



**CCF GLOBAL NEWS CLIPS
LITERATURE REVIEW
June 2009**

NEW DRUGS & CLINICAL TRIALS

Clinical trials for new drugs to be used in the treatment of carcinoid and other neuroendocrine tumors are underway at Cylene Pharmaceuticals, Inc.; Lexicon Pharmaceuticals, Inc.; Molecular Pharmaceuticals Inc.; and Novartis.

Cylene's Nucleolus Targeting Technology has produced **Quarfloxin (CX-3543)**, a small molecule agent that is in Phase II development for the treatment of carcinoid/NETs. This drug "disrupts an essential protein: DNA complex in cancer cells, thereby knocking out a critical source of support for tumor cells and selectively causing cancer cell death." Two separate Phase I trials have been completed on different dosing schedules.

Read more ➤ <http://tinyurl.com/l4nza6> or www.cylenepharma.com

Lexicon Pharmaceuticals recently gave a presentation during the Digestive Disease Week annual meeting in Chicago, the world's largest gathering of physicians and researchers in the fields of gastroenterology, hepatology, endoscopy, and gastrointestinal surgery, on **LX1032**, now entering a Phase 2 study in patients with carcinoid syndrome. LX1032, which has received Fast Track status from the U.S. Food and Drug Administration (FDA), is an oral drug candidate for managing gastrointestinal symptoms associated with carcinoid syndrome. To download the presentation, visit <http://www.lexpharma.com>. To read about Lexicon's carcinoid syndrome clinical trial on LX1606 go to <http://tinyurl.com/kv4e49>.

The European Medicines Agency (EMA) has approved Molecular Insight Pharmaceuticals' Phase III protocol for **Onalta (Yttrium-90 edotreotide)**. The drug is the company's "lead radiotherapeutic product candidate under development for the treatment of metastatic carcinoid and pancreatic neuroendocrine tumors in patients whose symptoms are not controlled by conventional therapy. The compound has shown the potential to selectively deliver lethal radiation to cancer cells. The proposed Phase III trial will confirm that administration of Onalta results in

stabilization, regression or complete remission of the carcinoid tumor, and improves carcinoid-related symptoms when compared to a high-dose regimen of the current standard therapy for this disease, Sandostatin.” The drug is intended to complement Azedra™, Molecular Insight’s other clinical stage radiotherapeutic candidate for treating neuroendocrine tumors.

Read more ➤ <http://www.molecularinsight.com/ultraface.aspx>

David Epstein, who leads Novartis’ cancer drug business, says the company hopes that **Afinitor** will be its next cancer bestseller. Already approved for patients with advanced kidney cancer who failed other treatments, Novartis is testing Afinitor simultaneously on five other tumor types including neuroendocrine tumors. The drug “suppresses a protein called MTOR (mammalian target of rapamycin), which receives growth signals from the surface of the cell and directs them to grow fatter, a necessary step before cell division.”

Sources: Health; Pg. 58, Vol. 183 No. 9; M2 Europharma, May 14, 2009; Market News Publishing, May 14, 2009; FD (Fair Disclosure) Wire, May 11, 2009 and May 13, 2009; PR Newswire, April 28, 2009, May 19, 2009 and May 27, 2009; Oncology Business Week, June 7, 2009

SANDOSTATIN LAR: NEW FINDINGS

In a recently published study, Sandostatin LAR, which has been used for years as a treatment of symptoms for patients with NETs, has been shown to delay progression of disease. This is an important finding for patients with functioning tumors (i.e. tumors that cause symptoms such as diarrhea or flushing) and for patients with nonfunctioning (non-secreting) tumors, which is a far larger pool of patients. Results were presented at ASCO, the American Society for Clinical Oncologists, in June.

Read more ➤ <http://tinyurl.com/lb7pg2>

Sources: FD (Fair Disclosure) Wire, May 13, 2009; ENP Newswire, May 28, 2009

INSULINOMA

A retrospective study of 237 patients, from 1987 to 2007, was conducted at the Mayo Clinic in Rochester, MN, to “assess changes in the presentation and diagnostic and radiological evaluation of patients with surgically confirmed insulinoma.” The researchers concluded: “Trends in the evaluation and preoperative management

include a shift to outpatient diagnostic testing, an emphasis on successful preoperative localization to avoid blind pancreatic exploration, and a validation of the diagnostic criteria for hyperinsulinemic hypoglycemia. (*Journal of Clinical Endocrinology and Metabolism* 94: 1069-1073, 2009).

Read more ➤ <http://tinyurl.com/2gjcwh>

Source: Biotech Law Weekly, Expanded Reporting, Pg. 2019, June 5, 2009

New insights into insulinoma have been provided by study data from the National Institutes of Health. “Selective intraarterial calcium injection of the major pancreatic arteries with hepatic venous sampling [calcium arterial stimulator (CaStim)] has been used as a localizing tool for insulinomas at the National Institutes of Health (NIH) since 1989.” The goal of the study was to “assess the accuracy and track record of the CaStim over time and in the context of evolving technology and to review issues related to result interpretation and procedure complications.” Findings were published in the *Journal of Clinical Endocrinology and Metabolism*, 2009;94(4): 1074-1080.

Read more ➤ <http://tinyurl.com/n37cy4>

Source: Biotech Law Weekly, Expanded Reporting, Pg. 2020, June 5, 2009

Researchers in Beijing, People’s Republic of China, studied laparoscopic surgery for pancreatic insulinomas. During a seven-year period laparoscopic pancreatectomy was attempted in 29 consecutive patients with insulinomas. “The localization of tumors, operating characteristics, and clinical outcomes were analyzed. Tumors were precisely localized in 28 or 29 (96.6%) patients by a combination of preoperative imaging techniques and intraoperative ultrasonography.” Y. Luo and colleagues published their study in the *Journal of Gastrointestinal Surgery*, 2009;13(5):845-950.

Read more ➤ <http://tinyurl.com/ktsd5j>

Source: Hospital Business Week, Expanded Reporting, Pg. 349, June 7, 2009

PHEOCHROMOCYTOMAS

Accurate diagnosis and localization are the keys to successful treatment of pheochromocytomas. Researchers investigated the accuracy of PET using a specific

amino acid transporter substrate as an independent marker for detection of benign and malignant pheochromocytomas.

Read more ➤ <http://tinyurl.com/lt9hhl>

Source: The Journal of Nuclear Medicine, pg. 513, Vol. 50, No. 4, April 2009

HEREDITY AND CARCINOID

Researchers at the German Cancer Research Center in Heidelberg undertook a study “to characterize the familial nature of gastrointestinal carcinoid tumors using the Swedish Family-Cancer Database, which includes &t; 11.5 million individuals.” Familial relative risks (RRs) of carcinoid tumors were estimated for people with a family history of invasive cancer as well calculating RRs of invasive cancers for the offspring of patients with carcinoid tumors. The study, published in *Annals of Oncology* 2009;20(5):950-4, found that “The risk of carcinoid tumors was significantly increased among individuals with a parental history of carcinoid tumors (RR 4.33). An association was also found between carcinoid tumors in the offspring and parental invasive cancers of the brain, breast, liver, endocrine glands and urinary organs. In addition, parental invasive cancers of the kidney as well as squamous cell skin cancer associated with small intestinal carcinoids in the offspring. The risk of carcinoid tumors was elevated among those whose siblings were affected by colon and rectal cancers.”

Read more ➤ <http://tinyurl.com/n5j75n>

Source: Disease Risk Factor Week, Expanded Reporting, Pg. 43, May 17, 2009

QUALITY OF LIFE AND NEUROENDOCRINE TUMORS

Developing a disease-specific questionnaire to identify areas that have the greatest impact on the quality of life (QOL) for NET patients was the goal of a study undertaken at Eastern Virginia Medical School. “Patient responses to clinical interviews provided an 80-item initial pool for the development of the QOL-NET.” Forty percent of the total QOL score was based on physical functioning, which the researchers concluded is “a greatest contributor to QOL impairment in NETS.”

Read more ➤ <http://tinyurl.com/levaw6>

Source: Obesity, Fitness & Wellness Week, Expanded Reporting, Pg. 1406, May 23, 2009

CGA VS 5-HIAA TESTING: WHICH MARKER IS RECOMMENDED?

Scientists in the Netherlands studied 39 patients with metastatic gastrointestinal NETs during treatment with Sandostatin LAR. They compared serum CgA and urinary 5-HIAA in relation to quality of life, “assessed by the EORTC QLQ-C30

questionnaire, supplemented with questions specific to carcinoid symptoms. Correlations were found between CgA and physical functioning ($p=0.01$) and quality of life ($p=0.03$), while no significant correlations were observed between 5-HIAA levels and any of the self-reported health outcomes.” In their study, published in *Neuroendocrinology*, 2009;89(3):296-301, the researchers concluded: “Stronger correlations of CgA compared to 5-HIAA with physical functioning and well-being, the convenience of measuring in blood, as well as the prognostic value of CgA for survival, makes CgA the recommended marker in the management of patients with metastatic NETs.”

Read more ➤ <http://tinyurl.com/lvl54w>

Source: Oncology Business Week, Expanded Reporting, Pg. 586, May 10, 2009

ELEVATED CHROMOGRANIN A AND RECURRENT TUMORS

A retrospective study of 56 patients with radically operated midgut carcinoids focused on comparing the usefulness of various methods to detect recurrence in these tumors. “Patients with malignant midgut carcinoids are occasionally diagnosed with limited tumor spread, and surgery with radical intention is performed. Despite curative intent, recurrences occur frequently, motivating long-term biochemical and radiological follow-up,” according to scientists in Uppsala, Sweden. The researchers found that blood CgA “was the first marker to indicate tumor recurrence in the majority of radically operated midgut carcinoid patients,” as reported in *Neuroendocrinology*, 2009;89(3):302-7. The researchers concluded: “To avoid unnecessary and costly examinations in asymptomatic patients, we suggest that follow-up should comprise measurements of P-CgA twice a year and annual ultrasonography until P-CgA is elevated or clinical symptoms occur, at which time all efforts should be made to identify recurrent tumor lesions in order to give the patient the best possible treatment which, if possible, should be surgical removal of the recurrence.”

Read more ➤ <http://tinyurl.com/le9rkf>

Source: Hospital Business Week, Expanded Reporting, Pg. 402, May 10, 2009

IDENTIFYING PRIMARY TUMORS

Researchers at Brigham and Women’s Hospital in Massachusetts have released new data about determining which markers would be useful to predict the primary site of metastatic well-differentiated neuroendocrine tumors. In total, the researchers studied 64 gastrointestinal carcinoids (5 stomach, 5 duodenum, 31 ileum, 11 appendix, and 12 rectum), 39 pancreatic endocrine tumors, and 20 pulmonary

carcinoid tumors. They found that a panel of four markers – CDX-2, PDX-1, TTF-1 and the neuroendocrine secretory protein-55 (NESP-55) -- a recently described member of the chromogranin family -- would be useful in predicting the site of the primary tumor. Results were published in the *American Journal of Surgical Pathology*, 2009;33(4):626-632.

Read more > <http://tinyurl.com/na9219>

Source: Hospital Business Week, Expanded Reporting, Pg. 238, May 24, 2009

LOCATING PRIMARY TUMORS USING DBE

German investigators evaluated the use of double balloon enteroscopy (DBE) to detect primary tumors in patients with neuroendocrine tumors. “Neuroendocrine tumors (NET) account for one-third of all small bowel neoplasms. The search for the primary tumor in NET is important, even though it is difficult to localize, as its surgical excision leads to a better prognosis, even in metastasized stages of the disease,” reported the scientists in *Digestive Diseases and the Sciences*, 2009;54(5):1050-58. In this study of 12 patients, the primary tumor was detected with DBE in 33% of the patients with metastatic or suspected NET. The researchers concluded: “Although endoscopic small bowel investigation by DBE seems to enrich the diagnostic possibilities for the diagnosis of small bowel-NET, at the present time DBE should only be performed in selected cases, possibly based on a positive previous work-up.”

For more information about double balloon enteroscopy, click here:
<http://www.doubleballoonenteroscopy.com/>.

Read more > <http://tinyurl.com/kwcnor>

Source: Medical Device Law Weekly, Expanded Reporting, Pg. 389, May 24, 2009

IBD & APPENDICEAL CARCINOID

Researchers at Mt. Sinai Hospital in New York City conducted a retrospective case-control study of “incidental appendiceal neoplasms in colectomy specimens of adults with and without inflammatory bowel disease (IBD) (cases and controls, respectively) based on surgical pathology records spanning 54 months.” Six appendiceal carcinoid tumors were identified among 705 IBD cases. The researchers concluded: “IBD does not predispose to the development of appendiceal carcinoids.”

Read more > <http://tinyurl.com/mnyzuc>

Source: Disease Risk Factor Week, Expanded Reporting, Pg. 65, May 10, 2009

ZOLLINGER-ELLISON SYNDROME

Recent research in Liverpool, the United Kingdom, focused on strategies to determine whether hypergastrinaemia, the presence of an excess of gastrin in the blood, is due to Zollinger-Ellison Syndrome rather than a more common benign cause. "As gastrinomas may cause serious complications and be potentially life threatening, investigation of hypergastrinaemic patients should particularly focus on confirming or refuting the diagnosis of Zollinger-Ellison syndrome." The study was published in *Alimentary Pharmacology & Therapeutics*, 2009;29(10):1055-68.

Read more > <http://tinyurl.com/kmunbx>

Source: Pharma Investments, Ventures & Law Weekly, Expanded Reporting, Pg. 2515, May 10, 2009

OVARIAN CARCINOID

Turkish researchers conducted a study "to present an extremely rare case of a primary carcinoid tumor arising in a mature cystic teratoma of the ovary." The conclusion of the study, published in the *European Journal of Gynaecological Oncology*, 2009;30(2):223-225, was that "treatment for early-stage ovarian carcinoid tumors confined to one ovary is surgery along and excellent outcomes can be expected in these cases."

Read more > <http://tinyurl.com/kjr46u>

Source: Oncology Business Week, Expanded Reporting, Pg. 283, May 24, 2009