamaged bone marrow cells remain to respond and who have no irreversible damage to other tissues and organs such as the skin and lungs.

These drugs may make a difference in some radiological or nuclear events, but, as in all of medicine, prevention is better than cure. Stopping terrorists from gaining access to radioactive materials, radiological devices and nuclear weapons and preventing the spread of nuclear weapons are better strategies. And don't count on G-CSF or GM-CSF to bail us out of nuclear war; there won't be physicians left to give them to survivors or hospital to treat them in—and, maybe, no one to treat.

The author is a visiting professor at the Haematology Research Centre Division of Experimental Medicine, Imperial College London.

Footnotes

1) Radiation doses in the A-bomb survivors are typically given in Sieverts (Sv). Under exposure conditions I discuss a Sv and a Gy are approximately equivalent.

2) Currently the Federal State Institution A.I. Burnazyan Federal Medical and Biophysical Center (SRC IBR).

3) Gale RP, Vorobiov A. First use of myeloid colony-stimulating factors in humans. Bone Marrow Transplant 2013;48:1358.

4) Butturini A, De Souza PC *et al*. Use of recombinant granulocyte—macrophage colony stimulating factor in the Brazil radiation accident. Lancet 1988;2:471-4

FBI Probes Who Knew What In Power Morcellation Imbroglio

(Continued from page 1)

According to the Wall Street Journal, the FBI's Newark, N.J. office interviewed three people, including Robert Lamparter, a retired pathologist who alerted Ethicon, a J&J subsidiary, about potential problems with morcellators in 2006.

A full account of Lamparter's 2006 complaint can be found at the Pittsburgh Business Times, which reported on the whistleblower case in May 2014.

FBI agents also interviewed Amy Reed, the doctor who led the campaign against power morcellation, as well as Sarah Robinson, a physician assistant in Los Altos, Calif., who told the WSJ she sent an FBI agent a list of 386 names of patients and their families who may have been harmed by the device.

It's not publicly known whether a formal investigation has been launched. The FBI declined to comment, in response to a previous inquiry from The Cancer Letter, on the "existence or nonexistence" of an investigation (The Cancer Letter, April 10).

J&J officials told the WSJ that they were not aware of an FBI investigation. The company pulled its power morcellators from the market in July 2014, after the FDA issued a warning, and after an FDA advisory panel expressed low confidence in power morcellation as a treatment for uterine fibroids (The Cancer Letter, Aug. 1, 2014).

The FBI may be looking into whether J&J had violated federal law by neglecting to report adverse events, Hooman Noorchashm, Reed's husband, said previously to this reporter (The Cancer Letter, April 10). Noorchashm is a cardiac surgeon at the Thomas Jefferson University Hospital.

Reed and Noorchashm's interview with The Cancer Letter appeared on the ABC News coverage of the FBI investigation May 27.

Federal Appeals Court Instructs Tobacco Companies to Issue "Corrective Statements"

The U.S. Court of Appeals for the D.C. Circuit Court upheld on May 22 a lower court's order requiring nine tobacco companies to publish "corrective statements" about the dangers of tobacco and its practices of marketing to children.

The ruling stems from a case the federal government brought against a group of the largest tobacco companies in 1999 under anti-racketeering law.

In 2006, U.S. District Judge Gladys Kessler found this group of tobacco companies liable for defrauding the public as they mischaracterized the addictiveness and health risks of their products.

The May 22 ruling upholds the specific language of the five corrective statements ordered by Kessler, which instructed the companies to disseminate the statements via television and newspaper advertising, their websites, and cigarette packaging.

These statements will address:

- Adverse health effects of smoking;
- Addictiveness of smoking and nicotine;
- False advertising of low-tar and light cigarettes as less harmful than regular cigarettes;
- Design of cigarettes to maximize nicotine delivery and addiction; and
- Health effects of secondhand smoke.

The question of whether the tobacco companies must also make the corrective statements through retail point-of-sale displays, as Kessler originally ordered, is the subject of ongoing litigation.

According to Kessler:

"[This case] is about an industry, and in particular these Defendants, that survives, and profits, from selling a highly addictive product which causes diseases that lead to a staggering number of deaths per year, an immeasurable amount of human suffering and economic loss, and a profound burden on our national health care system. Defendants have known many of these facts for at least 50 years or more.

"Despite that knowledge, they have consistently, repeatedly and with enormous skill and sophistication, denied these facts to the public, the Government, and to the public health community. The evidence in this case clearly establishes that Defendants have not ceased engaging in unlawful activity."

The D.C. Circuit Court overturned only one part of Kessler's ruling, rejecting a requirement that all corrective statements include a preamble stating that

"[a] Federal Court has ruled that [the manufacturers] deliberately deceived the American public" about the dangers of cigarettes and has "ordered [them] to make this statement."

The American public needs to be fully informed about the tobacco industry's "unconscionable behavior," the American Heart Association said in a statement.

"While we are disappointed with this part of the ruling, the court did not argue against the accuracy of the preamble language itself," the AHA said. "The ruling was based solely on a determination that requiring the preamble is not an acceptable legal remedy under RICO (Racketeer Influenced and Corrupt Organizations Act).

"Despite ongoing efforts by the industry to get the courts to weaken the corrective statements, today's ruling brings us one step closer to holding it accountable for decades of deception and profiting from the death and disease caused by its products. We now look forward to the publication of the corrective statements."

Six public health organizations—the American Cancer Society, American Heart Association, American Lung Association, Americans for Nonsmokers' Rights, National African American Tobacco Prevention Network, and the Tobacco-Free Kids Action Fund (a 501c4 affiliate of the Campaign for Tobacco-Free Kids)—joined the case as interveners in 2005.

ASCO Conquer Cancer Foundation Names 2015 Winners of Young Investigator, Career Development, And Clinical Research Awards

The Conquer Cancer Foundation of the American Society of Clinical Oncology announced the recipients of the 2015 Young Investigator Awards, Career Development Awards, Advanced Clinical Research Award in Breast Cancer, and the Comparative Effectiveness Research Professorship in Breast Cancer.

The recipients will be recognized during the 2015 ASCO Annual Meeting taking place May 29 - June 2 in Chicago.

Their research focuses on topics including methods for improving the quality and safety of breast cancer care, identifying biomarkers in several cancer types, and highlighting risks and new treatments for lung cancer.

• **Dawn Hershman**, of Columbia University Medical Center, was awarded the **Comparative Effectiveness Research Professorship**, providing flexible funding of $500,000 over five years, to evaluate reducing overuse and underuse of cancer therapies to improve the quality and safety of breast cancer care. The grant is supported by the Breast Cancer Research Foundation.

• **Priyanka Sharma**, of University of Kansas Medical Center, received the **Advanced Clinical Research Award in Breast Cancer**. Sharma will receive $450,000 over three years to evaluate the BRCAness phenotype as a prognostic marker in triple-negative breast cancer. This grant is also supported by the Breast Cancer Research Foundation.

The Career Development Award provides funding to clinical investigators recently appointed at an academic center to establish an independent clinical cancer research program. This year, 11 awardees will each receive a three-year, $200,000 grant. The 2015 CDA recipients and their research projects are:

• **Sandra D'Angelo,** Memorial Sloan Kettering Cancer Center; "Identifying biomarkers predictive of response to nivolumab +/- ipilimumab in patients with metastatic sarcoma." Mentored by William Tap.

• **Ayca Gucalp**, Memorial Sloan Kettering Cancer Center; "A randomized multicenter phase II study of docosahexaenoic acid (DHA) in patients with a history of breast cancer, premalignant lesions, or benign disease." Mentored by Clifford Hudis.

• **Siwen Hu-Lieskovan**, David Geffen School of Medicine at UCLA; "Mechanistic study of double immune suppression blockade combining CSF-1R inhibitor PLX3397 with anti-PD-1 antibody pembrolizumab to treat advanced melanoma/solid tumors." Mentored by Antoni Ribas.

• **Douglas Johnson**, Vanderbilt University Medical Center; "Optimizing targeted and immune therapy approaches for non-BRAF V600 melanoma." Mentored by: Jeffrey Sosman

• **David Margel**, Rabin Medical Center; "Personalized prostate cancer screening among male BRCA carriers- a prospective cohort study." Mentored by Baruch Brenner.

• **Sean Matthew McBride,** Sloan-Kettering Institute for Cancer Research; "A phase II randomized controlled screening trial of nivolumab with image guided, stereotactic body radiotherapy versus nivolumab alone in patients with metastatic head and neck squamous cell carcinoma who have received previous platinum therapy." Mentored by Nancy Lee.

• **Katherine Reeder-Hayes**, University of North Carolina at Chapel Hill; "Adoption of breast cancer gene expression profiling, effects on chemotherapy utilization and disease outcomes." Mentored by Ethan Basch.

• **Rizwan Romee**, Washington University; "A

phase 1 study of cytokine induced memory-like NK cells in patients with relapsed and refractory AML." Mentored by John DiPersio and Todd Fehniger.

• **Florian Schroeck**, White River Junction VA Medical Center/The Dartmouth Institute; "Understanding risk-aligned care for early stage bladder cancer." Mentored by Philip Goodney, and Todd MacKenzie.

• **Vamsidhar Velcheti**, The Cleveland Clinic; "Novel pharmacologic approach to enhance the epigenetic and immune priming effect of decitabine in patients with advanced non-small cell lung cancer." Mentored by: Afshin Dowlati, Roy Herbst and Yogen Saunthararajah.

• **Jason Westin**, MD Anderson Cancer Center; "Smart start: a phase Ib/II study of rituximab, lenalidomide, ibrutinib and EPOCH in patients with newly diagnosed diffuse large b-cell lymphoma." Mentored by R. Eric Davis and Sattva Neelapu.

The Young Investigator Award provides research funding to promising physicians to support the transition from fellowship to faculty appointment, encourage continued interest in clinical cancer research, and assist them in their careers as both physicians and researchers. This year's YIA recipients will each receive a one-year grant of $50,000 to fund their investigative studies as they begin their careers in oncology research.

The full list of YIA recipients is available on the Conquer Cancer Foundation website.

In Brief

Shahabi Named Chief of Gynecologic Oncology at Northwestern University

SHOHREH SHAHABI was named chief of the division of gynecologic oncology at **Northwestern Memorial Hospital and Northwestern University Feinberg School of Medicine.**

Shahabi has also assumed a leadership role as a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University's executive committee and the Clinical Cancer Center's executive council.

Shahabi previously worked as system chair of the department of obstetrics, gynecology and reproductive biology at Western Connecticut Health Network's Danbury and New Milford Hospitals, chair of the Reproductive Tumor Biology Research Laboratory at Danbury Hospital Biomedical Research Institute, and a clinical professor in the Department of Obstetrics and Gynecology at the University of Vermont School of Medicine.

She was appointed to the Association of Professors of Gynecology and Obstetrics Board of Directors in 2014, and is a member of the Society Gynecologic Oncology, the New England Association of Gynecologic Oncologists, and the American College of Obstetrics and Oncology.

VARIAN MEDICAL SYSTEMS and **Flatiron Health** will collaborate to develop electronic health record analytics and decision support software for cancer care providers. The goal is to offer a suite of cloud-based software solutions that support oncologists from screening to survivorship.

Both companies will offer customers OncoEMR, Flatiron Health's cloud-based medical oncology EHR. OncoEMR features integrated pathways from multiple organizations such as Via Oncology, as well as a library of managed clinical content including the NCCN Chemotherapy Order Templates. Later this year, OncoEMR will be made interoperable with Varian's ARIA oncology information system.

ABBVIE completed its acquisition of **Pharmacyclics Inc.**, includiing Imbruvica (ibrutinib).

Pharmacyclics will be a wholly-owned subsidiary of AbbVie and will operate from its previous California headquarters. Wulff-Erik von Borcke, former head of AbbVie's global marketing, will lead Pharmacyclics as president. Combined with its existing facilities AbbVie now employs more than 900 people in California.

Imbruvica is approved for use in four indications in the U.S. and is the only product to have received three Breakthrough Therapy designations by the FDA. As part of a worldwide partnership with Janssen Biotech Inc., Imbruvica is now approved in nearly 50 countries.

Imbruvica is in mid- and late-stage development for additional hematological oncology indications, with more than 60 clinical trials underway, including 13 in phase III development. Imbruvica is also in early-stage development for solid tumors. AbbVie will market Imbruvica in the United States.

Across its oncology pipeline, AbbVie has five late-stage assets in clinical development positioned to launch within the next several years. Two programs, venetoclax, a Bcl-2 inhibitor, and duvelisib, a dual PI3 kinase inhibitor, are in development for hematological cancers. AbbVie intends to explore these assets in combination with Imbruvica, according to the company.

Drugs and Targets

Aloxi Approved in EU For CINV in Pediatric Patients

The European Commission approved Aloxi (palonosetron HCl) injection for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, in pediatric patients one month of age and older.

This is the first European approval of a product for the prevention of acute chemotherapy-induced nausea and vomiting in children aged one to six months.

The approval of the pediatric indication is based on a randomized, double-blind, non-inferiority pivotal trial comparing single-dose intravenous Aloxi 20 mcg/kg given 30 minutes prior to chemotherapy to a standard of care IV ondansetron regimen of 0.15 mg/kg given 30 minutes prior to chemotherapy followed by ondansetron infusions four and eight hours after the first dose. Within the first 24 hours after chemotherapy, complete response, defined as no vomiting, no retching and no antiemetic rescue medication, was achieved in 59.4 percent of patients who received Aloxi and in 58.6 percent of those who received ondansetron.

Treatment-emergent adverse events were comparable across both treatments, with headache being the most frequent event in the palonosetron group. Although pediatric patients were administered a higher dose per kg than adults to prevent CINV, palonosetron safety profile was consistent with its established profile in adults.

The approval follows a positive opinion from the European Medicines Agency Committee for Medicinal Products for Human Use. Aloxi is sponsored by the Helsinn Group.

The Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion recommending a change to the terms of the marketing authorization for Imbruvica (ibrutinib) in the European Union to indicate the treatment of adult patients with Waldenström's macroglobulinemia who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

Imbruvica is also the first and only FDA-approved treatment for WM in the US. Imbruvica is jointly developed and commercialized in the United States by Pharmacyclics Inc. and Janssen Biotech Inc. In Europe, Janssen-Cilag International NV holds the marketing authorization and its affiliates market Imbruvica in Europe, Middle East and Africa, as well as the rest of the world.

Imbruvica is already approved in Europe to treat adult patients with relapsed or refractory mantle cell lymphoma and 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.

The CHMP recommendation was based on a multi-center, phase II study that evaluated the efficacy and tolerability of Imbruvica in 63 patients with previously treated WM. Initial data from the study submitted for review in the EU showed an overall response rate of 87.3 percent after a median duration of treatment of 11.7 months.

Updated results from the study were published on in the April 9, 2015 edition of The New England Journal of Medicine, indicating an ORR of 90.5 percent after a median duration of treatment of 19.1 months using criteria adopted from the International Workshop on WM. At 24 months, the estimated rate of progression-free survival was 69.1 percent (95% CI, 53.2 to 80.5), and the estimated rate of overall survival was 95.2 percent (95% CI, 86.0 to 98.4).

No new safety issues were observed in the clinical trial. The most commonly occurring adverse reactions in WM patients treated with Imbruvica were neutropenia and thrombocytopenia.

Halozyme Therapeutics Inc. and Ventana Medical Systems Inc., a member of the Roche Group, will collaborate and develop a Ventana companion diagnostic assay for use with Halozyme's investigational new drug PEGPH20.

The assay will be used to identify high levels of hyaluronan, or HA, a glycosaminoglycan that can accumulate around cancer cells. Halozyme has announced plans for rollout of a global phase III clinical study in 2016 targeting metastatic pancreatic cancer patients with high HA levels using its PEGPH20 in combination with Abraxane (nab-paclitaxel) and gemcitabine.

Under the agreement, Ventana will develop an in vitro diagnostic under design control using Halozyme's proprietary HA binding protein, with the intent of submitting it for regulatory approval in the United States, Europe and other countries. The financial terms of the agreement were not disclosed.