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-- PRESS BRIEFING MONDAY, JUNE 4, 8:00 AM CDT --

**NEW TREATMENT OPTIONS FOR PATIENTS WITH ADVANCED
GASTROINTESTINAL CANCERS**

**-- Sorafenib Extends Survival for Patients with Liver Cancer;
Chemotherapy Reduces Recurrence of Liver Metastases in Patients with Colorectal
Cancer;
Cetuximab Impedes Growth of Advanced Colorectal Cancer --**

CHICAGO—New research on treatments for advanced gastrointestinal cancers was discussed today at a press briefing at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO).

“Treating late-stage cancers of the digestive tract is very challenging,” said A. William Blackstock, MD, professor of radiation oncology at the Wake Forest University School of Medicine and moderator of the press briefing. “Today we’ll hear about the first effective, systemic treatment for advanced liver cancer, as well as some important new treatment options for advanced colorectal cancers.”

Study findings include:

- The targeted therapy sorafenib (Nexavar) helps patients with advanced liver cancer live about 44 percent longer—a significant advance in the management of liver cancer, the third leading cause of cancer death globally.
- Chemotherapy given prior to and following surgery to remove liver metastases in patients with colorectal cancer significantly reduces the risk of cancer recurrence.

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- Adding the monoclonal antibody cetuximab (Erbix) to the standard first-line chemotherapy combination reduced the risk of metastatic colorectal cancer growth or spread by 15 percent.

For consumer-oriented information on these studies and more than 120 cancer types and cancer-related syndromes, please refer your readers to ASCO's oncologist-vetted patient Web site, www.plwc.org.

This study is embargoed until 8:00 AM CDT, Monday, June 4.

**PLENARY PRESENTATION
MONDAY, JUNE 4, 1:00 PM CDT
N HALL B1**

**Lead Author:
Joseph Llovet, MD
Mount Sinai School of Medicine
New York, N.Y.**

Sorafenib Extends Survival for Patients with Advanced Liver Cancer

Researchers have found that the targeted therapy sorafenib helps patients with advanced liver cancer live about 44 percent longer compared with patients who did not receive the anti-cancer drug. The finding is a significant advance in the management of liver cancer, which is the third cause of cancer death globally, often resulting in death within a year of diagnosis. In the United States, more than 19,000 people are diagnosed with liver cancer and nearly 17,000 people die from it each year.

“This is the first time that we’ve had an effective systemic treatment for liver cancer,” said Joseph Llovet, MD, director of research in liver cancer at the Mount Sinai School of Medicine in New York, professor of research at the Institut d’Investigacions Biomediques August Pi i Sunyer Hospital Clinic, Barcelona, Spain (IDIBAPS), and lead author of the study. “Our findings demonstrated survival advantages that are both statistically significant and clinically meaningful.”

Sorafenib, a tablet that is taken orally, is approved in the United States for treating a form of advanced kidney cancer, and is currently being evaluated in patients with other cancers. Some 40 percent of liver cancers (and up to 80 percent in Asia and sub-Saharan Africa) are diagnosed at an advanced stage. Therapy for advanced liver cancer may include surgery (if possible), radiation therapy and/or regional chemotherapy (delivered directly into the liver). However, no systemic treatment—anti-cancer medication that enters the bloodstream, either as an oral or intravenous medicine—has proven effective to date for advanced liver cancer.

Researchers examined overall survival and the time it took for cancer to grow among patients with previously untreated liver cancer who were randomly assigned to receive either 400 mg of sorafenib twice daily (299 patients) or a placebo (303 patients) for six months.

Patients who received sorafenib lived a median of 10.7 months compared with 7.9 months for those who received a placebo. Time to cancer progression was also significantly longer in the treatment group: 5.5 vs. 2.8 months. Due to the positive findings, the study was terminated early.

The incidence of adverse side effects was similar between the two groups (52 percent in the sorafenib group and 54 percent for placebo). The most common moderate to serious side effects were diarrhea (11 percent versus 2 percent), skin reactions in the hands and feet (8 percent versus 1 percent), fatigue (10 percent versus 15 percent) and bleeding (6 percent versus 9 percent).

“Although much progress has been made in cancer research, the number of lives lost to liver cancer is increasing,” said Jordi Bruix, MD, co-principal investigator and head of the Barcelona Clinic Liver Cancer, associate professor of medicine, University of Barcelona, IDIBAPS. “These results represent a significant achievement—sorafenib could become the first widely approved new therapy for this difficult to treat cancer.”

***LBA1**

Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): Results of a Phase III randomized placebo-controlled trial (SHARP trial)

J. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, J. Raoul, S. Zeuzem, M. Poulin-Costello, M. Moscovici, D. Voliotis, J. Bruix, For the SHARP Investigators Study Group

Background: HCC is the 3rd cause of cancer death globally with most deaths occurring within 1 year of diagnosis. No standard therapy exists for advanced HCC. Sorafenib (Sor) is a multikinase inhibitor with anti-angiogenic, pro-apoptotic and Raf kinase inhibitory activity, with clinical activity in a phase II HCC trial. This large, multicenter, randomized, placebo-controlled phase III trial evaluated the efficacy and safety of Sor vs placebo (P) in pts with HCC.

Methods: Patients with advanced measurable HCC, no prior systemic treatment, ECOG PS 0-2 and Child-Pugh status A received Sor 400 mg bid or P. Primary efficacy endpoints were overall survival (OS) and time to symptomatic progression (TTSP). Time to progression (TTP) and disease control rate (DCR; CR+PR+SD for at least 2 cycles) were secondary endpoints. Treatment arms were compared for OS and TTSP using a 1-sided log-rank test [overall a of 0.02 (OS) and 0.005 (TTSP)] stratified by region, ECOG PS and tumor burden. An O'Brien-Fleming-type error spending function determined criteria for early stopping for efficacy.

Results: 602 pts (Sor n=299; P n=303) were randomized. Baseline characteristics were similar for Sor vs P: median age (67 vs 68 y), male (87% vs 87%), ECOG PS 0 (54% vs 54%), Child-Pugh A (95% vs 98%), and BCLC stage C (82% vs 83%). Based on 321 deaths (Sor n=143; P n=178), the hazard ratio (HR) for OS (Sor/P) was 0.69 (95% CI: 0.55, 0.87; p=0.0006), representing a 44% improvement in OS vs P which met early stopping criteria. Median OS was 10.7 vs 7.9 mos (Sor vs P). Primary TTSP analysis demonstrated no statistically significant difference for Sor vs P. HR for TTP (independent assessment) was 0.58 (95% CI: 0.45, 0.74; p=0.000007). Median TTP was longer (5.5 vs 2.8 mos) and DCR was higher (43% vs 32%) with Sor vs P. Incidence of serious adverse events was similar for Sor vs P (52% vs 54%). The most frequent grade 3/4 events were diarrhea (11% vs 2%), hand-foot skin reaction (8% vs 1%), fatigue (10% vs 15%), and bleeding (6% vs 9%) for Sor vs P.

Conclusions: Sorafenib was well tolerated and is the first agent to demonstrate a statistically significant improvement in OS for pts with advanced HCC. This effect is clinically meaningful and establishes sorafenib as first-line treatment for these pts.

Disclosures for Research Team: Employment or leadership position with Bayer.

This study is embargoed until 8:00 AM CDT, Monday, June 4.

**PLENARY PRESENTATION
MONDAY, JUNE 4, 1:00 PM CDT
N HALL B1**

**Lead Author:
Bernard Nordlinger, MD
Ambroise Paré
Hospital, Public Assistance Hospitals of Paris
Paris, France**

Chemotherapy with Surgery Can Reduce the Risk of Liver Metastases Recurrence in Colorectal Cancer Patients

A new international study has found for the first time that chemotherapy given prior to and following surgery to remove liver metastases in colorectal cancer patients significantly reduces the risk of liver tumor recurrence. It is the first study to date to evaluate this treatment and was organized by the European Organization for Research and Treatment of Cancer (EORTC), with the participation of four major European cancer organizations.

“This approach may become the standard of care for patients with liver metastases from colorectal cancer that can be surgically removed,” said Bernard Nordlinger, MD, professor of surgery and chairman of surgery and oncology at Ambroise Paré Hospital, Assistance Publique-Hôpitaux de Paris. “The findings also support a multidisciplinary approach to care, with all members of the patient’s health care team collaborating to determine the optimal combination of chemotherapy and surgery.”

Up to 50 percent of the one million people diagnosed with colorectal cancer each year develop liver metastases. Until now, the standard of care has been surgery to remove the liver tumors whenever possible, but recurrence is common and only 30 to 35 percent of patients with liver metastases survive five years after surgical removal of liver tumors.

Between September 2000 and July 2004, researchers randomly assigned 182 patients with colorectal cancer that had spread to the liver and who were initially candidates for surgery to receive six cycles of FOLFOX4 chemotherapy (the drugs 5-fluorouracil, leucovorin and oxaliplatin) to shrink the tumors before surgery as well as six cycles after surgery; 182 similar patients were assigned to receive surgery alone.

For various medical reasons, not all of the patients remained eligible for surgery. Overall, 151 patients in the chemotherapy group and 152 patients in the control group had liver tumors removed. With a median follow-up of 3.9 years, 42.4 percent of patients in the chemotherapy group had no recurrence of liver tumors, compared with 33.2 percent of the control group.

***LBA5**

Final results of the EORTC Intergroup randomized phase III study 40983 [EPOC] evaluating the benefit of peri-operative FOLFOX4 chemotherapy for patients with potentially resectable colorectal cancer liver metastases.

B. Nordlinger, H. Sorbye, L. Collette, B. Glimelius, G. J. Poston, P. M. Schlag, P. Rougier, W. Bechstein, E. Walpole, T. Gruenberger

Background: The 5-year survival after resection of colorectal cancer liver metastases is 30% but recurrence is common. This study evaluates the benefit of combining peri-operative chemotherapy and surgery for patients with initially resectable liver only metastases from colorectal cancer (LM).

Methods: Between September 2000 and July 2004, 364 pts with up to 4 LM were randomized between peri-operative FOLFOX4 (oxaliplatin 85mg/m² and LV5FU2), 6 cycles before and 6 cycles after surgery, (CT), and surgery alone (S). The primary endpoint was progression free survival (PFS) with the goal to increase median PFS by 40% (HR=0.71). Safety was a secondary endpoint (already reported at ASCO 2005). PFS results are reported at the 2-sided 0.0434 significance level (adjusting for one interim analysis).

Results: Baseline characteristics were similar in both arms. Eleven of 182 pts were ineligible in each arm, mostly for more advanced disease. In the CT arm, a median of 6 pre-op cycles were delivered and 151 patients were resected. 115 pts (63%) received post-op CT, with a median number of 6 cycles and a relative dose intensity of 79% to 86%. In the S arm, 152 pts were resected. Due to the nature of the trial, evaluation of resectability (relevant for eligibility) was based on pre-op imaging, but 31/182 pts (CT arm) and 30/182 pt (S arm) could not undergo resection.

There were 2 (S arm) and 1 (CT arm) deaths after surgery. At a median follow-up of 3.9 years, 254 PFS events were reported (240 in eligible pts) and the results are as follows:

	N pts CT	N pts Surgery	% absolute difference in 3-y PFS	HR (CI)	P-value
All patients	182	182	+7.2% (28.1% to 35.4%)	0.79 (0.62-1.02)	P=0.058
All eligible	171	171	+8.1% (28.1% to 36.2%)	0.77 (0.60-1.00)	P=0.041
All resected	151	152	+9.2% (33.2% to 42.4%)	0.73 (0.55-0.97)	P=0.025

Conclusions: Peri-operative FOLFOX4 chemotherapy improved PFS over surgery alone in patients whose metastases were actually resected. The benefit was slightly diluted when also pts considered resectable on imaging but eventually not resected were taken into account. FOLFOX4 given peri-operatively is safe and does not prevent the pts from undergoing surgery.

Disclosures for Research Team: Nothing to disclose.

This study is embargoed until 8:00 AM CDT, Monday, June 4.

**CLINICAL SCIENCE SYMPOSIUM
TUESDAY, JUNE 5, 11:00 AM CDT
E ARIE CROWN THEATER**

**Lead Author:
Eric Van Cutsem, MD, PhD
University Hospital
Gasthuisberg
Leuven, Belgium**

Cetuximab in First Line Therapy Impedes Growth of Metastatic Colorectal Cancer

[Note: This summary contains updated data not in the abstract.]

A new study has shown that adding the targeted therapy cetuximab to a standard first line chemotherapy combination called FOLFIRI [5-fluorouracil (5-FU), irinotecan (Camptosar) and leucovorin] reduced the risk of metastatic colorectal cancer growth or spread by 15 percent.

Cetuximab is currently approved by the FDA as second-line or third-line therapy, meaning it is used to treat metastatic colorectal cancer that has continued to grow despite previous therapy. Other options for first-line treatment of advanced colorectal cancer include various combinations of 5FU and leucovorin with either irinotecan or oxaliplatin (FOLFOX) with or without bevacizumab (Avastin). The current study is the first phase III clinical trial to assess cetuximab plus FOLFIRI as first-line therapy for metastatic colorectal cancer.

“These findings suggest we have a new option for the initial treatment of metastatic colorectal cancer,” said Eric Van Cutsem, MD, PhD, a professor at the University Hospital Gasthuisberg in Leuven, Belgium, and lead author of the study. “Future studies will be necessary to see how the different therapies compare with each other and to determine which treatment option is best for each patient.”

In the CRYSTAL trial (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer), the researchers compared the time it took for a cancer to grow or spread (progression-free survival), response rate (the percentage of tumors that shrank) and rate of tumor resection (the percentage of patients whose tumors were completely removed by surgery) between 599 patients who were randomly assigned to receive FOLFIRI plus cetuximab and 599 patients who received FOLFIRI alone between August 2004 and October 2005.

Progression-free survival was significantly longer in the cetuximab plus FOLFIRI arm (8.9 months) compared with the FOLFIRI group (8 months) —a risk reduction of 15 percent. Significantly more patients (46.9 percent) responded to cetuximab plus FOLFIRI than FOLFIRI alone (38.7 percent). Overall, the number of complete resections was three times higher in the cetuximab plus FOLFIRI arm. In addition, more than twice as many patients with liver metastases had their tumors completely removed in the cetuximab plus FOLFIRI group (10 percent) compared to the FOLFIRI group (4.5 percent). These findings are important because they point to the potential for this combination to help patients who were initially unable to undergo a complete resection.

Side effects were generally similar between the two groups, although more patients in the cetuximab plus FOLFIRI group experienced grade 3/4 diarrhea (15.2 percent versus 10.5 percent) and grade 3 skin reactions (18.7 percent versus 0.2 percent) than those who received FOLFIRI alone.

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Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): the CRYSTAL trial.

E. Van Cutsem, M. Nowacki, I. Lang, S. Cascinu, I. Shchepotin, J. Maurel, P. Rougier, D. Cunningham, J. Nippgen, C. Köhne

Background: Cetuximab (Erbix[®]) in combination with irinotecan-based regimens has proven activity in previously-treated patients (pts) with mCRC. The present trial investigated the effectiveness of cetuximab in combination with standard FOLFIRI compared with FOLFIRI alone in the first-line treatment of pts with epidermal growth factor receptor (EGFR)-expressing mCRC. **Methods:** Pts were randomized 1:1 to receive either cetuximab (400 mg/m² initial dose then 250 mg/m²/week [w]) plus FOLFIRI q 2 w (irinotecan 180 mg/m², FA 400 mg/m², 5-FU bolus 400 mg/m², 5-FU infusion 2400 mg/m² over 46 hours) (Group A) or FOLFIRI alone (Group B). The primary endpoint was progression-free survival (PFS), with secondary endpoints of overall survival (OS), response rate (RR), disease control rate and safety. 633 events were required to statistically differentiate PFS between groups with 80% power. **Results:** Between August 2004 and October 2005, 1217 pts were randomized, 608 to Group A and 609 to Group B (60% male, median age 61 [19-84], ECOG performance status: 0=54%; 1=43.5%; 2=3.5%). Median PFS was significantly longer for Group A compared to Group B (8.9 months [8 - 9.5] for Group A vs. 8 months [7.6 - 9] for Group B, p=0.036). Response Rate was also significantly increased by cetuximab (46.9% vs. 38.7%, p=0.005). Treatment was generally well tolerated with neutropenia (26.7% Group A, 23.3% Group B), diarrhea (15.2% and 10.5% respectively) and skin reactions (18.7% and 0.2% respectively) being the most common grade 3/4 adverse events. **Conclusions:** Cetuximab in combination with FOLFIRI significantly increases response rate and significantly prolongs PFS in the first-line treatment of pts with mCRC, reducing the relative risk of progression by approximately 15%. Treatment-related side effects of cetuximab in combination with FOLFIRI were as expected, with diarrhea being moderately and skin reactions significantly more frequent as compared to FOLFIRI alone.

Disclosures for Research Team: Employment or leadership position with Merck KGaA; consultant or advisory role with Merck and Pfizer; honoraria from Merck and Pfizer; research funding from Merck and Pfizer.

Moderator Dr. Blackstock made the following disclosures: Consultant or advisory role for Eli Lilly Oncology, sanofi-aventis and Protherics; honoraria from Eli Lilly Oncology and sanofi-aventis; research funding from Eli Lilly Oncology, Merck, sanofi-aventis and AstraZeneca.

The American Society of Clinical Oncology (ASCO) is the world's leading professional organization representing physicians of all oncology subspecialties who care for people with cancer. ASCO's nearly 25,000 members from the United States and abroad set the standard for patient care and lead the efforts to discover more effective cancer treatments, increase funding for clinical and translational research and ultimately, improve cancer care for the estimated 10 million people diagnosed with cancer worldwide each year. ASCO publishes the *Journal of Clinical Oncology*, the preeminent, peer-reviewed medical journal on clinical cancer research and produces People Living With Cancer (www.plwc.org), a comprehensive consumer Web site providing oncologist-vetted cancer information to help patients and families make informed health care decisions.

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