Gemcitabine has been the standard of care for the treatment of pancreatic cancer for more than 15 years, and despite many clinical trials, very few have shown superior results. But there has been a "turning point" in clinical research on pancreatic cancer, says Margaret A. Tempero, MD, professor of medicine at the University of California, San Francisco. Speaking here at the 14th World Congress on Gastrointestinal Cancers (WCGC), she said that the improvement over gemcitabine in both progression-free survival (PFS) and overall survival (OS) seen with the FOLFIRINOX chemotherapy regimen (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) is the "type of stride forward that we hope to see."

These results, from the PRODIGE4-ACCORD 11 trial, were published last year in the *New England Journal of Medicine* (2011;364:1817-1825). Conducted in 342 patients with metastatic pancreatic cancer, the trial showed a significant improvement in median OS — from 6.8 months with gemcitabine to 11.1 months with FOLFIRINOX. PFS also improved, from 3.4 to 6.4 months. The authors said these survival times were the best ever seen in metastatic pancreatic cancer.

**New Standard of Care?**

So should FOLFIRINOX be the new standard of care? This was the question being debated at the Barcelona meeting. Marc Ychou, MD, PhD, Centre Regional de Lutte Contre le Cancer Val D’Aurelle - Paul Lamarque, Montpellier, France, emphasized that this was one of the first times that a study has shown efficacy better than that with gemcitabine alone. "There have been lots of negative trials," he said, and while the combination of erlotinib (Tarceva, Genentech) with gemcitabine showed a statistically significant improvement (and is approved for first-line treatment), this difference was not "clinically significant."

However, the FOLFIRINOX regimen was more toxic than gemcitabine alone. "The toxicity is very concerning," Dr. Tempero commented, noting in particular the myelosuppression and fatigue. However, Dr. Ychou pointed out that the toxicity "is manageable, especially if we use prophylactic G-CSF" (granulocyte colony-stimulating factors). There was no degradation in quality of life, he noted, pointing out that the Global Health Status was similar in both treatment groups, and the time to definition of quality-of-life degradation was actually worse in the gemcitabine group, probably because of progression of disease.

The results are generalizable to quite a large proportion of patients with metastatic cancer, he said, and concluded that "this is the best treatment" for such patients if they are younger than 75 years of age, have a good performance status, and have low bilirubin levels (<1.5 times the upper limit of normal). Dr. Tempero was more circumspect, and she questioned how generalizable the results were. Among the participants in this trial, fewer patients had the head-of-pancreas lesions that would be typically seen in a metastatic pancreatic cancer population. This may have resulted in fewer patients having indwelling pancreatic stents, which can be an infection risk, especially with myelosuppressive regimens.
This may have resulted in an "unintentional bias," she suggested.

She also quoted verbatim the conclusions of the NEJM authors, who were headed by Thierry Conroy, MD, from the Centre Alexis Vautrin, Vandoeuvre lès Nancy, France. They concluded that FOLFIRINOX is now a first-line option for patients with metastatic pancreatic cancer "who are younger than 76 years, and who have a good performance status ([Eastern Cooperative Oncology Group score (ECOG)] 0 or 1), no cardiac ischemia and normal or nearly normal bilirubin levels."

"Clearly they did not feel it is a standard of care," she said, emphasizing that the authors had proposed it as an option.

Dr. Tempero asked her epidemiology colleagues to estimate how many patients with metastatic pancreatic cancer fit the criterion proposed by the authors as being suitable for FOLFIRINOX. They estimated that from the patient populations seen at their respective centers, about 40% are older than age 76 years, about 50% have biliary stents, 20% have coexisting heart disease, and, although the percentage who have a good performance status is unknown, she would hazard a guess that it was about 50%.

"So clearly it is not a standard of care for all patients," Dr. Tempero said, but she emphasized that it offers a new option for some patients, and having options is "very, very good."

Data from the United States show that the FOLFIRINOX regimen was taken up soon after the results were presented for the first time at the American Society of Clinical Oncology annual meeting in June 2010 but indicate that it is being used in a small percentage of all patients. In a poster presented here, Victor Gastanaga, PhD, and colleagues from the Center for Observational Research at Amgen Inc reported that they used proprietary electronic health records data from approximately 650,000 cancer patients from institutions comprising 330 oncology clinics in the United States. Those data provide "a unique resource to evaluate actual clinic practice," they comment.

They looked specifically at the period between July 2010 and February 2012 and found that the use of FOLFIRINOX was "steadily increasing." They identified 3519 patients with active pancreatic cancer. Of those who had staging information, 1004 were metastatic at the time of diagnosis; of these, 623 were treated with chemotherapy or a biological agent. FOLFIRINOX was used in 81 patients (13%) at any time after the diagnosis, and 50 patients (8%) received it as first-line therapy.

Dr. Tempero commented that in the United States, the FOLFIRINOX regimen has been taken up but has also been modified by various centers, with some opting to delete the bolus 5-fluorouracil and others reducing the doses to decrease toxicity. However, from a show of hands among the audience, it appeared that European clinicians are sticking to the FOLFIRINOX regimen as described in the NEJM paper, and Dr. Ychou argued that there is no evidence to support modifications.

Eileen O'Reilly, MD, assistant professor at the Memorial Sloan-Kettering Cancer Center, New York, New York, said FOLFIRINOX had "convincingly demonstrated superiority" over gemcitabine alone in the metastatic pancreatic cancer setting, and is now being tested in locally advanced disease, and in the neoadjuvant and adjuvant settings.

**Another Chemotherapy Option Soon?**

Several speakers at the meeting mentioned the anticipation surrounding an ongoing phase 3 trial of nab-paclitaxel in pancreatic cancer, from which results are expected to be announced in about 6 months. Earlier results from a phase 2 trial had shown a median OS greater than 11 months with nab-paclitaxel.

Another phase 3 that is in its final stages, which also follows promising results from a phase 2 trial, is investigating a monoclonal antibody directed against prostate stem cell antigen (PSCA); the drug is designated AGS-PSCA.

Other new therapeutic approaches being explored in pancreatic cancer and highlighted at the meeting by Dr. O'Reilly include drugs targeting the insulin growth factor-1 receptor, such as MK-0646, AMG-479, and OSI-906, and compound targeting the hedgehog pathway, including GDC-0449/ vismodegib, IPI-926/saridegib, and LDE225.

**ADJUVANT CETUXIMAB FAILS TO BOOST FOLFOX IN STAGE III COLON CANCER**

Adding cetuximab to standard adjuvant chemotherapy for resected stage III colon cancer does not benefit patients, according
to interim results from a large, phase III, European trial. In the multicenter randomized study, the combination of FOLFOX4 plus cetuximab (Erbitux) did not prolong disease-free survival compared with FOLFOX4 alone, even in patients with KRAS wild-type tumors. The disease-free survival rate at 3 years was 75.1% in 791 patients given FOLFOX4 with cetuximab and 78% in 811 patients in the control group. These preliminary results of the PETACC8 cooperative group trial were presented for the first time on June 29 at the European Society for Medical Oncology’s (ESMO’s) 14th World Congress on Gastrointestinal Cancer. The disappointing outcome follows a negative report from the North Central Cancer Treatment Group (NCCTG) N0147 trial, which also looked at the benefit of cetuximab added to FOLFOX in the adjuvant colorectal cancer setting (JAMA 2012;13:1383-93).

The FOLFOX regimen, a combination of oxaliplatin, leucovorin, and 5-fluorouracil (5-FU), has been the standard of care since the MOSAIC trial (Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer) reported its results (Cancer Treat. Rev. 2004;30:711-13). The MOSAIC benefit was confirmed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial, with attainable 3-year disease-free survival rates of around 70% (J. Clin. Oncol. 2007;25:2198-204).

In addition to the U.S. trial of cetuximab, two other trials of the antiangiogenesis inhibitor bevacizumab (Avastin) - the AVANT and NSABP C-08 trials - have also failed to show a benefit in disease-free survival at 3 years in this clinical setting, however. The current study specifically looked at patients with the KRAS wild type. These are patients who should, in theory, still be able to respond to an epidermal growth factor receptor (EGFR) inhibitor, such as cetuximab. It has been known since 2008 that patients with mutated KRAS tumors do not respond to EGFR inhibition. The PETACC8 trial was originally designed to compare 12 cycles of FOLFOX4 versus FOLFOX4 plus additional cetuximab. The trial protocol was amended in 2008, when it became possible to select patients for cetuximab therapy based on their KRAS status.

Of the 2,559 patients recruited into the trial at 340 sites in Europe, nearly two-thirds had KRAS wild-type disease and 1,602 of them were randomized. The mean age of the KRAS wild-type patients was 58 years. All had completely resected, pathologically confirmed stage III colon cancer, a good WHO performance status, and a life expectancy of at least 5 years at enrollment.

The primary end point was disease-free survival, defined as the period before recurrence, second colorectal cancer, or death. However, the hazard ratio for disease-free-survival was 1.047 (P = .66). The differences in rates at 1, 2, and 4 years were also not statistically significant for FOLFOX4 with cetuximab (90.4%, 79.7%, and 72.4%, respectively) or without (92%, 81.5%, and 75.5%).

There were trends for women; patients 70 years and older; and groups with a WHO performance status of 0, pT1-3 and pN1 tumors, and no bowel obstruction or perforation to do a little better. Tolerability was as might be expected for the agents tested, but with a higher chance of hypersensitivity reactions, acnelike rash, diarrhea, and mucositis in the cetuximab-containing arm. There was an overall 15% difference in the occurrence of grade 3 and 4 adverse events between the FOLFOX4 with cetuximab and FOLFOX4 arms (80.9% vs. 66.2%, respectively).

**THRILLING NEW AGENT' FOR LIVER CANCER**

The investigational drug tivantinib (Daicchi Sankyo) has shown promising results in a phase 2 trial in liver cancer and was described as one of the "most thrilling new agents reported in the last few months" by Jordi Bruix, MD, PhD, head of the Barcelona Clinic Liver Cancer Group, Spain.

Chairing a session here at the 14th World Congress on Gastrointestinal Cancer (WCGC), Dr. Bruix said that liver cancer has been relatively neglected in the past, but now increased research efforts are being directed at this disease. So far, however, there have been few successes, he noted.

Tivantinib is one of the few, and it represents a new approach to the treatment of liver cancer. It is an oral tyrosine kinase inhibitor but is selective for cMET and it showed a "major advantage" in patients whose tumors showed high expression of
MET when tested by immunohistochemistry (MET+).

"This is the first ever trial showing a survival advantage with a MET inhibitor, and identifying a subgroup of patients who have responded," reported lead investigator Camillo Porta, MD, from the Universitario San Matteo, Pavia, Italy.

The phase 2 trial investigated tivantinib as a second-line therapy in patients with unresectable hepatocellular carcinoma (HCC) in whom 1 systemic therapy had failed. Of 107 enrolled patients, 71 patients received tivantinib (of whom 22 were MET+) and 36 received placebo (of whom 15 were MET+).

In the subgroup of patients who were MET+, there was a significant improvement in median overall survival (OS; 7.2 months with tivantinib vs 3.8 months on placebo; P = .01) and in the time to treatment progression (TTP; 11.7 weeks vs 6.1 weeks; P = .01). The relative risk for dying was reduced by 60% and the relative risk for TTP was reduced by 56%, Dr. Porta commented. However, neither OS nor TTP was improved in patients with Met– tumors.

The safety profile of tivantinib was predictable and manageable, Dr. Porta commented, and the main adverse effect was neutropenia.

A phase 3 trial of tivantinib in MET+ HCC is now planned, he said. In answer to a question from the audience, he said that MET+ expression should be seen in a similar percentage of previously untreated patients with HCC, so he would expect to see similar results from first-line use of the drug.

**Biopsies for Research**

These new data on tivantinib were highlighted in an overview of new agents on the horizon in HCC delivered by Ghassan Abou-Alfa, MD, from the Memorial Sloan-Kettering Cancer Center in New York, New York. He emphasized that this is a new direction in liver cancer research.

This is a "promising start," he said, and noted that this is the first time that clinical research in HCC has moved to a phase 3 trial with an "enrichment approach" (ie, selecting the trial participants by a biomarker that increases the chances of responding to therapy).

Testing tumors for MET+, as for any other biomarkers, requires a liver biopsy, but Dr. Bruix noted that this is usually required only for research purposes, and hence much be preceded by informed consent, he emphasized.

"There is a difference here between research and clinical practice," he said. Liver cancer is not a case of "no meat, no treat" as is the case for some other types of cancer. Usually, liver cancer can be diagnosed after imaging, he said, so a liver biopsy is not necessary to confirm diagnosis in most patients. Patients should be told this, he continued.

**So Far, Only Sorafenib**

In his overview of new agents being investigated for liver cancer, Dr. Abou-Alfa noted that to date, much of the research effort has been directed at the antiangiogenic approach because of the success of sorafenib (Nexavar, Bayer Healthcare). This was the first targeted agent to be approved for use in HCC, in 2006.

So far, however, it remains the only one, he added.

Despite intense efforts with similar compounds, none have been successful. A phase 3 trial of sunitinib vs sorafenib was negative, and recently there was an announcement that an ongoing phase 3 trial of linifanib vs sorafenib was discontinued for lack of benefit, Dr. Abou-Alfa reported. Recently reported results from a phase 2 trial of brivanib in second-line treatment were negative, although a phase 3 trial of brivanib vs sorafenib is ongoing. Results of that study are eagerly awaited.

"There has been a big effort from the pharmaceutical companies, but so far nothing has improved on sorafenib," he commented. "With antiangiogenic therapy, it may be that a ceiling has been reached," he said. The future may need a combination therapy approach, he added.

This is being explored in ongoing trials, which include studies pitching sorafenib against a combination of erlotinib with bevacizumab, sorafenib vs sorafenib with erlotinib, and doxorubicin with sorafenib vs doxorubicin alone.
Several speakers stressed the need for new therapies in liver cancer. Despite other therapeutic options, including resection, radiofrequency ablation, percutaneous ethanol injection, and ultimately liver transplantation, there is a pressing need for therapeutic advances.

Liver cancer is the sixth most common cancer in the world, with 750,000 new cases diagnosed each year. There is a preponderance of cases (470,000) in Eastern Asia. But even in the United States, liver cancer is a problem, commented Joseph Llovet, MD, PhD, director of HCC Research at Mount Sinai School of Medicine. In the United States, the liver cancer death rate is increasing at a rate faster than that of any other cancer. The only other cancers that are increasing are esophageal cancer and melanoma; the cancer death rates for other types are all decreasing, he said.

**SIMPLE WAY TO AVOID SEVERE TOXICITY FROM 5-FU AND RELATED DRUGS**

A simple screening process can identify people who will react badly to the fluoropyrimidine group of chemotherapy drugs, which includes 5-fluorouracil and the related oral products capecitabine (Xeloda), tegafur, and S-1.

In some cases, this prescreen is life-saving. Drugs in the fluoropyrimidine group are widely used in the treatment of many different types of cancer, including colorectal and breast cancer.

However, these drugs carry a risk of early severe toxicity (seen in about 25% of patients after the first cycle) and even death as a result of severe toxicity (in about 0.4% to 0.6% of patients, which amounts to some 1300 patients per year in the United States).

The toxic reaction is related to an asymptomatic deficiency of the dihydropyrimidine dehydrogenase (DPD) enzyme. People who have a complete DPD deficiency — which is rare — suffer multiorgan toxicity, which can be fatal; in these people, fluoropyrimidine drugs should be avoided. In people with the more common partial DPD deficiency, the drugs can be used but at reduced doses to reduce the risk of toxic effects.

Currently, there is some screening being carried out for the genetic mutations responsible for DPD deficiency, but it does not identify all patients who are at risk.

The screen developed by researchers at the Institut de Cancérologie de l'Ouest at the University of Angers uses a 2-pronged approach. It combines genotyping (searching for 24 DPYD deleterious gene variants by pyrosequencing) with testing for deficient phenotypic status (using uracil and dihydrouracil quantification and the dihydrouracil/uracil ratio as an index of metabolism). In addition, physiologic and physiopathologic parameters are considered.

This multiparametric approach — marketed as ODPM Tox by Onco Drug Personalized Medicine (ODPM), which is based in Angers, France — is superior to just testing for mutations, which misses many people.

**Analysis After Toxicity**

In his presentation, Dr. Metges reported data on 247 patients screened only after they had developed severe toxicity (grade 4) or had died after the first cycle of treatment with a fluoropyrimidine-containing regimen.

Only the ODPM Tox test identified all 27 patients who died. Screening for genetic mutations identified only 16 patients (59%) and deficient phenotypic status identified only 24 patients (89%), Dr. Metges reported.

Of the 247 patients who developed severe toxicity, ODPM Tox identified 242 (98%), mutation testing identified 82 (33%), and deficient phenotypic status identified 211 (85%).

**Prescreening Saved Lives**

The remaining data presented come from prescreening; during the past few years in the Angers region, the test was used...
A total of 11,104 patients were prescreened. Of these, 266 patients (2.4%) were found to have 1 or more genetic mutation, which indicates that they are likely to suffer toxic effects and therefore need a dose reduction or modification. Two patients were found to be completely DPD deficient — 1 had a homozygote DPYD2A and 1 was double mutated, Dr. Metges reported. "Pretreatment screening saved their lives," he told meeting attendees. "We are now using this prescreen in routine clinical practice," Dr. Metges reported. He estimated that around 2400 patients are screened annually in cancer centers in the Angers region. The test is conducted on a single blood sample, and results are available in 8 days. The cost is around €180 (~US$224) per patient, Dr. Metges said.

A poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium earlier this year reported that the cost of prescreening all the new patients in this region of France was less than the cost (in emergency and intensive care costs) of treating severe toxicity in 1 patient. Such prescreening should be recommended before fluoropyrimidine administration, concluded Sory Traoré, MD from the Institut de Cancérologie de l'Ouest, and colleagues.

**NEW TEST FOR KRAS MUTATIONS: FASTER, CHEAPER, BETTER**

A simpler, cheaper, more accurate test for KRAS mutations has been developed by a group of Italian researchers. Routine testing for KRAS mutations in the treatment of colorectal cancer is now recommended by many expert bodies. Testing identifies patients who carry this mutation and are unlikely to respond to treatment with the anti–epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab (Erbitux, Bristol-Myers Squibb, Lilly) and panitumumab (Vectibix, Amgen). Targeted therapies are indicated only for use in patients with KRAS wild-type disease.

Details on the new test were presented in a poster exhibited here at the 14th World Congress on Gastrointestinal Cancer, which was organized in partnership with the European Society for Medical Oncology. "This new test is cheaper, quicker, and more sensitive, so the genotyping of patient[s] is more accurate," senior author Christiana Lo Nigro, PhD, from the Laboratory for Cancer Genetics and Translational Oncology at the S. Croce General Hospital, in Cuneo, Italy.

Currently, the gold standard for KRAS mutation testing is Sanger sequencing of polymerase chain reaction (PCR) products. Although this detects and identifies all mutations in an amplified sequence, it is time-consuming, cost-ineffective, and has a maximum sensitivity of around 15 to 20%.

Another method — high-throughput pyrosequencing (PS) — is faster but still takes about a day. "It too is cost-ineffective," she said, because the equipment is expensive and is available in only a few centers. In addition, although PS has a detection limit of around 5%, about 5% to 10% of samples fall into a "gray area," in which the results are undeterminable. The new method developed by the Italian group is based on primer exclusion peptide nucleic acid (PNA)-directed PCR clamping (PNA assay). There is PCR competition between a standard primer and a newly synthesized PNA \[\text{NH}_2-\text{GGAGCTGGTGGCGTA-CONH}_2\] to act as the comparator in order to perform the test. The new test takes only 1 hour and is more sensitive than any other currently available strategy, the researchers report. While the sensitivity limit is around 20% for Sanger sequencing and around 10% for pyrosequencing, for the new test it is only 2%.

With this new test, there is only a 2% chance of patients with the mutation being incorrectly identified as KRAS wild type [not having KRAS mutations]. This is important, as identifying patients incorrectly could lead them to receive a drug from which they won't benefit but which may cause side effects.

**Study Compares Different Approaches**

In the poster, the researchers reported results from a comparison of the 3 methods when used for blind testing for KRAS muta-
tions in tumor samples taken from 68 patients with colorectal cancer. Sanger sequencing found KRAS mutations in 29 of 68 samples (42.6%), pyrosequencing found them in 32 of 68 samples (47.1%), and the new PNA-mediated clamping PCR method found them in 53 of 68 samples (77.9%).

Another study, which used 3 independent experiments to determine the sensitivity of the PNA-mediated clamping PCR for the detection of KRAS mutations, found that the test reached a sensitivity as high as 1.4% for the mutated versus the wild-type allele (P < .005).

**PROPHYLACTIC ANTICOAGULANTS IN UPPER GI CANCER PATIENTS**

Although cancer itself elevates the risk for venous thromboembolism (VTE), and chemotherapy elevates it still further, the general consensus of expert opinion is that evidence is insufficient to recommend prophylactic use of anticoagulants in all patients. However, it has long been argued that a special case can be made for patients with certain types of cancer. 2 separate groups of researchers from the United Kingdom proposed that patients with upper gastrointestinal (UGI) malignancies represent such a special case.

"We have already changed our practice as a result of an earlier trial in pancreatic cancer patients," Rajarshi Roy, FRCR, from the department of oncology at the Hull & East Yorkshire NHS Trust, in Hull, United Kingdom. That study, the UK Fragem Trial, showed that prophylactic anticoagulation with dalteparin significantly reduced the risk for all VTE in pancreatic cancer patients being treated with gemcitabine (European Journal of Cancer. 2012;48;1283-1292). As a result of that study, Dr. Roy and colleagues use prophylactic dalteparin to treat their patients with pancreatic cancer, which is notorious for being highly thrombogenic.

Now, they propose extending this to other patients with UGI malignancies, because these patients are also at high risk for VTE.

In a poster presentation at the meeting, investigators reported a particularly high rate of VTE in patients with gastroesophageal junction (GOJ) cancers. In the literature, this has been estimated at around 10% to 13%, but researchers reported a much higher rate of 21.5%. Their data were derived from a retrospective analysis of 65 patients with GOJ cancer, which found that 14 patients developed a VTE during or after completion of neoadjuvant chemotherapy with a platinum-containing regimen. Of these, 8 patients (12%) had a pulmonary embolism, 5 (8%) had lower limb deep vein thrombosis, and 1 had subclavian vein thrombosis with an indwelling venous line. Four of the patients who developed a pulmonary embolism died within 30 days of surgery, despite therapeutic anticoagulation with low molecular weight heparin, the authors note.

Dr. Roy commented that there may be a case to be made for the use of prophylactic anticoagulation in all patients with UGI malignancies, and his team is proposing a clinical trial in this population. "One option is to use prophylaxis during the preoperative period when patients are receiving chemotherapy and/or radiotherapy," he added.

Also proposing such a trial was another group of UK researchers, led by Caroline Chau, from the department of medical oncology, at the Queen Alexandra Hospital, Portsmouth, United Kingdom. This group also presented a retrospective review of data, this time from 115 patients with upper GI malignancies who underwent neoadjuvant chemotherapy and surgery. More than half of these patients (59%) had cancer of the esophagus, 28% had GOJ cancer, and 13% had stomach cancer.

Dr. Chau and colleagues reported a 12.2% incidence of VTE, with 7 patients developing a pulmonary embolism and another 7 developing deep vein thrombosis.

"Patients who suffered a VTE have inferior outcomes in terms of survival, at least in the early stages of treatment," researchers note. This was independent of all other variables analyzed, including age, gender, disease site, histology, tumor size, and nodal involvement.

"We propose a prospective randomized controlled study of the use of prophylactic anticoagulation in outpatients receiving neoadjuvant chemotherapy for UGI malignancies," Dr. Chau and colleagues conclude.