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Pancreatic cancer remains one of the most difficult cancers to treat. Its high cost is represented by lives lost, patient morbidity, and considerable resources spent to treat the disease. Treatment costs associated with pancreatic cancer are estimated at about $750 million annually in the USA.

Although about 20% of patients first presenting with pancreatic cancer have operable disease that may result in a cure, regionally advanced or metastatic disease present in the remaining 80% is mostly treated palliatively with chemotherapy, radiotherapy (RT) or chemoradiotherapy (CRT). Even after resection, median survival time (MST) is only 12 to 18 months and <10% to 20% patients with resected pancreatic cancer survive 5 years. Currently, published survival rates in clinical trials in advanced pancreatic cancer indicate a 1-year survival ranging from <10% to 28%.

CURRENT TREATMENT MODALITIES

All commonly used cancer management approaches, including surgery, RT and chemotherapy, mostly in combination, are used to treat all stages of pancreatic cancer.

Surgery

Between 15% and 20% of pancreatic tumors are resectable. Surgery may be combined with intraoperative radiation therapy (IORT) or brachytherapy to improve local control, and is used for palliation to remove obstructions and insert stents to improve QoL. Also, laparotomy is performed as an alternative to biopsy for exploration. Sometimes neoadjuvant chemotherapy is used to render tumors operable, and often surgery is combined with RT and/or chemotherapy to improve outcomes in locally advanced disease.

The main reasons that pancreatic cancer is usually inoperable are invasion by the tumor of the surrounding major blood vessels that supply blood flow to the intestine and liver, and distant metastasis. However, despite intended curative resection, patients with pancreatic ductal adenocarcinoma (PDAC) have high rates of both local and distant recurrence. Patient selection for curative resection remains a challenge. In a high percentage of cases considered operable, micrometastases that remain undetected prior to surgery usually negate the curative objective of the intervention, resulting in metastatic disease and death. Also, specific disease characteristics within the operable category, may determine outcome.

Outcomes in operable disease are often determined by the tumor's biological behavior. Among 193 patients who underwent curative resection at the National Cancer Center Hospital (Tokyo, Japan), 38 (20%) survived for more than 5 years. The 5-year survival rates for Stages I, II, III, and IV disease were 41%, 17%, 11%, and 6%, respectively. According to a multivariate analysis, significant prognostic factors were lymph-node metastasis, intrapancreatic perineural invasion, and portal vein invasion. A subgroup analysis was performed to assess 5-year survival in patients with or without nodal metastasis and with or without intrapancreatic perineural invasion. Among those without nodal metastasis, the 5-year survival rate for those without perineural invasion was 75%, whereas that for those with perineural invasion was 29%, a significant difference. Among those with nodal metastasis, the 5-year survival rate for those without perineural invasion was 17%, while that for those with perineural invasion was 10%. The most favorable 5-year survival of 89% was observed in the subgroup of patients with Stage I disease without perineural invasion (Ozaki H, etal, Surg Today 1999;29(1):16-22).

Also, patients with resected disease have different survival outcomes despite the emergence of metastases. According to investigators at Fox Chase Cancer Center (Philadelphia, PA), there was improved survival among patients with resected PDAC with isolated pulmonary recurrence compared to patients with other sites of recurrence. Between 1987 and 2001, 228 patients underwent resection with curative intent for PDAC. Retrospectively, survival data from 88 patients with documented recurrences was categorized as pulmonary (Group 1, n=16) or nonpulmonary (Group 2, n=72). Group 2 included patients with extrapulmonary recurrences or pulmonary plus another site(s) of disease. MST after recurrence in Group 1 was significantly longer than in Group 2 (10.5 months versus 4 months). The overall MST for Group 1 was 29 (range=5 to 86) months versus 14 (range=4 to 50) months in Group 2. At the time of data analysis, 3 (18.8%) patients in Group 1 were alive with disease, 43, 36, and 64 months from the time of resection, compared to 3 (4.2%) patients in Group 2, alive with disease at 14, 15, and 55 months after resection. Therefore, it appears that survival following recurrence in patients with resected PDAC is influenced by site. Patients with isolated pulmonary recurrence have a more favorable prognosis and should be stratified separately in treatment protocols for metastatic PDAC (Meszoely IM, etal, ASCO03, Abs. 1488:371).

There are several surgical procedures used in PDAC. The most common pancreatic resection is pancreaticoduodenectomy (Whipple procedure) that generally involves removal of the gallbladder, common bile duct, part of the duodenum, and the head of the pancreas. The end of the bile duct and remaining part of the pancreas are then connected to the small intestine to permit flow of bile and pancreatic enzymes. This operation was first described by Dr. Alan O. Whipple of New York Memorial Hospital, now Memorial Sloan-Kettering Cancer Center, hence the name. It has undergone a number of changes since it was first described nearly 70 years ago and, today, doctors perform several variations of the operation. Sometimes part of the stomach is removed as well. The procedure has risks, including infection and bleeding. In addition, leaking of pancreatic juices after surgery can cause the pancreas to begin digesting itself and nearby tissues. The median length of stay for patients undergoing this procedure is about 9 days, with inhospital operative mortality of ~2%.

In a more radical procedure, pancreatectomy, the surgeon removes the entire pancreas as well as the bile duct, gallbladder, and spleen, part of the small intestine and stomach and most of the lymph nodes in the area. After total pancreatectomy, patients need insulin injections and pancreatic enzymes. This operation is associated with serious risk and its value has been questioned in some studies.

In another procedure, distal pancreatectomy, primarily used to treat islet-cell cancer, only the tail, or the tail and a small portion of the body of the pancreas is removed. Sometimes the spleen may also be removed.

Palliative surgical procedures are used to reroute the flow of bile by bypassing tumors that block the bile duct, pancreatic duct or duodenum that can cause pain, digestive difficulties, nausea, vomiting, jaundice and severe itching. When a bypass operation isn't an option, a stainless steel or plastic stent may be inserted in the bile duct to keep it open.

Pancreatic surgery is a complex procedure requiring unique surgical and perioperative management skills. Currently, there is enough evidence supported by findings from studies conducted in four countries, Finland, the USA, UK, and the Netherlands with advanced health care systems to advocate the regionalization of pancreatic cancer surgery into large specialized multidisciplinary units. The complexity and high risk associated with pancreatic surgery makes it particularly suitable for regionalization. A significant inverse correlation was noted between PDAC resection case volume and postoperative mortality. Further analysis also revealed lower complications, reduced hospital stay, reduced hospital costs, and improved

survival of patients treated in hospitals performing a high volume of procedures. Interestingly, the positive influence of high procedure volume was linked to institutional rather than a single surgeon's caseload. In the UK, the National Health Service Executive has instructed Regional Health Authorities to concentrate pancreatic cancer surgery into designated regional centers serving populations of 2 to 4 million (Andren-Sandberg A and Neoptolemos JP, Pancreatology 2002; 2(5): 431-9).

Radiation Therapy (RT)

Radiation therapy (RT), either alone or in combination with chemotherapy, is a mainstay in the treatment of PDAC. CRT modestly improves MST in both localized and locally advanced disease. Interstitial brachytherapy and intraoperative RT (IORT) improve local control without significantly extending overall survival. More recent advances in RT, such as 3-dimensional conformal external beam RT, and intensity-modulated radiation therapy (IMRT) that offer improved efficacy and lower morbidity, are now becoming widespread. Systemic radiation-sensitizing chemotherapy is also a promising approach to take advantage of additive or synergistic effects with radiation locally, and in systemic disease. Better understanding of the mechanisms associated with tumor killing with RT, and development of more effective radiosensitizers, may make RT more effective for the treatment of PDAC.

External beam radiation therapy (EBRT)/3-dimensional conformal RT (3D-CRT) are commonly used in combination with surgery and/or chemotherapy or, rarely, as a stand-alone treatment, in advanced PDAC. However, potential toxicity to normal tissue in the upper abdomen limits total RT doses to >45-60 Gy, usually administered in 25 to 30 fractions. This dose is inadequate to treat an inoperable tumor, as evidenced by high local failure rates seen in studies of EBRT monotherapy alone, and when combined with chemotherapy. In CRT trials conducted by the Gastrointestinal Tumor Study Group (GITSG) in the 1980s, local failure rates ranged from 26% to 58% of cases. Even at higher doses of EBRT (63-70 Gy), local failure rates exceeded 78%.

3D-CRT is a CT-based procedure that allows for 'unconventional' beam orientations, so that the target volume can be treated with lesser exposure to nontarget tissues, as is the case with conventional EBRT. This new technique is now being used to treat pancreatic cancer to minimize radiation to the radiosensitive kidneys. In addition, using computer-based planning, nonuniform radiation treatment can be delivered to the target area, creating a more precise and conformal dose pattern and further reducing healthy tissue exposure. 3D-CRT has an excellent acute toxicity profile and a relatively low rate of late toxicity. However, several problems limit the effectiveness of 3D-CRT, including respiration-induced and nonrespiratory motion of the upper abdominal organs (pancreas, liver and kidneys) in the pancreatic region (Bussels B, etal, Radiother Oncol, Jul 2003;68(1):69-74, and Horst E, etal, Radiology, Mar 2002;222(3):681-6).

Intensity-modulated radiation therapy (IMRT) is also under evaluation in pancreatic cancer as a means of delivering higher doses to the target volume without exceeding the tolerance of the surrounding organs at risk. A comparison of 3 different IMRT plans in 3 patients with inoperable cancer of the pancreatic head, found IMRT to be a feasible and powerful tool allowing safe escalation of doses to the target tumor with less toxicity to the surrounding tissues than reported possible in published data [Ashamalla H and Tawadrous W, ASCO Gastrointestinal Cancer Symposium 2004 (ASCOGI04), Abs.121]. IMRT plans have also been investigated using higher energy electrons (Korevaar EW, etal, Int J Radiat Oncol Biol Phys, 1 Jan 2002;52(1):236-53).

3D-CRT used with IMRT allows for inverse treatment planning so that computer-based treatment optimization can be performed rather than standard 'trial and error' planning. Between July 1999 and May 2001, at Johns Hopkins Oncology Center (Baltimore, MD) and Emory University (Atlanta, GA), 10 randomly selected patients with adenocarcinoma of the pancreatic head were treated concomitantly with 3D-CRT and inverse-planned IMRT. To evaluate the influence of IMRT with inverse treatment planning on the dose-volume histograms (DVH) of normal tissue compared to the standard 3D-CRT, DVH and normal tissue complication probability (NTCP) were calculated using the IMRT plan and 3D-CRT plan. The aim of the treatment plan for these 10 cases was to deliver 61.2 Gy to the gross tumor volume (GTV) and 45 Gy to clinical treatment volume (CTV) while maintaining critical normal tissues to below specified tolerances. Based on a prediction model, the probability of small bowel injury employing these two approaches was 9.3% ± 6% with IMRT compared to 24.4% ± 18.9% with 3D-CRT. Therefore, IMRT with inverse treatment planning may significantly improve RT of pancreatic cancer by reducing normal tissue dose exposure while simultaneously allowing escalation of dose to further enhance locoregional control (Yang GY, etal, ASCO02, Abs. 2203).

In another clinical trial to see if CRT using IMRT permits an increased radiation dose to GTV without severe acute radiation-related toxicity to the surrounding normal tissue, 21 patients with locally advanced PDAC were treated with IMRT at a dose of 21 Gy to 30 Gy in 7 to 10 fractions within two weeks after conventional RT of 30 Gy in 15 fractions over 3 weeks, with 5-FU or gemcitabine administered concurrently with RT, during the course of treatment. A total of 16 patients completed the RT plan at doses of 51 Gy (n=3), 54 Gy (n=3), 57 Gy (n=3) and 60 Gy (n=7). In 13 patients with high levels of CA19-9 before RT, median levels of CA19-9 prior to and after RT were 716 U/ml and 255 U/ml, respectively. Also, in 14 patients with pain before treatment, analgesic intake was reduced by at least 1/3 to 1/2 (total pain relief was seen in 5 patients) and

performance status improved in 10. One-year survival rate was 35%. No >Grade 3 acute toxicities were seen with RT. A protocol of IMRT at a dose of 60 Gy in 25 fractions over 5 weeks, combined with concurrent 5-FU chemotherapy, have a palliative benefit with tolerable acute radiation-related toxicity for patients with advanced PDAC (Bai YR, etal, World J Gastroenterol, Nov 2003;9(11):2561-4).

Intraoperative radiation therapy (IORT) allows higher radiation doses to be delivered to the tumor as is possible with EBRT. Delivery of IORT was originally technically cumbersome and often relied on transporting the patient from the operating room to the RT unit during surgery or were performed in operating rooms with built-in IORT systems and personnel shielding systems. These technical and financial limitations to IORT delivery placed a substantial constraint to the widespread adoption of IORT in a variety of hospital settings. Subsequently, technological advances in miniaturization of RT sources enabled the development of mobile IORT devices associated with fewer technical and logistical limitations.

IORT is currently being used in patients with inoperable, locally advanced PDAC, in an effort to improve local control while limiting toxicity to the surrounding normal tissues. IORT may be combined with EBRT and chemotherapy. In intraoperative electron radiation therapy (IOERT), a single, high dose electron-beam radiation is administered focally to the tumor while normal tissues are moved out of the treatment field and shielded. This technique takes advantage of the inherent rapid dose fall off properties of electrons. A single intraoperative dose of electron radiation is equivalent to 2 to 5 weeks of daily external radiation therapy (10 to 25 daily radiation treatments).

To date the value of IORT has not been clearly established. No increase in MST has been seen with IORT in inoperable PDAC in reported studies. Significant improvement in local control rates in resectable PDAC were seen when IORT was combined with surgery, compared to the standard treatment of surgery and postoperative RT. Also, there may be a trend towards delayed disease recurrence following IORT treatment in resectable PDAC, and improved patient QoL without any compromise in patient survival.

Investigators at Jefferson Medical College, Thomas Jefferson University (Philadelphia, PA) combined IORT with postoperative chemotherapy and EBRT in a treatment protocol designed to improve QoL of patients with inoperable, locally advanced PDAC. A retrospective review was conducted involving 149 patients who underwent exploratory laparotomy, enteric and/or biliary bypass and IORT between 1988 and 2002. These patients were also treated with standard chemotherapy consisting of 5-FU, and EBRT, and participants enrolled in later years were also treated with gemcitabine. Study endpoints included overall survival and, in patients with complete follow-up data, pain-free survival and freedom from local treatment failures. There was one perioperative death. MST was 14 months; 1-year survival was 44%, 2-year survival 11%, and 3-year survival 4%. There are 3 (2%) long-term survivors alive for >5 years. Complete follow-up data regarding pain control was available for 64 patients, and data regarding local control of disease for 39 patients. These patients experienced relief of pain for 71% of their total survival time, and local control was obtained for 70% of total survival time, an average of 8.1 and 7.6 months, respectively. IORT, when combined with postoperative chemotherapy and EBRT is well tolerated. Although overall survival is not improved, pain control, local treatment failures and 1- and 2-year survival rates compare favorably with historical controls. Long-term survivorship was seen in a minority of patients (Rosato FE, etal, ASCO03, Abs. 1397:348).

Among IORT devices is the Intrabeam System, marketed by Carl Zeiss (Stuttgart, Germany), in which X-rays are generated by an electron beam created by an accelerator. The beam travels down an evacuated needle, hits a thin gold target and X-rays are emitted from the needle tip in a spherically symmetric pattern, irradiating the tumor or tumor cavity directly during tumor resection. Intrabeam can generate X-ray beam energy of up to 50 kV. Only minimal shielding is required for personnel in the operating room. Intrabeam has been granted FDA and CE approval for use as a 'booster treatment' with standard RT.

One of the earliest IORT systems is the Novac 7 developed in Italy by the ENEA (Italian National Agency for New Technologies, Energy and the Environment) and Hitesys (Aprilia-Latina, Italy). Novac 7 obtained 510(k) clearance from the FDA in June 2000. The original developers are collaborating in ongoing research to incorporate in the system advanced treatment planning and real time dosimetry.

Another IORT is the Mobetron, a mobile, self-shielded electron linear accelerator. Originally developed by Intraop Medical (Santa Clara, CA), the Mobetron was approved by the FDA in July 1998 and received the CE Mark in Europe, in October 2001. Originally, the system was manufactured and distributed by Siemens Oncology Care Systems (Concord, CA), the radiotherapy division of Siemens. However, in April 2001, Intraop assumed responsibility for worldwide distribution of the Mobetron, and a new manufacturer, CDS Systems (Freemont, CA), was appointed in October 2002.

Interstitial brachytherapy involves implantation of radioactive seeds such as iodine-125 or phosphorus 32, applied directly to the tumor bed, sparing healthy tissue and critical structures. This approach maximizes dose to the target. In a phase I clinical trial, up to 2,000,000 cGy of brachytherapy could be safely injected into tumors. In contrast, doses of traditional external RT are limited to 5,000-6,000 cGy, which is generally insufficient for tumor destruction.

In an ongoing phase II clinical trial (protocol ID: CMM-95079, CH/UMC-95079, NCI-V95-0760), interstitial colloidal

phosphorus 32 (P32), followed by EBRT and chemotherapy, is being integrated into the treatment of patients with inoperable PDAC to determine the response/remission rate, survival, and degree of local control. A total of 48 patients with inoperable PDAC limited to the head, body, or tail of the pancreas, were to be accrued for this trial. According to the protocol, in this outpatient procedure, patients are stratified by prior therapy (yes versus no) to be treated with dexamethasone intratumorally. Subsequently, after local anesthesia and under CT-guidance, a fine needle is placed into the pancreatic tumor. A solution of macroaggregated albumin is injected which acts as a 'gel' to restrict the subsequent injection of colloidal P32. Most patients are treated with a second course of this brachytherapy. Patients then proceed to CRT beginning 7-14 days after brachytherapy. Subsequently, patients are treated with 3D-conformal external radiation (6000 cGy minimum tumor dose), including regional lymph nodes, concurrently with four IV infusions of bolus 5-FU (500 mg) on alternating days within the first two weeks of external RT. Patients are followed monthly for 1 year then every 3 months thereafter. The trial is being conducted under the leadership of Stanley Order, MD, at the Center for Molecular Medicine (Garden City, NY) and at Northside Hospital Cancer Center (Atlanta, GA).

According to interim results from the phase II clinical trial, 30 patients (T1b=2, T2=3, T3=25) completed the prescribed course of infusional brachytherapy and CRT. Assessment of response was performed by CT scan, CA19-9 or CEA. QoL surveys were taken before and one month after therapy. A total of 63 infusions of 32P brachytherapy were delivered with tumor doses ranging from 54273 to 1960476 cGy (median=1010000 cGy). Local tumor control was achieved in 29/30 (97%) of patients. There were 3 deaths from unrelated causes, 1 each of pneumonia, diabetes, and septicemia. Metastases occurred in liver (n=6), lung (n=2), mesenteric nodes (n=2), and ascites (n=3). MST had not been reached within a median follow-up of 9 (range=2.5 to 42) months; 8 patients were alive at 1 year, 2 at 2 years, and 1 remained disease free at 4 years. In patients with localized, nonmetastatic, inoperable PDAC, this approach resulted in reduction in tumor volume, tumor markers and pain while providing a satisfactory QoL (Court W, etal, ASCO00, Abs. 1096).

Image-guided, fractionated, stereotactic radiosurgery focuses high intensity radiation to the tumor sparing the surrounding healthy tissue. It permits noninvasive treatment free from any anesthesia, hospital stay, surgical convalescence or rigid frames associated with older techniques. Developed nearly 40 years ago to treat brain tumors, this RT approach is currently used for treatment of extracranial, internal lesions.

Advanced image-guidance is used to verify tumor position throughout RT delivery to ensure accurate targeting without the need for rigid patient immobilization. Internal reference points in the anatomy (skeletal landmarks or small implanted markers) enable frameless treatment of lesions anywhere in the body. By focusing radiation beams from many different positions, the effects on the normal healthy tissue are minimized while the target is exposed the desired prescribed treatment. Fractionation exploits the difference between normal tissues and tumors resulting in a safer and superior outcome. It allows healthy, surrounding tissues to repair radiation effects not possible with a single fraction.

In radiosurgery in PDAC, prior to the procedure, 3-5 gold seeds are implanted into the tumor as fiducial markers placed through a needle under CT guidance. This procedure takes about 1 hour and is performed by interventional radiologists on an outpatient basis. These markers are visible to normal diagnostic x-rays and are used to track the position of the pancreatic tumor during radiosurgery. Approximately 1 week after the seeds are placed, a treatment planning session is performed that may involve construction of a mold to hold the body in place during the procedure. A specialized pancreatic protocol CT scan is also completed. The images are downloaded into treatment planning software and a customized radiosurgery plan is developed according to each patient's anatomy and the shape/location of the tumor.

In a phase I clinical trial, conducted at Stanford University (Palo Alto, CA), 15 patients with locally advanced PDAC were treated with 3 dose levels of radiosurgery (15 Gy=3, 20 Gy=5 and 25 Gy=7). No Grade 3 or higher toxicity was encountered and the trial was stopped when the clinical endpoint was achieved in 6/7 patients treated with 25 Gy of radiosurgery.

Several systems have been designed for radiosurgery applications. The CyberKnife, marketed by Accuray (Sunnyvale, CA), is a 100% frameless, noninvasive, image-guided, robotic, radiosurgery system that is being used in combination with Dynamic Tracking Software (DTS) to treat lesions in the brain, spine, pancreas, liver, and lung. The CyberKnife system uses large doses of accurately targeted radiation fired from multiple directions to destroy tumors and other lesions while minimizing damage to surrounding healthy tissue. The CyberKnife technology, which was developed in cooperation with Stanford University, was cleared by the FDA in August 2001 and received CE approval in Europe in September 2002 to provide radiosurgery for lesions anywhere in the body when RT is indicated. Among the new capabilities of the DTS system are greater accuracy and fiducial tracking to compensate for changes caused by patient movement during treatment delivery. Its image-guidance system verifies tumor position throughout radiation delivery to ensure accurate targeting of radiation without the need for rigid patient immobilization. To date, the CyberKnife System has been used to treat more than 6,500 patients worldwide.

CyberKnife treatment is typically performed on an outpatient basis in 1 to 5 treatment sessions. Patients are awake during the procedure, which is painless, noninvasive, and typically lasts 30 to 60 minutes per session. A

flexible robotic manipulator positions a miniature linear accelerator at multiple points around the patient, and a beam of high-energy radiation is fired at the tumor from each position. The beams converge to deliver a high dose of radiation to the tumor while minimizing radiation to nearby normal tissue. The CyberKnife system tracks and automatically retargets a lesion using robotics, even if the patient has moved. The CyberKnife claims radiation delivery at submillimeter total clinical accuracy with T4 or 'tight-to-the-tumor' conformality. The submillimeter accuracy allows higher doses of radiation to be used for greater tumor-targeting accuracy.

Another radiosurgery system, the Elekta Synergy system marketed by Elekta (Stockholm, Sweden), is equipped with an advanced kilovoltage X-ray volume imaging system (XVI) with flat-panel AmSi detector technology that provides sophisticated imaging capabilities with the patient in the treatment position. This new treatment platform directly addresses such problems of modern RT, as internal organ motion and errors in patient set-up. The Elekta XVI concept and prototype were developed in 1997 in collaboration with William Beaumont Hospital (Royal Oak, MI). The Elekta Synergy system was granted 510(k) premarket clearance by the FDA in October 2003, while in Europe, it received CE marking in July 2003.

The Elekta Synergy system comprises of a linear accelerator equipped with a kV source and a solid state detector to allow planar or X-ray volume imaging of the patient in the treatment position. Elekta Synergy uses innovative x-ray volume imaging technology that is integrated directly onto the treatment system itself, so that routine pretreatment imaging of a tumor can be performed immediately prior to treatment, decreasing the risk that a tumor or internal organs will change position. In addition, since the patient doesn't have to be moved from an imaging device to the RT treatment machine, the problem of errors from patient re-setup are eliminated.

Another image-guided radiosurgery system is the Novalis Shaped Beam Surgery system marketed by BrainLAB (Munich, Germany). The system uses a miniature radiation beam-shaping device (m3), a motorized micro multileaf collimator cleared by the FDA for sale in the USA in July 1997. This device consists of independently motorized tungsten leaves that configure the radiation beam to the shape of the tumor. Novalis combines photon beam technology with beam shaping to effectively and safely perform high resolution intensity modulated radiosurgery (IMRS).

Chemotherapy

Chemotherapy may be administered to patients with PDAC as an adjuvant treatment after curative resection in those with resectable disease, in the neoadjuvant setting to downstage disease with the intent of curative resection, and for palliation in advanced/metastatic disease. The standard first line chemotherapy regimen used alone or in combination with RT is a gemcitabine-based or 5-FU-based regimen, often including cisplatin. Several approved drugs have been evaluated in combination in PDAC (see Exhibit 1), and numerous clinical trials are ongoing that combine gemcitabine and other approved chemotherapeutics with novel agents. Several active drugs in combination are described below.

Pancreatic cancer is also being addressed by newly approved novel anticancer agents. A randomized phase II clinical trial (protocol ID: NCCTG-N014C) that compared the effectiveness of bortezomib (Velcade; Millennium Pharmaceuticals) with or without gemcitabine in treating metastatic PDAC was closed in November 2003. Another novel agent, pemetrexed disodium (Alimta; Lilly), approved by the FDA in February 2004, in combination with cisplatin, for the treatment of inoperable mesothelioma, has also shown promise in pancreatic cancer (see Part III of this article). However, in *in vitro* studies, STI571 (Gleevec/Glivec; Novartis) did not appear to be a likely candidate for the treatment of pancreatic cancer (Li J, etal, Mol Cancer, 17 Sep 2003;2(1):32).

Chemotherapy is mostly delivered systemically via IV infusion. However, delivery of chemotherapeutics is also possible intratumorally, intraperitoneally (IP) and intra-arterially. The European Study Group for Pancreatic Cancer (ESPAC) has undertaken a clinical trial, ESPAC-2, to evaluate intra-arterial delivery of chemotherapeutics in pancreatic cancer. Among 46 patients recruited in this trial, as of mid-2003, only 9 completely followed the whole protocol, which is difficult for both patients and doctors.

Investigators at Tokyo Metropolitan Komagome Hospital, in Japan, treated 13 patients with inoperable PDAC with IORT in combination with EBRT plus locally intensive intra-arterial chemotherapy consisting of gemcitabine, cisplatin, and 5-FU. In order to increase drug delivery to the primary tumor, the splenic and major pancreatic arteries, except for the gastroduodenal artery (GDA), were embolized by radiological intervention prior to intra-arterial chemotherapy. Values of serum tumor markers decreased in all patients, and tumor regression was detected on CT scan in 6 (Matsumoto G, etal, Gan To Kagaku Ryoho, Oct 2003;30(11):1575-8).

IP gemcitabine therapy may also be a promising regional therapy for advanced PDAC. Its high clearance and low local toxicity make gemcitabine an ideal drug for IP therapy. Using multiple exchanges of a dialysate containing gemcitabine, delivered via a tenchkoff catheter, prolonged (over 24 hours) IP exposure of the drug was possible in 9 patients participating in a phase II clinical trial involving multimodality therapy for advanced PDAC. During a 24-hour period, 4 6-hour IP infusions of gemcitabine (50 mg/m^2) were administered with a second 24-hour cycle of therapy repeated one week later. Plasma and peritoneal fluid samplings were analyzed to determine concentrations of gemcitabine and its metabolite (dFdU) to assess absorption and systemic exposure. Among the 9 patients treated with IP gemcitabine, 8 underwent two cycles of IP therapy. Treatment was well tolerated with no significant

systemic toxicities. Low plasma concentrations (<0.5 µg/ml) of gemcitabine were present transiently in 7/9 patients and absent in the remainder. Low plasma dFdU concentrations increased gradually until 18 hours and then declined little if any. IP gemcitabine quickly declined and was seldom present prior to the next scheduled 6-hour infusion. Gemcitabine concentration in peritoneal fluid was very low (<0.5 µg/ml) throughout the treatment. The quick drop of peritoneal gemcitabine and lack of dFdU imply almost total drug absorption. Based on the steady state of plasma gemcitabine and the dose of administered drug, it is certain that virtually all IP-administered drug was absorbed. Despite this, minimal to no plasma concentrations of gemcitabine could be detected and no significant systemic side effects were encountered (Gamblin TC, etal, ASCOGI04, Abs 110).

Chemotherapy is also used to treat pancreatic neuroendocrine tumors. As in PDAC, disease is inoperable in the majority of patients, who are commonly treated with combinations of chemotherapy, biotherapy, chemoembolization and tumor-targeted RT. A regimen of streptozocin, in combination with 5-FU or doxorubicin, has become the standard first line treatment as it produced responses of 40%-60% in phase III clinical trials. Among 15 patients with inoperable, metastatic neuroendocrine tumors, treated systemically with a regimen of infusional 5-FU, folinic acid and streptozocin, the overall objective response rate was 53% with excellent tolerability (Gonzalez MA, etal, Br J Cancer, 4 Aug 2003;89(3):455-6). Cisplatin-based regimens have also been shown to be effective in anaplastic neuroendocrine tumors, but at the expense of increased toxicity.

5-Fluorouracil (5-FU) has been the standard drug treatment of PDAC in the adjuvant setting or as a palliative in metastatic disease. The current standard local treatment for inoperable pancreatic carcinoma is RT with concurrent 5-FU. Phase I and II clinical trials have also demonstrated that protracted infusional 5-FU with concurrent RT is tolerable and effective in patients with pancreatic cancer. In a phase I clinical trial, conducted by the Eastern Cooperative Oncology Group (ECOG), 25 patients with recurrent, residual, or inoperable carcinoma of the pancreas or biliary tract were treated with 5-FU based CRT. The maximum tolerated dose (MDT) of continuously infused 5-FU in combination with RT (59.4 Gy in 33 fractions) over 6 to 7 weeks, was established at 250 mg/m^2. The dose-limiting toxicity (DLT) was oral mucositis. MST was 11.9 months, and the 2-year survival rate was 19%; 11/25 (40%) patients remained free of local progression and 4 were without evidence of progression at 18+, 18+, 34+, and 44+ months following treatment (Whittington R, etal, J Clin Oncol, Jan 1995;13(1):227-32).

Currently, 5-FU is being evaluated in phase II clinical trials in combination with other chemotherapeutics and/or various RT approaches (Exhibit 1). ESPAC-3 is comparing 5-FU with gemcitabine in the adjuvant setting in locally advanced operable PDAC.

Newer analogs of 5-FU have been developed that act as prodrugs to modulate 5-FU metabolism by inhibiting the activity of dihydropyrimidine dehydrogenase (DPD) that accounts for much of the variability observed with 5-FU treatment. Inhibition of DPD lessens 5-FU variability, and may improve 5-FU pharmacology. One such 5-FU prodrug is capecitabine (Xeloda: Roche), an orally available tumor-selective fluoropyrimidine (see below).

Two other 5-FU prodrugs, TS-1 and UFT, both marketed outside the USA by Taiho Pharmaceutical (Tokyo, Japan), have been evaluated in PDAC. UFT, marketed since 1984 for GI malignancies, combines tegafur, a 5-FU prodrug with uracil, a DPD inhibitor. TS-1, approved in 1999 for gastric cancer, is a novel oral fluoropyrimidine anticancer drug that combines tegafur, a prodrug of 5-FU, with gimestat (5-chloro-2,4-dihydroxypyridine), an inhibitor of DPD activity that is 200-fold more potent than uracil used in UFT, and potassium oxonate, which reduces gastrointestinal toxicity (Fukushima M, etal, Anticancer Drugs 1998;9:817-823, and Shirasaka T, etal, Anticancer Drugs 1996;7:548-557).

A phase II clinical trial of UFT plus leucovorin in 14 patients with advanced PDAC, was conducted at the University of Chicago Pritzker School of Medicine by a phase II consortium, to determine the activity and evaluate the toxicity of this combination. Patients were treated with daily PO UFT (300 mg/m^2) and PO leucovorin (90 mg), administered in divided doses every 8 hours, for 28 days, repeated every 35 days. Objective tumor response was evaluated after 2 courses of therapy. All 14 patients were evaluable for response and toxicity. There were no objective responses; median TTP and MST were 14, and 15 weeks, respectively. Toxicity was mild with severe (Grade 3/4) hyperbilirubinemia, pain, diarrhea, transaminitis, venous thrombus, weakness, renal failure, confusion, and edema/ascites seen in 3 (21%), 1 (7%), 2 (14%), 1 (7%), 1 (7%), 1 (7%), 1 (7%), and 2 (14%) patients, respectively. There was no neutropenia, significant oral mucositis or diarrhea (Mani S, etal, Ann Oncol, Sep 1998;9(9):1035-7). UFT is currently being evaluated in combination with gemcitabine in pancreatic cancer (Exhibit 1).

In a phase II clinical trial conducted at National Cancer Center Hospital (Tokyo, Japan) between June 2000 and January 2001, single agent S-1 (40 mg/m^2) was administered orally *bid* for 28 consecutive days, repeated every 6 weeks, to 19 patients with advanced PDAC. Objectives were to determine the activity, toxicity, and pharmacokinetics of S-1 in this setting. Median number of courses completed was 2 (range=1 to 9+). Among 19 evaluable patients, objective responses were observed in 4 (21.1%), disease stabilized in 10, and progressed in 5. MST was 167 days. Toxicities observed were Grade 3/4 erythrocytopenia (21.1%), anorexia (15.8%), and nausea (15.8%). Other Grade 3/4 toxicities such as ileus, abdominal pain, colitis, and abdominal distension, were less frequent (Okada S, etal, ASCO02, Abs. 682:171a).

Exhibit 1
Interim and Final Results from Selected Clinical Trials with Approved Chemotherapy Agents in Combination and Multimodality Regimens in Pancreatic Cancer

Regimen and Protocol	Clinical Status ❑ Clinical Indication ❑ Enrollment (#)	Toxicity	Response	Institution ❑ Reference ❑ Protocol ID
Gemcitabine				
Gemcitabine + 5-FU Gemcitabine (1000 mg/m^2) was administered as a 30-minute infusion and 5-FU (2000 mg/m^2) as a 24-hour infusion, weekly, on an outpatient basis, for 3 consecutive weeks, followed by 1 week rest, until disease progression.	Phase II (begin 2/98, completed 1/01)➢Europe (Germany) ❑ metastatic pancreatic cancer (Stage IVb) ❑ 23 patients **Eval Resp:** 23 patients **Eval Tox:** 23 patients	No chemotherapy-induced Grade 3/4 toxicity occurred; there was 1 tumor-related Grade 3 anemia and 2 stent occlusions with Grade 3 increases in bilirubin.	**PR:** 9% **SD:** 61% **PD:** 30% **MST:** 8.3 (range=2.0-19.8) months **1-year survival:** 30%	University of Erlangen-Nuernberg (Germany) ❑ *Wein A, etal, ASCO02, Abs. 620:156a*
Gemcitabine + 5-FU; RT Gemcitabine (1000 mg/m^2) is administered weekly for 3 weeks followed by 1-week rest, followed by 5-6 weeks of 3D conformal RT and concurrent continuous infusion (CI) 5-FU (200 mg/m^2/day); after a 4-week rest period, gemcitabine is reinitiated for 12 weeks.	Phase II (ongoing 6/03)➢ Australia ❑ nonmetastatic, inoperable or at high risk of relapse following surgery, pancreatic cancer ❑ 47 patients **Eval Resp:** 20 patients **Eval Tox:** 20 patients	Among 20 evaluable patients 9 completed all planned treatment; 3 patients discontinued treatment and 1 died of colitis; 20 patients completed the initial gemcitabine treatment and 18/19 completed RT, 2/19 required reduction in 5-FU; 5/20 reduction in gemcitabine pre RT, and 17/18 reduction post RT. Grade 4 diarrhea (n=1), Grade 3 fatigue (n=1), febrile neutropenia (n=1), Grade 3 neutropenia (n=8), Grade 3 thrombocytopenia (n=1), Grade 3 dehydration (n=1), Grade 3 TIA (n=1), ARDS (n=1), aspiration (n=1) and DVT (n=1).	**PD:** 7 (35%);	Prince of Wales Hospital (NSW, Australia), Sir Charles Gardiner Hospital (WA, Australia) ❑ *Goldstein D, etal, ASCO03, Abs. 1216:303*
Gemcitabine + docetaxel Dose was escalated in 5 dose levels (5 patients each) with gemcitabine (800, 850, 900, 950, 1000 mg/m^2) administered as a 30-minute infusion, followed by docetaxel (25, 30, 35, 40, 45 mg/m^2) on days 1, 8, and 15 in a 28-day cycle; 2 0r 3 cycles were administered preoperatively for 8 to 12 weeks, when reassessment of resectability was done by CT scan, MRI, and/or laparoscopy. MTD was gemcitabine at 900 mg/m^2 and docetaxel at 35 mg/m^2. Surgery was performed within 4 weeks after cytotoxic chemotherapy. Successful radical (R0) resection (partial duodenopancreatectomy) was possible in 39/48 (81%) patients. There was no surgical mortality.	Phase II (completed 5/02)➢ Austria ❑ locally advanced, nonmetastatic, pancreatic cancer ❑ 48 patients **Eval Resp:** 48 patients	An 8-week outpatient treatment schedule with 2 cycles of gemcitabine (900 mg/m^2) and docetaxel (35 mg/m^2) on days 1,8,15 every 28 days was tolerated with moderate toxicity.	**OR:** substantial tumor marker responses were seen preoperatively in most patients **1-year survival:** 85% **OS:** 28/39 (72%) patients with R0 resection were alive at a median follow-up time of 26 months; actuarial 3-year survival was 67%. OS and PFS rates were significantly better than those of patients with T1-T3 disease operated without neoadjuvant chemotherapy	University of Vienna (Austria) ❑ *Gnant MF, etal, ASCO02, Abs. 593:149 and Gnant MF, etal, ASCOGI04, Abs. 98)*

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Gemcitabine + docetaxel Gemcitabine (1000 mg/m^2) and docetaxel (35 mg/m^2) are administered on days 1, 8 and 15, repeated every 28 days following restaging; treatment continues until progression or unacceptable toxicity	Phase II (completed 11/02)➢ Europe (Germany) ❑ locally advanced, inoperable or metastatic pancreatic cancer ❑ 58 patients (primary, locally advanced, inoperable =19, metastatic, predominantly affecting the liver=39) **Eval Resp:** 57 patients **Eval Tox:** 55 patients	Grade 3/4 toxicities were neutropenia (15%), leukopenia (13%), anemia (4%), thrombocytopenia (2%), diarrhea (15%), nausea (15%), vomiting (4%), alkaline phosphatase elevations (6%), and transaminase elevations (4%).	**CR:** 1 (2%) **PR:** 10 (18%) **SD:** 30 (53%) **PD:** 16 (28%). **MST:** 8 months **Median TTP:** 4.5 months	Multicenter ❑ *Schmidt C, etal, ASCO02, Abs. 577:145a; ASCO03, Abs. 1439:358*
Gemcitabine + docetaxel Gemcitabine (750 mg/m^2) and docetaxel (35 mg/m^2), are administered weekly for 3 weeks on a 28-day cycle.	Phase II (begin 11/99, completed 3/01)➢USA ❑ advanced pancreatic cancer ❑ 40 patients (locally advanced disease=9 and metastatic disease=29; 2 never treated) **Eval Resp:** 37 patients **Eval Tox:** 37 patients	Grade 4 (n=10), and Grade 3 (n=27); 1 serious adverse effect was attributed to therapy. Grade 4 granulocytopenia (n=5), pulmonary dysfunction (n=2), anemia, hepatic dysfunction, infection, edema, anorexia, and splenic infarction (n=1); Grade 3 leukopenia (n=11), granulocytopenia (n=9), nausea/vomitting and pain (n=6), fatigue and anemia (n=4), diarrhea, pulmonary and hepatic dysfunction (n=3), lymphopenia (n=2), myalgia, ascites, thrombocytopenia, edema, dehydration, infection, and neurologic and cardiac dysfunction (n=1).	**PR:** 9 (24%) with a median duration of response of 16 (range=8-48) weeks **SD:** 13 (35%) **Median TTP:** 22.4 (range=2.9-57.1) weeks **1-year survival:** 27.3% with a median follow-up of 23.6 (range= 1.1-65) weeks	Indiana University Cancer Center (Indianapolis, IN), Washington University (St. Louis, MO), Cancer Treatment Centers of America (Goshen, IN), Hoosier Oncology Group (Indianapolis, IN) ❑ *Schneider BP, etal, ASCO02, Abs. 546:137a*
Gemcitabine + docetaxel + capecitabine Docetaxel (40 mg/m^2) was administered in the middle of weeks 1 and 3 alone, capecitabine (1500 mg/m^2/day) on weeks 2 and 4, and gemcitabine (750 mg/m^2) over 75 minutes on Wednesday. This alternating regimen was administered 4 weeks on and 2 weeks off as a cycle. Patients were reassessed after 2 cycles.	Phase II (completed 6/03)➢ USA ❑ advanced/metastatic, relapsed or refractory, pancreatic cancer ❑ 10 patients **Eval Resp:** 10 patients **Eval Tox:** 10 patients	Toxicity included Grade 2 neutropenia (30%), erythrodyesthesias (20%), diarrhea(40%), and asthenia (10%); there were no neutropenic fever or deaths.	**CR:** 1 (10%) **PR:** 2 (20%) **OR:** 3 (30%) median duration of response was 5.5 months **SD:** 4 (40%) median duration of SD was 5.5 (range=2-13) months	Columbia Presbyterian Medical Center (New York, NY); Morristown Memorial Hospital (Morristown, NJ) ❑ *Fogelman DR, etal, ASCO03, Abs. 1517:378*
Gemcitabine + docetaxel; RT IV docetaxel (65mg/m^2) is administered over 1 hour and IV gemcitabine (4000 mg/m^2) over 30 minutes on days 1, 15 and 29. On day 43, therapy continues with RT at 1.8 Gy per fraction to a dose of 50.4 Gy, together with IV gemcitabine (50 mg/m^2) over 30 minutes twice weekly for 12 doses. Following completion of therapy, patients were restaged and considered for resection.	Phase II (begin 1/02, ongoing 6/03)➢USA ❑ untreated pancreatic adenocarcinoma (Stage I/III) ❑ 13 patients **Eval Resp:** 9 patients	Toxicity included Grade 3 nausea/vomiting, fatigue, and dehydration, and Grade 3/4 hematologic toxicity (n=4). Neutropenic fever did not occur.	**CR:** 1 (11%) (radiographic) **OR:** 6 (67%) No local tumor progression occurred; one patient developed liver metastases on treatment and died of progressive disease; among 4 patients who underwent a Whipple procedure, 3 had margin-negative resections.	Dartmouth Hitchcock Medical Center (Lebanon, NH) ❑ *Pipas JM, etal, ASCO03, Abs. 1392:347*

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Gemcitabine + cisplatin IV cisplatin (25 mg/m²) is is followed by IV gemcitabine (1000 mg/m²) on days 1, 8, and 15, every 4 weeks. Among 434 chemo doses, there were delays (16%) and reductions of at least 25% (24.7%, mostly on day 15).	Phase II (completed 6/03)➢ Europe (UK) ❑ advanced pancreatic cancer ❑ 36 patients (locally advanced disease=12 and metastatic disease=24) **Eval Resp:** 32 patients **Eval Tox:** 32 patients	Nonhematologic toxicity was Grade 3 constipation (8.6%), Grade 3/4 neutropenia (8.6%/2.9%; mostly cholangitis associated with indwelling biliary stents), Grade 3 lethargy (11.4%), and Grade 3/4 thromboembolism (8.6%; DVT=2, PE=1); hematologic toxicity (mostly asymptomatic)included Grade 3/4 leukopenia (40%), neutropenia (60%), and thrombocytopenia (60%). There were 3 episodes of neutropenic sepsis and 2 significant bleeding complications (melena=1, hematuria=1)	**PR:** 9.4% **SD:** 53% **MST:** 10.1 months **6-month survival:** 75%; **1-year survival:** 38.2% (exceed the 18% achievable with gemcitabine monotherapy)	Christie Hospital NHS Trust (Manchester, UK) ❑ *Clayton AJ, etal, ASCO03, Abs. 1330:331*
Gemcitabine + cisplatin Gemcitabine (1000 mg/m²) and cisplatin (25 mg/m²) were administered on days 1,8 and 15 of a 28 day cycle.	Clinical trial (begin 2/01, completed 5/02)➢Israel ❑ locally advanced or metastatic pancreatic cancer ❑ 28 patients (chemonaive=17 and single agent gemcitabine refractory=11; locally advanced disease/abdominal spread=7 or distant metastases=20) **Eval Resp:** 27 patients **Eval Tox:** 27 patients	Therapy was well tolerated. Grade 3/4 hematologic toxicity in 26% of patients was the main reason for treatment delay or for dose reduction.	**PR:** 4/17 (23%) chemonaive and 3/10 (30%) refractory **SD:** 4/17 (23%) chemonaive lasting >2 months and 2/10 (20%) refractory **MST:** 6.5 months chemonaive and 11 months refractory **Median TTP:** 7 months in both groups **1-year survival:** 43% chemonaive and 41% refractory **OR:** clinical benefit response 9/17 (53%) chemonaive and 5/10 (50%) refractory	Rambam Medical Center (Haifa, Israel), and Western Galilee Hospital (Nahariya, Israel) ❑ *Epelbaum R, etal, ASCO03, Abs. 1202:299*
Gemcitabine + cisplatin + 5-FU IV gemcitabine (1000 mg/m²) was administered on days 1, 8 and 15, IV cisplatin (50 mg/m²) on days 1 and 15 and 5-FU (175 mg/m²/day) for 14 days by continuous IV infusion.	Phase II (completed 5/02)➢ USA ❑ metastatic, chemotherapy-naïve, pancreatic cancer ❑ 30 patients **Eval Resp:** 23 patients **Eval Tox:** 30 patients	Major Grade 3/ 4 toxicities were neutropenia (19%), thrombocytopenia (38%) and mucositis/stomatitis (15%); 4 patients required hospitalization and 31% were treated with red packed cell transfusions. There was only 1 episode of neutropenic fever.	**PR:** 3 (13.0%) after cycle 2 there was no difference in PR rates between patients with or without a CA 19-9 level decline of at least 50% **SD:** 18 (78.3%) **MST:** preliminary among the first 26 patients was 8.4 months **Median TTP:** 4.2 months	Karmanos Cancer Institute (Detroit, MI); Comprehensive Cancer Center/ University of Michigan (Ann Arbor, MI) ❑ *Philip P, etal, ASCO2, Abs. 590:148a*

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Gemcitabine + cisplatin + 5-FU + capecitabine Gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) were administered on days 1,8 and 15 of a 28 day cycle.	Phase II (begin 7/00, completed 6/03)➢Europe (UK) ❑ inoperable pancreatic cancer ❑ 17 patients (locally advanced disease=9 and metastatic disease=8) **Eval Resp:** 15 patients **Eval Tox:** 17 patients	There were 3 (18%) Grade 3/4 events (nausea/vomiting, neutropenia, and lethargy). Dose was reduced in 2 patients treated with 5-FU for mucositis and in 2 treated with capecitabine for palmar-planter erythema. Cisplatin was stopped in 1 patient and another was switched to carboplatin for nausea.	**PR:** 6 (40%) **1-year survival:** 6 (35%)	Wessex Medical Oncology Unit, Royal South Hants Hospital (Southampton, UK) and Salisbury District Hospital (UK) ❑ *Crabb SJ, etal, ASCO03, Abs. 1266:315*
Gemcitabine + cisplatin + nadoparine calcium (LMWH) Gemcitabine (800 mg/m^2) and cisplatin (35 mg/m^2), administered on days 1 and 8, repeated every 21 days in both groups. Subcutaneous nadoparine calcium (2850 IU/day) was added to the treatment regimen in one group. Treatment was continued until progression or further 2 cycles after disease stabilization, with a median of 6 cycles (range= 2-9) delivered in the LMWH group and 3 (range=2-8) cycles in the control group.	Phase II (begin 11/99, completed 7/02)➢Turkey ❑ advanced or metastatic pancreatic cancer ❑ 42 patients (locally advanced disease=10, metastatic disease=32)	Toxicity was similar and acceptable in both groups. There was no Grade 4 toxicity.	**CR:** 11.7% in LMWH group; 0% in control group **OR:** 64.7% in LMWH group and 12% in control group **MST:** 9.0±1.9 months with LMWH and 4.0±0.4 months without LMWH **Median TTP:** 6.0±0.9 months with LMWH and 3.0±1.5 without LMWH **1-year survival:** 47.7% with LMWH and 13.5% without LMWH	Ankara University (Turkey) and Dicle University (Diyarbakir, Turkey) ❑ *Icli F, etal, ASCO03, Abs. 1149:286*
Gemcitabine + irinotecan + 5-FU + leucovorin (LV) + cisplatin Every 2-week cycles of sequential gemcitabine (500 mg/m^2), irinotecan per dose escalation schedule, bolus 5-FU (400 mg/m^2) and LV (300 mg) were administered on day 1, followed by a 24-hour 5-FU (1500 mg/m^2) infusion, followed by cisplatin (35 mg/m^2) on day 2. Irinotecan starting dose was 80 mg/m^2, escalated by 20 mg/m^2 in cohorts of 3 patients until MTD.	Phase I (ongoing 6/03)➢ USA ❑ pancreatic cancer and other solid tumors ❑ 16 patients (pancreatic cancer=8, gallbladder cancer=5, squamous cell of head & neck cancer=2 and hepatocellular carcinoma=1) **Eval Resp:** 13 patients **Eval Tox:** 15 patients	Grade 1-2 toxicities were diarrhea (25%), nausea/ vomiting (66%), constipation (31%), and fatigue (56%). There was 1 case of Grade 3 nausea/vomiting at dose level 1 (100 mg/m^2). Grade 3/4 hematologic toxicities were thrombocytopenia (6%), anemia (12%), neutropenia (25%), and neutropenic fever (6%). There were 6 cases of Grade 3/4 thrombosis and the protocol was amended to encourage use of coumadin (1 mg/d).	**CR:** 1 (7.7%) in pancreatic cancer **PR:** 4 (30.8%) in gallbladder cancer=3 and pancreatic cancer=1 **SD:** 6 (46.1%) in pancreatic cancer=5 and hepatocellular carcinoma=1 **Median TTP:** 17.5 (range= 10-25) weeks	St Luke's Roosevelt Hospital (New York, NY); Beth Israel Medical Center (New York, NY) ❑ *Rachamalla R, etal, ASCO03, Abs. 1353:337*
Gemcitabine + cisplatin; RT Gemcitabine and cisplatin are administered twice weekly for 3 weeks during radiotherapy (50.4 Gy in 28 fractions) in escalating doses. Six dose levels were administered: IV gemcitabine at 5, 10, 20, 30, 30, and 45 mg/m^2 and cisplatin at 5, 5 , 5, 5, 10 and 10 mg/m^2.	Phase I (completed 5/02)➢ USA ❑ locally advanced gastric or pancreatic cancer ❑ 24 patients **Eval Tox:** 24 patients	Grade 3 neutropenia in 2 patients (1 each at dose level 2 and 5) and Grade 3 thrombocytopenia in 2 (1 each at dose level 5 and 6); most common Grade 3/4 toxicity was vomiting (n=7) and nausea (n=6).		North Central Cancer Treatment Group (Rochester, MN) ❑ *Martenson JA, etal, ASCO02, Abs. 583:146a*

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Gemcitabine + cisplatin; RT Concurrent with radiotherapy, 4 applications of gemcitabine (300mg/qm) and cisplatin (30mg/qm) were administered. After chemoradiation, 4 additional courses of gemcitabine (1000mg/qm) and cisplatin (50mg/qm) were administered.	Phase II (begin 00, completed 02)➢Europe (Germany) ❑ locally advanced, incompletely resected pancreatic cancer ❑ 30 patients **Eval Resp:** 30 patients **Eval Tox:** 30 patients	Hematologic toxicities were Grade 3/4 (50%/3%) leucocytopenia and Grade 3/4 (30%/7%) thrombocytopenia; there were no Grade 3/4 GI toxicities.	**Median PFS:** 13.5 months **MST:** 22.8 months **1-year survival:** 85% **2-year survival:** 45% **3-year survival:** 27%. **PD:** after completion of CRT, distant metastases occurred in 12 (40%) patients during a median follow-up time of 15.0 (range=4.6-30.5) months; 1 patient developed both, local recurrence and distant metastasis	Klinik für Strahlentherapie und Radioonkologie (München, Germany) ❑ *Wilkowski R, etal, ASCO03, Abs. 1164:290*
Gemcitabine + cisplatin; RT Induction therapy with gemcitabine and cisplatin, was followed by concurrent chemoradiation (CCRT) with the same agents. Gemcitabine (1000 mg/m^2) and cisplatin (30 mg/m^2) were administered weekly for 3 weeks, every 4 weeks, for 2 cycles. After re-evaluation, those whose disease did not progress were treated with RT (5040 cGy in 180 Gy fractions) to a standard pancreatic field with concurrent weekly (for 6 weeks) gemcitabine and cisplatin in 4 escalating doses. After a second re-evaluation, those with resectable disease underwent curative surgery and those whose disease did not progress but could not be resected were treated with an additional 2 cycles of gemcitabine and cisplatin.	Phase I/II (completed 6/03) ➢USA ❑ locally advanced pancreatic cancer ❑ 21 patients **Eval Resp:** 21 patients **Eval Tox:** 21 patients	During induction therapy, toxicity included Grade 3 (n=6) and Grade 4 (n=2) neutropenia, Grade 3 (n=5) thrombocytopenia and Grade 3 (n=1) nausea. There was no Grade 4 toxicity.	**SD:** 5 (23.8%) after CCRT **PD:** 11 (52.4%) 5 after induction therapy and 6 after CCRT **MST:** 12.9 months **OS:** 17/21 (80.9%) patients died at a median follow up of 11.5 months	New York University Medical Center (NY) ❑ *Newman E, etal, ASCO03, Abs. 1408:351*
Gemcitabine + cisplatin; EBRT EBRT (50.4-59.4 Gy) in 1.8 Gy fractions was administered 5 times per week with weekly chemotherapy consisting of cisplatin (20 mg/m^2), and gemcitabine, starting at 100 mg/m^2 and increasing at 50 mg/m^2 increments.	Phase I (completed 5/02)➢ USA ❑ pancreatic or peri-ampullary cancer ❑ 20 patients (resected=9 or not=11) **Eval Tox:** 20 patients	The most common toxicities were nausea, fatigue and bone marrow suppression, particularly neutropenia and thrombocytopenia. There was 1 case of Grade 4 thrombocytopenia, 2 of Grade 3 thrombocytopenia, and 7 of Grade 3 neutropenia; 1 patient developed an anastomotic perforation at the site of surgical bypass.	10 patients are alive with the longest survival being 27 months	Harvard Medical School (Boston, MA) ❑ *Aitken CL, etal, ASCO02, Abs. 2221: 102b*

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Gemcitabine + cisplatin + interferon α (IFN-α) + granulocyte microphage colony stimulating factor (GM-CSF); hyperthermia Escalating dose of cisplatin (50 to 100 mg/m²) on day 1, with fixed subcutaneous dose of daily IFN-α (100,000 IU) beginning on day 1 to the end of the protocol; fever-range, long-duration whole-body hyperthermia (FR-WBH) at 40.0 degrees C, for 6 hours, plus simultaneous gemcitabine (600 mg/m²) over 60 minutes on day 3, and gemcitabine (600 mg/m²) over 60 minutes on day 10, GM-CSF 250 mg/m²/day beginning on day 14 to day 24. Treatment cycles were repeated at day 28. FR-WBH was induced using the Heckel 2001 radiant heat device. Light concious sedation using fentanyl, lorazapam and phenergan. Median treatment cycles was 4 (range=1-9), and time to reach target core temperature was 60-140 minutes.	Phase I (begin 11/99, completed 10/02)➢USA ❑ advanced or metastatic solid tumors ❑ 24 patients (previously treated with 1-5 chemotherapy regimens=91.6%) **Eval Resp:** 24	Grade 3 thrombocytopenia at 70 mg/m² of gemcitabine ocurred in 2/3 patients, Grade 2 thrombocytopenia after 3 cycles of cisplatin 70 mg/m² in 1/3 patients. There were 3 cases of Grade 1 leukopenia at cisplatin 70 mg/m², 1 case of Grade 3 ototoxicity at cisplatin 70 mg/m², and 2/3 patients developed Grade 2 neuropathy at cisplatin 70 mg/m².	**PR:** 9 (38%); 2/9 >90% tumor shrinkage **SD:** 3 (13%) >12 weeks **OR:** 5 (21%) >5 month **PD:** 7 (29%) PR was seen in 5/7 patients with pancreatic cancer, and 3/3 with neuroendocrine tumors.	University of Texas Houston Medical School (Houston, TX) ❑ *Bull JMC, etal, AACR03, Abs. 5334*
Gemcitabine + 5-FU + cisplatin + epirubicin; surgery + RT A total of 179 cycles of cisplatin and epirubicin (40 mg/m²) on day 1, gemcitabine (600 mg/m²) on day 1 and 8, and 5-fluorouracil (200 mg/m²/day) by continuous infusion (PEFG regimen) were administered (mean=3.5/patient; range=0-4) to 51 enrolled patients; cisplatin and epirubicin were delivered at 100%, gemcitabine at 89% and 5-FU at 92% of the intended dose. After PEFG, 39 patients were treated with RT. A CT scan was performed every 3 months or when relapse was suspected.	Phase II (begin 10/97, closed 5/02) Europe (Italy) ❑ resectable, Stage II/IVa pancreatic cancer ❑ 51 patients (resection-margin positive=51% and lymph-node positive=90%; Stage II=4, Stage III=34 and Stage IVa=13; Grade I=4, Grade II=25 and Grade III=22)	The chief toxicity was Grade 3/4 neutropenia (30%/21%), thrombocytopenia (16%/2%), and anemia (3%/1%); Grade 3 cardiovascular events, vomiting, stomatitis, diarrhea, fever, asthenia and liver toxicity occurred in 1% to 3% of cycles; 16 (31%) patients were treated with <4 cycles because of early progression (n=7), toxicity (n=1), catheter-related complications (n=3), protocol violation (n=3), or refusal (n=2).	**PFS:** 15 patients were failure free at a median of 28 (range=12-71) months from surgery **OS:** Actuarial 2-year and 5-year OS was 54±7%, and 23±8%, respectively; 20 patients were alive at a median follow-up of 28 (range=15-71) months.	San Raffaele-H Scientific Institute (Milan, Italy) ❑ *Reni M, etal, 2004 ASCO Gastrointestinal Cancers Symposium (ASCOGI04), Abs. 90*
Gemcitabine + raltitrexed Raltitrexed (3 mg/m²) is administered as a 15-minute infusion on day 1 and gemcitabine (1000 mg/m²) on days 1 and 8, every 21 days.	Phase II (completed 5/02)➢ Europe (Switzerland) ❑ advanced pancreatic cancer ❑ 26 patients (metastatic=20 and locally advanced=2) **Eval Resp:** 24 patients **Eval Tox:** 26 patients	Grade 3/4 toxicity was rare and symptomatic in only 1 patient who experienced Grade 4 diarrhea. Four patients experienced Grade 3 and 1 patient Grade 4 hematologic toxicity; the remaining Grade 3/4 toxicities were elevation of liver enzymes (n=8) and serum bilirubin (n=2), mainly related to disease progression.	**PR:** 2 (8%) **SD:** 11 (42%) **MST:** 21+ weeks, with 6 patients still alive at the time of this report	Institute of Medical Oncology (Berne, Switzerland) ❑ *Borner MM, etal, ASCO02, Abs. 2206:98b*

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Gemcitabine + raltitrexed Raltitrexed (3 mg/m²) was infused over 15 minutes followed by gemcitabine (1000 mg/m²) over 30 minutes on day 1. Gemcitabine (1000 mg/m²) alone was administered over 30 minutes on day 8, repeated on day 21 (one cycle = 21 days).	Phase II (completed 5/02) ➢Europe (Belgium) ❑ advanced pancreatic cancer ❑ 34 patients (locally advanced disease=5 and metastatic disease=29) **Eval Resp:** 34 patients **Eval Tox:** 34 patients	Grade 3 or 4 neutropenia and thrombocytopenia were observed in 30% and 9% of the patients, respectively, with one case of febrile neutropenia. Relevant nonhematologic toxicity (Grade 3/4) consisted of anorexia, abdominal pain, fatigue, vomiting and diarrhea (23%).	**PR:** 10 (29.4%) confirmed **SD:** 3 (12.5%) ≥24 weeks and 7 (20.5%) <24 weeks **PD:** 14 (41.2%) **OR:** 29.4%; median duration of response was 5.9 (range=2.5-9.1) months **MDR:** 5.9 (range=2.5-9.1) months **MST:** 7.5 months **Median TTP:** 2.8 months **6-month survival:** 56%	Multicenter ❑ *Van Laethem JL, etal, ASCO02, Abs. 547:137a*
Gemcitabine + raltitrexed Gemcitabine (1000 mg/m²) is administered on day 1 and 8 with raltitrexed (3.0 mg/m²) on day 1 of a 21 day cycle. Gemcitabine dosage is escalated by 200 mg/m² for each cohort up to a maximum dose of 1400 mg/m².	Phase I/II (ongoing 5/02)➢ Europe (UK) ❑ pancreatic cancer, locally advanced or metastatic ❑ 24 patients **Eval Resp:** 19 patients **Eval Tox:** 24 patients	Patients in cohort 2 experienced unexpected toxicity involving neutropenia (n=3), thrombocytopenia (n=1), infection (n=3) and asthenia and 10 serious adverse events. After the first 9 patients, raltitrexed dose was reduced to 2 mg/m² with no further gemcitabine dose escalation resulting in only one Grade 3 toxicity.	**SD:** 4 (21%) **OR:** 2 (10.5%) **PD:** 13 (68.5%) **1-year survival:** 32%	Multicenter ❑ *Michael A, etal, ASCO02, Abs. 675:169a*
Gemcitabine + oxaliplatin Gemcitabine (1500 mg/mg) as a 30-minute IV infusion is administered on days 1 and 8, followed 1 hour after by oxaliplatin (100 mg/mg) as a 2-hour IV infusion on day 1, every 3 weeks.	Phase II (ongoing 5/02)➢ Europe (Italy) ❑ inoperable locally advanced or metastatic pancreatic cancer ❑ 20 patients **Eval Resp:** 14 patients **Eval Tox:** 20 patients	Toxicities were Grade 2 (n=4) and Grade 3 (n=1) anemia, Grade 2 (n=5) and Grade 3 (n=1) thrombocytopenia, Grade 2 (n=3) and Grade 3 (n=1) neutropenia, and Grade 1/2 (n=9) nausea and vomiting. No neurotoxicity was observed.	**CR:** 1 (7.0%) **PR:** 2 (14.4%) **SD:** 7 (50.0%) **PD:** 4 (28.6%) **OR:** 15%	Gruppo Oncologico Italia Meridionale (GOIM) ❑ *Maiello E, etal, ASCO02, Abs. 2236:106b*
Gemcitabine + oxaliplatin Oxaliplatin (100 mg/m²) was administered IV over 2 hours on day 1, and gemcitabine (1000 mg/m²) IV over 30 minutes on days 1 and 8, on a 3-week cycle.	Phase II (completed 5/02)➢ USA ❑ unresectable locally advanced or metastatic adenocarcinoma of the pancreas ❑ 46 patients **Eval Resp:** 38 patients **Eval Tox:** 46 patients	Toxicity was modest comprising Grade 3 neutropenia (29%) and Grade 4 neutropenia (20%), and (Grade 3 thrombocytopenia (20%).	**CR:** 1 (2.6%) **PR:** 4 (10.5%) **SD:** 24 (63%) **OR:** 13% **MST:** 5.7 months (median follow-up was 7.6 months). **6-month survival:** 45.7%	Multicenter ❑ *Alberts SR, etal, ASCO02, Abs. 501:126a*
Gemcitabine + oxaliplatin Gemcitabine (1500 mg/m²) is administered as a 10-minute IV infusion followed by oxaliplatin (85 mg/m²) as a 2-hour IV infusion, on day 1, every 2 weeks.	Phase II (completed 6/03)➢ Europe (Spain) ❑ advanced pancreatic or ductal biliary adenocarcinoma ❑ 33 patients (pancreatic cancer=25 and ductal biliary carcinoma=8) **Eval Resp:** 33 patients **Eval Tox:** 33 patients	Hematologic toxicities were Grade 2 anemia (n=5, 15%), Grade 3/4 neutropenia (n=3) with febrile neutropenia (n=1) and Grade 3/4 thrombocytopenia (n=4, 12%). Nonhematologic toxicity was mild and included Grade 1/2 (n=20, 60%) and Grade 3 (n=1) sensitive neuropathy.	**PR:** 9 (27.3%); 4/8 (50%) ductal biliary carcinoma **SD:** 12 (36.4%) **OR:** 33.3 % **Median PFS:** 7.8 months at a median follow-up of 10+ months **MST:** 10.3 months	OncoCenter (Madrid, Spain) ❑ *Ciruelos EM, etal, ASCO03, Abs. 1469:366*

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Gemcitabine + 5-FU + oxaliplatin Gemcitabine was administered as a 30-minute infusion, followed after a 30-minute rest by oxaliplatin as a 2-hour infusion, and 5-FU, as a 24-hour infusion) on days 1, and 8, every 3 weeks. Dose level 1 comprised doses of 900/65/1500 mg/m^2, level 2 900/80/1500 mg/m^2, and level 3 1000/80/1500 mg/m^2, respectively.	Phase I (completed 6/03) ➢Europe (Germany) ❑ chemonaive, advanced or metastatic pancreatic, gallbladder, or biliary tract adenocarcinoma ❑ 11 patients **Eval Resp:** 8 patients **Eval Tox:** 8 patients	There was no DLT (0/3) at dose level 1. At dose level 2, 2/5 patients experienced DLT manifested as Grade 3 diarrhea (n=1), Grade 3 nausea and infection and Grade 4 anorexia (n=1); **MTD:** gemcitabine 900 mg/m^2, oxaliplatin 80 mg/m^2, and 5-FU 1500 mg/m^2	**PR:** 4 (50%) dose level 1=1 and dose level 2=3 **SD:** 2 (25%) dose level 1=1 and dose level 2=1 **PD:** 2 (25%) dose level 1=1 and dose level 2=1	Multicenter ❑ *Wagner AD, etal, ASCO03, Abs. 1298:323*
Gemcitabine + oxaliplatin + 5-FU + leucovorin Oxaliplatin (30 mg/m^2), leucovorin (20 mg/m^2), and 5-FU (500 mg/m^2) were administered on days 1-3, and gemcitabine (1000 mg/m^2) on days 2, 9, and 16. Treatment was repeated every 28 days.	Phase II (ongoing 6/03)➢ India ❑ advanced pancreatic cancer ❑ 10 patients (liver metastases=7, locoreigonal inoperable disease=3) **Eval Resp:** 10 patients	Thrombocytopenia <50,000/mm^3 necessitating delay in chemotherapy occurred in 2 patients; 1 patient developed neutropenic fever. No neurotoxicity or nephrotoxicity was observed.	**CR:** 1 (10%) **SD:** 2 (20%) **OR:** 30%	Sir Ganga Ram Hospital (New Delhi, India) ❑ *Aggarwal S, etal, ASCO03, Abs. 1338:333*
Gemcitabine + capecitabine Gemcitabine (1000mg/m^2) was administered weekly with capecitabine (1600 mg/m^2) daily for 3 weeks, every 4 weeks (n=6) or gemcitabine (1000 mg/m^2) weekly with capecitabine (1300 mg/m^2) daily for 2 weeks, every 3 weeks (n=6).	Phase II (begin 1/01, completed 12/02)➢USA ❑ metastatic pancreatic cancer ❑ 12 patients (chemotherapy naïve=11) **Eval Resp:** 12 patients **Eval Tox:** 12 patients	Grade 3 neutropenia (n=4) and and Grade 3 diarrhea (n=2); dose modification was required in 6 patients. There were no deaths or treatment-related Grade 4 toxicity.	**PR:** 4 (33.3%) **SD:** 7 (58.3%); a 50% decrease in CA19-9 level was noted in 5 **MST:** 10 months **Median TTP:** 6.5 months **OS:** 7 patients were alive with a median follow up of 7.5 months	Roswell Park Cancer Institute (Buffalo, NY) ❑ *Melnyk M, etal, ASCO03, Abs. 1412:352*
Gemcitabine + celecoxib An initial dose of IV gemcitabine (750 mg/m^2) is administered at the rate of 10 mg/m^2/minute on days 1, 8, and 15, every 4 weeks. PO celecoxib (400 mg) is administered in divided doses continuously starting two days after the first dose of gemcitabine. Serial blood samples are taken during first and second dose of gemcitabine and the cellular gemcitabine triphosphate (dFdCTP) levels from peripheral blood mononuclear cells are analyzed.	Phase I (ongoing 5/02)➢ USA ❑ advanced, unresectable, chemotherapy-naïve, pancreatic cancer ❑ 6 patients (to date) **Eval Resp:** 3 patients **Eval Tox:** 3 patients	There were 3 episodes of Grade 3/4 granulocytopenia, and 1 of Grade 3 thrombocytopenia; celecoxib and gemcitabine may be more myelosuppressive than gemcitabine alone	**PR:** 1 (34%) after 8 weeks of treatment **SD:** 2 (66%)	M. D. Anderson Cancer Center (Houston, TX) ❑ *Xiong HQ, etal, ASCO02, Abs. 448:113a*

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Gemcitabine + celecoxib IV gemcitabine (1000 mg/m^2) is administered weekly for 7 weeks with concurrent daily oral celecoxib (400 mg) *bid*. Daily oral low-dose aspirin (81 mg) is administered throughout the study as a precaution for increased risk of thrombotic events. Responders or those with stable disease continued treatment with IV gemcitabine (1000 mg/m^2), weekly, for 3 weeks and concurrent oral celecoxib.	Phase II (ongoing 6/03) ➢USA ❑ advanced pancreatic cancer ❑ 20 patients (locally advanced disease=6, metastatic disease=14) **Eval Resp:** 18 patients **Eval Tox:** 20 patients	Toxicities included neutropenia (35%) and anemia (20%); there were no unexpected drug-related adverse events	**PR:** 3/18 (17%) **SD:** 4/18 (22%)	Arizona Cancer Center (Tucson, AZ), Sarah Cannon Cancer Center (Nashville, TN), Indiana University Cancer Center (Indianapolis, IN), University of Arizona Health Sciences Center (Phoenix, AZ) ❑ *Smith SE, etal, ASCO03, Abs. 1502:374*
Gemcitabine + UFT + levofolinic acid Gemcitabine (1250 mg/m^2) is administered on days 1 UFT (750 mg/m^2), daily, on days 1-14, and daily levofolinic acid (12.5 mg) every 12 hours. Courses are repeated every 28 days until disease progression or unacceptable toxicity.	Pilot study (begin 9/99, completed 3/01)➢Europe (Spain) ❑ locally advanced or metastatic pancreatic cancer ❑ 12 patients [locally advanced=3 (25%), metastastic=9 (75%)] **Eval Resp:** 12 patients **Eval Tox:** 12 patients	Toxicity was mild and treatment was well tolerated. There were 2 cases of Grade 3/4 toxicity (Grade 3 diarrhea=1 and Grade 3 thrombocytopenia=1).	**PR:** 1 (8%) **SD:** 5 (42%) **OR:** 6 (50%) **MST:** 8 (range= 3-55) months **Median TTP:** 6 (range=2-44) months	Corporacio Sanitaria Parc Tauli (Sabadell, Spain) ❑ *Fernandez-Morales LA, etal, ASCO02, Abs. 2362:137b*
Gemcitabine + UFT + levofolinic acid Gemcitabine (1250 mg/m^2) was administered as a 30-minute infusion weekly for 2 consecutive weeks, plus oral UFT (750 mg/m^2/day) for 21 consecutive days, and levofolinic acid (25 mg/day) for 28 days, in 6 cycles every 28 days. Response was evaluated every 3 cycles.	Phase II (ongoing 6/03)➢ Europe (Spain) ❑ advanced pancreatic cancer ❑ 15 patients; 1 (7%) patient was not assessable **Eval Resp:** 15 patients		**PR:** 3 (20%) **SD:** 2 (13%) **PD:** 9 (60%) **OR:** 20%	ACROSS Cooperative Group (Spain) ❑ *Saigi E, etal, ASCO03, Abs. 1366:340*
Gemcitabine + UFT Gemcitabine (1200 mg/m^2) is administered as a 120-minute infusion weekly for 3 consecutive weeks, plus oral UFT (400 mg/m^2/day), in 2-3 daily doses, on days 1 to 21, every 28 days.	Phase II (completed 5/02)➢ Europe (Spain) ❑ advanced, chemotherapy-naïve, pancreatic cancer ❑ 43 patients [locally advanced disease=8 (19%) and distant metastases=35 (81%)] **Eval Resp:** 43 patients **Eval Tox:** 43 patients	Toxicities included neutropenia in 9 patients (21%), anemia in 5 (12%), thrombocytopenia in 4 (9%), diarrhea in 4 (9%) and asthenia in 1 (2%).	**CR:** 2 (5%) **PR:** 12 (28%) **SD:** 13 (30%) **PD:** 16 (36%) **OR:** 33%; 25 (64%) with clinical benefit **Median TTP:** 6 months **MST:** 11 months	Multicenter ❑ *Gonzalez-Baron M, etal, ASCO02, Abs. 601:151a*
Gemcitabine + UFT Gemcitabine (1000 mg/m^2) was administered once weekly for 3 consecutive weeks and oral UFT (390 mg/m^2/day) in three divided doses on days 1 to 14, every 28 days. Objective tumor response was evaluated after two courses of chemotherapy.	Phase II (begin 12/00, completed 9/02)➢Korea ❑ metastatic pancreatic adenocarcinoma ❑ 22 patients **Eval Resp:** 22 patients **Eval Tox:** 22 patients	This regimen was well tolerated; most common Grade 3/4 toxicities were neutropenia (18%), anemia (4.5%), and diarrhea (4.5%).	**PR:** 5 (20.8%) **SD:** 4 (18.2%) **OR:** 22.7% **PD:** 13 (59.1%) **Median TTP:** 4.2 (range= 0.9-13.6) months **OS:** 5.8 (range=5-13.6) months	Samsung Medical Center, Sungkyunkwan University School of Medicine (Seoul, Korea) ❑ *Lee J, etal, ASCO03, Abs. 1357:338*

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Gemcitabine + irinotecan (CPT-11) CPT-11 (100 mg/m^2) is administered as a 90-minute IV infusion followed by gemcitabine (1000 mg/m^2) as a 60-minutes IV infusion, both on days 1 and 8, every 3 weeks.	Phase II (ongoing 6/03)➢ Europe (Spain) ❑ Stage III/IV pancreatic cancer ❑ 22 patients (Stage III=14% and Stage IV=86%) **Eval Resp:** 19 patients **Eval Tox:** 22 patients	Grade 3/4 toxicities were thrombopenia (16%), anemia (4%), leucopenia (3%), neutropenia (2%), nausea (4%), diarrhea (3%), malaise (3%), asthenia (2%) and abdominal pain (2%).	**PR:** 5 (26.3%) **SD:** 6 (31.5%) **PD:** 8 (42.1%) **OR:** 26%; clinical benefit was seen in 8 (36%) patients	Multicenter ❑ *Ga Alfonso P, etal, ASCO03, Abs. 1449:361*
Gemcitabine + irinotecan (CPT-11) According to the protocol, patients were treated with repeated 21-day cycles at starting doses of IV gemcitabine of 1,000 mg/m^2 over 30 minutes followed immediately by IV irinotecan (100 mg/m^2) over 90 minutes, both on days 1 and 8	Phase II (completed 02)➢ USA ❑ advanced, unresectable or metastatic pancreatic cancer, first-line ❑ 45 patients **Eval Resp:** 45 patients **Eval Tox:** 45 patients	Severe toxicities were uncommon and primarily limited to Grade 4 neutropenia (2%) and vomiting (2%), and Grade 3 diarrhea (7%).	**PR:** 9 (20%) confirmed **OR:** among 44 patients with baseline CA 19-9 determinations, CA 19-9 decreased during therapy in 22 (50%) and were reduced by ≥50% in 13 (30%) **MST:** 5.7 (range=0.4 to 19.4+) months **1-year survival:** 27%	H. Lee Moffitt Cancer Center, University of South Florida (Tampa, FL) ❑ *Rocha Lima CM, J Clin Oncol, 1 Mar 2002; 20(5): 1182-91*
Gemcitabine + irinotecan According to the protocol, patients were treated with repeated 21-day cycles at starting doses of IV gemcitabine of 1,000 mg/m^2 over 30 minutes followed immediately by IV irinotecan (100 mg/m^2) over 90 minutes, both on days 1 and 8	Phase II (completed 02) ➢USA ❑ advanced, unresectable or metastatic pancreatic cancer, first-line ❑ 45 patients **Eval Resp:** 45 patients **Eval Tox:** 45 patients	Severe toxicities were uncommon and primarily limited to Grade 4 neutropenia (2%) and vomiting (2%), and Grade 3 diarrhea (7%).	**PR:** 9 (20%) confirmed **OR:** among 44 patients with baseline CA 19-9 determinations, CA 19-9 decreased during therapy in 22 (50%) and were reduced by ≥50% in 13 (30%) **MST:** 5.7 (range=0.4 to 19.4+) months **1-year survival:** 27%	H. Lee Moffitt Cancer Center, University of South Florida (Tampa, FL) ❑ *Rocha Lima CM, J Clin Oncol, 1 Mar 2002; 20(5):1182-91*
Gemcitabine + 13-cis-retinoic acid Gemcitabine (1,000 mg/m^2) is administered on days 8, 15, 22 plus 13-cis-retinoic acid (1 mg/kg), PO, on days 1-14.	Phase II (ongoing 6/03)➢ Europe (UK) ❑ unresectable, locally advanced or metastatic pancreatic cancer or cholangiocarcinoma ❑ 21 patients **Eval Resp:** 12 patients **Eval Tox:** 12 patients	Grade 3 toxicity (n=5) was primarily thrombocytopenia, neutropenia, and constipation.	**SD:** 4 (33.3%) **PD:** 8 (50.0%)	Multicenter ❑ *Maraveyas A, etal, ASCO03, Abs. 1386:345*
Gemcitabine; peripheral blood progenitor cell (PBPC) support Escalating doses of IV gemcitabine at a fixed dose rate of 10 mg/m^2/minute were administered with support from PBPC +G-CSF (5 mcg/kg/day) for 5 days. PBPC were mobilized with G-CSF (10 mcg/kg/day) for 5 days. Starting dose of gemcitabine is 3000 mg/m^2, escalated by 500 mg/m^2 every 3 patients. Treatment is administered every 14 days for 8-10 courses.	Phase I (ongoing 6/03)➢ Europe (Italy) ❑ advanced pancreatic carcinoma ❑ 16 patients (with locally advanced disease=3 and metastatic disease=13 **Eval Resp:** 16 patients **Eval Tox:** 16 patients	There were no Grade 4 hematologic or nonhematologic toxicity	**CR:** 1 (6.2%) **PR:** 3 (18.7%) **SD:** 2 (12.5%) **PD:** 8 (50.0%) **OR:** 24.9%	Multicenter ❑ *Bengala C, etal, ASCO03, Abs. 1479:368*

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Gemcitabine; (IEORT) + EBRT Gemcitabine (600 mg/m^2) by a 30-minute IV infusion is administered 24 hours prior to IORT, which is administered at 28 Gy and directed to the pancreatic tumor and regional lymph nodes. Eight days after IORT, concurrent 27 Gy EBRT (1.8 Gy/fraction x 15 fractions) and twice-weekly gemcitabine (40 mg/m^2 and 80 mg/m^2/week) for three weeks are administered. After the completion of concomitant therapy, patients whose disease did not progress are treated with weekly gemcitabine (1000 mg/m^2) on days 1, 8, 15, followed by a week rest.	Phase II (begin 10/01, ongoing 12/02)➢Japan ❑ metastatic pancreatic cancer ❑ 7 patients (Stage IVa=5 and Stage IVb=1) **Eval Resp:** 7 patients **Eval Tox:** 7 patients	There were 2 cases of Grade 3 hematologic toxicity	**CR:** 1 (14.3%) **PR:** 2 (28.6%) **SD:** 4 (57.1%) **OS:** 5 patients were alive without radiographic evidence of disease progression at a median follow-up of 5.5 months	Kobe City General Hospital (Japan); Institute of Biomedical Research and Innovation (Kobe, Japan) ❑ *Wada M, etal, ASCO03, Abs. 1256:313*
Gemcitabine; RT Gemcitabine (250 mg/m^2) as a 30-minute IV infusion was administered weekly for 6 weeks with RT, delivered concurrently as a single course of 50.4 Gy in 28 fractions. One month after completion of CRT, maintenance chemotherapy with gemcitabine (1000 mg/m^2) was administered weekly for 3 weeks with a 1-week rest until disease progression or unacceptable toxicity.	Phase II (begin 7/01, completed 03)➢Japan ❑ unresectable, locally advanced pancreatic cancer ❑ 42 patients **Eval Resp:** 40 patients	Grade 3/4 hematologic toxicity occurred in 52% and 5% of patients, respectively while Grade 3/4 nonhematologic toxicity in 31% and 33% of patients, respectively. There was one death attributed to duodenal bleeding and sepsis, and 4 patients discontinued CRT because of elevated transaminase (n=2), duodenal bleeding (n=1) and general fatigue (n=1). This regimen has an acceptable toxicity profile but may have more frequent acute toxicity compared with conventional CRT with 5-FU.	**PR:** 9 (21%) **SD:** 26 (62%) **MST:** 9.5 months **1-year survival:** 29% **6-month survival:** 88% after a median follow-up of 6 months	National Cancer Center Hospital (Tokyo, Japan) ❑ *Okusaka T, etal, ASCO03, Abs. 1203:300, and ASCOGI04, Abs. 93*
Gemcitabine; RT Gemcitabine (125 mg/m^2) was administered weekly as a 24-hour infusion for 5 consecutive weeks with concurrent EBRT (45Gy in 25 fractions).	Phase II (begin 6/99, completed 12/02)➢Korea ❑ locally advanced pancreatic cancer ❑ 23 patients **Eval Resp:** 19 patients **Eval Tox:** 23 patients	Grade 3/4 hematologic toxicity was neutropenia in 4 (17.4%) and thrombocytopenia in 5 (21.7%); nonhematologic toxicities included fatigue, diarrhea, nausea and vomiting which were not significant.	**CR:** 1 (5.3%) **SD:** 7 (36.8%) **OR:** 6/19 (31.6%) **PD:** 6 (31.6%) **Median PFS:** 6 (range=3-40+) months) **MST:** 10 months	Samsung Medical Center, Sungkyunkwan University School of Medicine (Seoul, Korea) ❑ *Park JO, etal, ASCO03, Abs. 1427:355*
Gemcitabine; RT Gemcitabine (1000 mg/m^2) was administered weekly for 3 weeks during RT. The starting RT dose of 30 Gy was increased in 5 fractions at 2.0 Gy increments.	Phase I (begin 4/01, completed 6/02)➢Japan ❑ unresectable, locally advanced, pancreatic cancer ❑ 12 patients **Eval Tox:** 12 patients	Treatment was well tolerated and all patients completed protocol. There were 3 Grade 3 neutropenia, 1 Grade 3 thrombocytopenia, and 2 Grade 2 nonhematologic toxicity.		Osaka Medical Center for Cancer & CVD (Osaka, Japan) ❑ *Ioka T, et al, ASCO03, Abs. 1512:376*

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Gemcitabine; hypofractionated radiation therapy (HRT) HRT (total dose, 45 Gy, 3Gy/day) was administered followed by gemcitabine (1g/m^2) on day 1, 8 and 15 of a 28-day cycle. Gemcitabine was started at least one week after completion of HRT, and after hematologic toxicities recovered to Grade 1.	Phase II (completed 6/03)➢ Japan ❑ locally advanced pancreatic cancer ❑ 16 patients **Eval Resp:** 14 patients **Eval Tox:** 15 patients	Severe toxicities (Grade 3/4) included GI bleeding (6/15), GI ulcer (4/15), anemia (5/15), neutropenia (3/15), thrombocytopenia (2/15), and nausea/vomiting (2/11)	**PR:** 4 (29%) **SD:** 9 (64%) **Median PFS:** 12 months **MST:** 11.8 months	National Cancer Center Hospital East (Kashiwa, Japan) ❑ *Nagase M, etal, ASCO03, Abs. 1348:336*
Gemcitabine; RT Gemcitabine (400 mg/m^2) is administered in 6 weekly cycles during RT, starting on the 1st day of radiation. RT (50.4 Gy in 28 fractions) is delivered to the primary region and to the lymphatics. Patients are assessed for radiological response, overall survival and toxicity.	Phase II (begin 1/99, completed 3/01)➢Turkey ❑ unresectable, locally advanced pancreatic cancer ❑ 20 patients (unresectable locally advanced disease=13 and potentially curatively resected disease=7) **Eval Resp:** 13 patients **Eval Tox:** 20 patients	Hematologic toxicity was mainly neutropenia. Other toxicities were nausea (n=5, 25%) and Grade 3 vomiting (n=2, 10%). All patients experienced abdominal discomfort during treatment.	**PR:** 5 (38.5 %) **SD:** 3 (23.1 %) **MST:** 20.3 (range=11.7-32.5) months for 7 patients after potentially curative resection, and 12.3 (range= 2-22.6) months for 13 inoperable cases	Hacettepe University (Ankara, Turkey) ❑ *Zorlu F, etal, ASCO02, Abs. 2300:122b*
Gemcitabine; RT RT was administered at the initial dose of 24 Gy in 1.6 Gy fractions, increased by 0.2 Gy increments, for 3 weeks. A fixed dose of gemcitabine (1000 mg/m^2) was administered weekly for 3 weeks. Following gemcitabine/RT, 1 additional cycle of gemcitabine is delivered prior to toxicity assessment.	Phase I (begin 11/97, ongoing 10/02)➢USA ❑ resectable pancreatic cancer ❑ 29 patients (following Whipple resection=27, following distal pancreatectomy=1, and following incomplete resection of a tumor involving the organ body=1) **Eval Tox:** 29 patients **Eval Res:** 29 patients	Among 4 cases of DLT, there were 3 with Grade 3 vomiting requiring hospitalization and 1 fatality secondary to pneumonia/ sepsis. At the final RT dose level (42 Gy), 2/2 patients experienced GI DLT. Accrual continuesat dose level 39 Gy.	**MST:** 16.2 month **PD:** isolated local/regional progression occurred in 2 (6.9%) while distant progression in 17 (58.6%) patients (7 with concurrent local/regional progression)	University of Michigan (Ann Arbor, MI), William Beaumont Hospital (Royal Oak, MI) ❑ *Allen AM, etal, ASCO02, Abs. 549:138a*
Gemcitabine; RT Gemcitabine was administered at a twice-weekly dose of 40mg/m^2 (80 mg/m^2/wk) by a 30-minute IV infusion on each Monday and Thursday with RT directed to the pancreatic tumor bed and regional lymphatics for a total dose of 50.4 Gy. At the completion of the concurrent therapy, patients without disease progression were treated with weekly gemcitabine (1000 mg/m^2) on days 1, 8 and 15 followed by a week rest, for 2 cycles.	Phase II (begin 6/99, ongoing 6/03)➢USA, Europe (France) ❑ previously resected pancreatic cancer ❑ 37 patients **Eval Resp:** 32 patients **Eval Tox:** 32 patients	Toxicity was primarily hematologic; there were 2 cases of Grade 4 toxicity (perforations within the irradiated volume).	**MST:** not reached in patients who completed therapy (n=32) **OS:** among 30 patients who completed all therapy, with a median follow-up of 14 months, 13 (43%) are alive without evidence of disease progression	Comprehensive Cancer Center of Wake Forest University; Hospitaux de Lyon (France) ❑ *Blackstock AW, etal, ASCO03, Abs. 1069:266* ❑ Protocol ID: CCCWFU-57198; NCI-104

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Gemcitabine; RT Gemcitabine (1000 mg/m^2) was administered on day 1, day 8 and day 15 every 28 days for two courses within 8 weeks after surgery and was followed by gemcitabine (300 mg/m^2) weekly plus concurrent continuous RT (45 Gy/25 fractions, 1.8 Gy/fractions).	Phase II (completed 6/03)➢ Europe (Belgium) ❑ Stage II/III curatively resected pancreatic cancer ❑ 30 patients **Eval Resp:** 30 patients **Eval Tox:** 30 patients	9/25 (36%) patients experienced Grade 3/4 hematologic toxicities (neutropenia=8, anemia=1) and 3/25 (12%) nonhematologic toxicity (diarrhea)	**PD:** 7 (23%) **DFS:** 7 months **OS:** 27/30 patients were alive after a median follow-up of 8 months while 3 patients died from progressive disease	Multicenter ❑ *Anne D, etal, ASCO03, Abs. 1133:282*
Gemcitabine; EBRT + surgery Treatment consisted of 7 weekly infusions of gemcitabine (400 mg/m^2) and 30 Gy of EBRT (3 Gy/Fx), Monday to Friday over 2 weeks beginning 3 days after the first dose of gemcitabine. Patients underwent complete restaging 4-6 weeks after the last dose of gemcitabine. Those without disease progression and with acceptable performance status underwent surgery.	Phase II (ongoing 5/02)➢ USA ❑ resectable pancreatic cancer ❑ 86 patients **Eval Resp:** 86 patients **Eval Tox:** 86 patients	Toxicity, although frequent, was manageable and did not prevent successful surgery; 47 (55%) patients required either drug dose reduction (n=11) or missed 1 or more doses (n=36) because of GI (34%) or hematologic (53%) toxicity, or endobiliary stent occlusion (12%); 37 (43%) patients were hospitalized prior to surgery; there were no CRT-related deaths.	83 patients were restaged following CRT (3 await re-staging); 12 (14%) patients did not undergo surgery, 7 because of disease progression at restaging; among 71 (86%) patients who underwent laparotomy, metastatic disease was found in 10 (12%); successful pancreaticoduodenectomy was performed in 61/83 (73%) patients	M. D. Anderson Cancer Center (Houston, TX) ❑ *Wolff RA, etal, ASCO02, Abs. 516:130a*
5-Fluorouracil (5-FU)				
5-FU + cisplatin 5-FU (160mg/m^2/day) is continuously infused over 24 hours using an implantable port and cisplatin (3mg/m^2/day) is infused for half an hour. The administration schedule consisted of 5-FU for 7 consecutive days and cisplatin for 5 days followed by a 2-day rest for each 4 weeks according to response and tolerance.	Phase II (begin 2/95, completed 3/01)➢Japan ❑ advanced or recurrent pancreatic cancer ❑ 39 patients (locally advanced=8, metastatic=23, recurrent=8) **Eval Resp:** 39 patients **Eval Tox:** 39 patients	Anorexia, the most common toxicity, occurred in 15.4% of patients. There was no Grade 3/4 toxicity. Hematologic toxicity (up to Grade 2) was observed in 7.7% of patients.	**PR:** 11 (2.9%) **SD:** 19 (48.7%) **OR:** clinical benefit was reported in 48.7% **MST:** 6.5 months **1-year survival:** 26% **2-year survival:** 8%	Kochi Municipal Central Hospital (Japan) ❑ *Tsuji A, etal, ASCO02, Abs. 628:158a*
5-FU + oxaliplatin + folinic acid Following failure with gemcitabine first-line therapy (with or without a farnesyltransferase inhibitor), IV 5-FU (2600 mg/m^2) over 24 hours/FA (500 mg/m^2) over 30 minutes were administered on days 1, 8, 15, 22 in combination with IV oxaliplatin (85mg/m^2) infused over 3-4 hours on day 8 and 22. No therapy was administered on days 29 and 36. Patients remained on treatment until progression; all treatments were administered on an outpatient basis.	Phase II (begin 11/00, completed 11/01)➢Europe (Germany) ❑ advanced, refractory, pancreatic cancer ❑ 23 patients (Stage IVa=1 and IVb=22) **Eval Tox:** 23 patients	The regimen was tolerated with moderate hematotoxicity (Grade 1/2). Grade 3 nausea/emesis occured in 2 patients. Grade 1/2 neurotoxicity was common with reversible Grade 3 in 2 patients.	**OS:** 12.5+ (range=3.5+ to 44.5+) months since primary diagnosis, with 17/23 (73.9%) patients alive at the time of this report	Charité Campus Virchow-Klinikum (Berlin, Germany) ❑ *Pelzer U, etal, ASCO02, Abs. 684:172a*

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5-FU + leucovorin + mitomycin C + dipyridamole Continuous infusion of 5FU (200mg/m^2/day) x 4 weeks, followed by 1 week rest, IV leucovorin(30mg/m^2) *q* week, IV mitomycin C (10 mg/m^2) not to exceed 15 mg total per dose, every 6 weeks times 4 doses, and dipyridamole (75 mg orally) *qid*.	Phase II (begin 9/97, completed 6/01)➢USA ❑ nonmetastatic, locally advanced, unresected, pancreatic cancer ❑ 49 patients **Eval Resp:** 49 patients **Eval Tox:** 49 patients	DLT was stomatitis. Grade 3 and 4 toxicities included anemia, diarrhea, fatigue, weakness, stomatitis, nausea and vomiting. Hemolytic uremic syndrome was seen in 2 patients both successfully treated. There were no treatment related fatalities.	**CR:** 2 (4.1%) **PR:** 8 (16.3%) 4 were not confirmed by a required second scan **OR:** 22% **MST:** 14 (range= to 45+) months *Abs. 544:137a*	UCLA (Los Angeles, CA), Saint Vincent's Cancer Care Center (New York, NY), M. D. Anderson Cancer Center (Houston, TX) ❑ *Isacoff WH, etal, ASCO02,*
5-FU + folinic acid + cisplatin + streptozocin A novel combination (FCiSt) of bolus 5-FU (500 mg/m^2), folinic acid (45 mg), cisplatin (70 mg/m^2), and streptozocin (1000 mg/m^2) was administered every 21 days as an outpatient basis. A total of 133 cycles were administered; median number of cycles was 6 (range=2-12).	Phase II (begin 96, completed 03)➢Europe (UK) advanced pancreatic neuroendocrine tumors ❑ 20 patients (liver metastases=16, locoregional lymphadenopathy=5, lung metastases=2, bone metastases=2, and subcutaneous deposits=1; gastrin tumor=5, insulin=1 glucagon=2,VIP + gastrin=1; 13 (65%) patients had elevated serum chromogranin B) **Eval Resp:** 20 patients **Eval Tox:** 20 patients	Grade 3/4 toxicities were neutropenia 4/20 (16%), thrombocytopenia 1/20 (5%), vomiting 4/20 (20%), fatigue 1/20 (5%) and diarrhea 1/20 (5%). There was only one episode of neutropenic sepsis and no treatment-related deaths. Grade 2 neurotoxicity occurred in 3 (15%) patients with 2 requiring cisplatin dose reduction. Grade 1 nephropathy occurred in 2 (10%) patients requiring cessation of cisplatin and change to carboplatin.	**PR:** 8 (40%) **SD:** 6 (30%) **PD:** 6 (30%) **Median PFS:** 15.1 months	Royal Free Hospital (London, UK) ❑ *Sarker D, etal, ASCOGI04*, Abs. 100*
5-FU + mitomycin C; neoadjuvant chemoradiation; pancreatectomy Radiotherapy (5040 cGy) plus 5-FU (1000 mg/m^2/day) were administered on days 2-5 and 28-32 and mitomycin C (10 mg/m^2) on day 2. Neoadjuvant chemoradiation converted locally advanced unresectable adenocarcinoma of the pancreas to resectable disease in 3/11 (27%) patients.	Phase II (completed 5/02)➢USA ❑ locally advanced pancreatic cancer ❑ 16 patients **Eval Resp:** 11 patients	Among 3 patients treated surgically, 1 died perioperatively	**MST:** 5.7 (resected=10.8 and unresected= 5.2 months) **5-year survival:** resected =25% unresected=0% **OS:** 1 patient with a pathologic CR was alive and free of disease 98 months after treatment; median follow-up for the entire group was 7.5 (range=0-98) months; among 3 operated patients 2 died of regional and distant disease 6 and 42 months after resection	Roswell Park Cancer Institute (Buffalo, NY) ❑ *Chu QD, etal, ASCO02, Abs. 2304:123b*
5-FU + cisplatin; RT + surgery Radiation (50 Gy) is administered within 5 weeks concurrent to continuous infusion of 5 FU (300 mg/m^2/day) 5 days/week, every 5 weeks. Cisplatin (20 mg/m^2/day) administered on days 1-5 and 29-33 and surgical resection performed between week 9 and 11. Those patients without disease progression underwent surgery	Phase II (begin 1/98, completed 6/03)➢Europe (France) ❑ resectable pancreatic cancer ❑ 41 patients **Eval Resp:** 40 patients **Eval Tox:** 40 patients	Grade 4 hematologic toxicity (n=4), 1 died of late sepsis 2 months post-surgery	**Median TTP:** disease progression during the 9-11 week preoperative period was rare (12%); 63% of patients underwent a potentially curative resection	Multicenter ❑ *Mornex FM, etal, ASCO02, Abs. 2344:133b; ASCO03, Abs. 1165:290* ❑ protocol ID: FFCD 9704-SFRO

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5-FU; intraoperative RT (IORT) and conformal EBRT Treatment consisted of IORT (25 Gy), followed by EBRT (40 Gy in 20 fractions, 5 times/week) and protracted 5-FU infusion (200 mg/m^2) after 2 to 4 weeks.	Phase II (completed 5/02)➢ Japan ❑ unresectable, locally advanced, pancreatic cancer ❑ 30 patients (metastatic cancer=11) **Eval Resp:** 30 patients **Eval Tox:** 28 patients	Grade 3/4 in 15/28 (53.6%) patients, including anorexia, nausea, vomiting, fatigue, leukopenia and/or transaminase elevation.	**PR:** 7 (23.3%) **OR:** 25.0%. (primary tumor) **MST:** 7.9 months for all 30 patients (MST of 19 patients without cancer spread in the abdominal cavity was 12.8 months and that of 11 with cancer spread was 6.8 months) **2-year survival:** 9.6%.	National Cancer Center Hospital East (Kashiwa, Japan) ❑ *Furuse J, etal, ASCO02, Abs. 666:167a*
5-FU; EBRT Chemotherapy consisted of 5-FU (1000 mg/m^2), administered as a 5-hour CI, once weekly, and EBRT (total dose 50 Gy; 2 Gy/day) delivered to the pancreas, concurrently, for 5-6 weeks.	Phase I (completed 5/02)➢ Japan ❑ advanced, treatment-naïve pancreatic cancer with liver metastasis ❑ 17 patients (no distant metastases on CT staging except to the liver) **Eval Resp:** 16 patients **Eval Tox:** 16 patients	Nausea and vomiting were the most common toxicity; there were 2 cases of =/>Grade 3 toxicity (nausea and vomiting); 4 patients developed gastroduodenal ulcers.	**PR:** 7 (41%) **MST:** 4.5 months **1-year survival:** 11.8%	National Cancer Center Hospital East (Kashiwa, Japan) ❑ *Ishii H, etal, ASCO02, Abs. 2281:117b*
Docetaxel				
Docetaxel; RT Four weekly doses of docetaxel by 1-hour IV infusion with 40 Gy of ERBT for 4 weeks. Patients who were stabilized or in response were treated 2 additional cycles of docetaxel with a boost of radiotherapy (10 Gy). Doses were escalated at 10 mg/m^2 increments in successive cohorts of 3 patients until the MTD.	Phase I (completed 5/02)➢ Europe (France) ❑ locally advanced, inoperable, pancreatic adenocarcinoma ❑ 13 patients **Eval Resp:** 11 patients **Eval Tox:** 11 patients	The most common toxicities were nausea, vomiting, asthenia and abdominal pains. Except for one patient, they were all reversible and do not exceed Grade 3. Hematologic toxicity was mild and has not required treatment interruption.	**SD:** 4 (36.4%)	Institut Paoli Calmettes (Marseille, France), Centre Val d'Aurelle (Montpellier, France) ❑ *Viret F, etal, ASCO02, Abs. 660:166a*
Oxaliplatin				
Irinotecan + oxaliplatin	Phase II (begin 1/00, completed 10/01)➢Italy ❑ advanced, pretreated pancreatic cancer ❑ 25 patients with histologically or cytologically confirmed pancreatic carcinoma, previously treated with at least one gemcitabine-containing regimen **Eval Resp:** 25 patients **Eval Tox:** 25 patients	Therapy was well tolerated with low incidence of Grade 3-4 toxicity (1 Grade 3 and 1 Grade 4 neutropenia, 1 Grade 3 neurotoxicity and 1 Grade 3 diarrhea).	**PR:** 1 (4%) who underwent radical surgery **OR:** 6 (24%) experienced clinical benefit **MST:** from start of regimen and from diagnosis was 5.6 and 11.4 months, respectively	Azienda di Ospedaliera C. Poma (Mantova, Italy), Oncology Department (Verona, Italy) ❑ *Cantore M, etal, ASCO02, Abs. 2197:96b*

Legend: ***DFS:*** *disease-free survival;* ***MDR=****median duration of response;* ***MST:*** *median survival time;* ***OR:*** *overall response (CR + PR);* ***PFS:*** *progression-free survival;* ***PR:*** *partial response;* ***SD:*** *stable disease;* ***TTP:*** *time-to-progression; chemoradiotherapy (CRT)*

Source: NEW MEDICINE's Oncology KnowledgeBASE (nm|OK), February 2004

Arsenic trioxide (Trisenox; Cell Therapeutics) blocks proliferation and induces apoptosis in human pancreatic cancer cells at low, nontoxic concentrations. The agent induced apoptosis in pancreatic cancer cells by activation of the caspase cascade via the mitochondrial pathway, GADD45 and GADD153 expression, and by modifying cell-cycle progression and changes in several cycle-regulating proteins (Li X, etal, Pancreas, Aug 2003;27(2):174-9).

However, despite promising *in vitro* data, arsenic trioxide did not demonstrate clinical activity in a phase II clinical trial in patients with locally advanced or metastatic PDAC that did not respond to gemcitabine. In this multicenter phase II clinical trial (protocol ID: UCCRC-NCI-5839; NCI-5839), initiated at the University of Chicago Cancer Research Center, under study chair Hedy L. Kindler, MD, arsenic trioxide (0.3 mg/kg) was administered IV over 1 hour, daily, on days 1 to 5. Courses were repeated every 28 days in the absence of disease progression or unacceptable toxicity. CT scans were performed every 2 cycles. A total of 12 patients, enrolled between December 2002 and July 2003, were treated with 20 cycles (median=2; range=1-2) of arsenic trioxide. Because of disease progression, 2 patients were treated with only 1 cycle. There were no Grade 3/4 hematologic toxicities. Grade 1/2 anemia occurred in 50% of patients and Grade 1/2 leukopenia in 25%; 2 patients developed Grade 4 small bowel obstruction attributed to the cancer. Grade 3 toxicities included fatigue (17%), thrombosis (17%), nausea/vomiting (8%), diarrhea (8%), constipation (8%), hypocalcaemia (8%), and transaminitis (8%). Only 1 patient developed Grade 1 prolongation of the QTc interval. There were no objective responses. Median PFS was 49 days. MST has not yet been reached (Aklilu M, etal, ASCOGI04, Abs. 116).

Trisenox approved as second-line treatment for acute promyelocytic leukemia (APL) and currently marketed in the USA, Europe and elsewhere, recorded worldwide sales of $22.1 million in 2003.

Capecitabine is a 5-FU prodrug that is converted intracellularly to 5-FU by 3 enzymes acting in sequence. These enzymes exist at higher levels in cancer cells than in normal tissues, thus the drug is selectively activated mostly in tumor cells. Capecitabine was approved in the USA in April 1998 as third line treatment of metastatic breast cancer, refractory to both paclitaxel and an anthracycline-based regimen. Since then the drug was also approved shore as first line treatment of metastatic colorectal cancer in 2001. Worldwide sales of Xeloda were $381.5 million in 2003, up 29% from $284 million in 2002. USA sales were $185.9 million in 2003.

A 3-drug combination of gemcitabine, docetaxel and capecitabine (GTX regimen) may exert a significant antitumor effect in pancreatic cancer based upon synergism that is p53 independent (see Exhibit 1). A phase I clinical trial, conducted at Columbia University, the University of Virginia, and University of Maryland in advanced PDAC, investigated a similar combination consisting of two PO doses of capecitabine (1500-2000 mg/m^2/day) on days 1 to 14, IV gemcitabine (750-1000 mg/m^2), over 2 hours, followed by low dose docetaxel (30 mg/m^2) on days 4 and 11. Response was evaluated after 3 cycles in 32 patients (metastatic to liver=24, surgically inoperable=8). PR was achieved in 50% of patients with liver metastasis, while disease stabilized in 25% and progressed in 25%. In the inoperable group, there were 5/8 CR and disease stabilized in 3. MST had not been achieved at the time of this report. Major toxicities were Grade 2/3 diarrhea and hand-foot syndrome (40%), and Grade 2 neutropenia (30%). There were no deaths or febrile neutropenia (Fine RL, etal, ASCO02, Abs. 575:144a).

Two randomized, phase III clinical trials are ongoing comparing gemcitabine with or without capecitabine in patients with advanced PDAC. One trial (protocol ID: SWS-SAKK-44/00, CECOG/PAN-1.3.001, EU-20142) investigating the combination in advanced PDAC, is being conducted in Europe and Israel, and the other (protocol ID: CRUK-GEM-CAP, EU-20116) investigating this same combination in metastatic disease is being conducted in the UK.

Celecoxib (Celebrex; Pfizer), an inhibitor of cyclooxygenase 2 (COX-2), is being evaluated in combination with gemcitabine in the treatment of pancreatic cancer (Exhibit 1). For additional information on COX-2 in PDAC, see FO pp 1635, and 1647.

A more feasible application of celecoxib may be as a chemoprevenative in PDAC. COX-2 is an attractive target for chemoprevention owing to the reported overexpression of this enzyme in a variety of human malignancies and the widespread availability of selective, relatively nontoxic COX-2 inhibitors that can be administered orally. In the absence of reproducible serologic or molecular markers for the early diagnosis of PDAC, a reasonable recourse might be empiric chemoprevention, targeted at those determined to be at high risk because of familial pancreatic carcinoma kindreds, or germline mutations in genes such as p16, BRCA2, msh2, STK11, or PRSS1.

Cisplatin is a common constituent of combination chemotherapy in advanced/metastatic PDAC, and many combinations with this agent are under investigation (Exhibit 1).

In a phase I clinical trial, conducted at the University of Michigan Medical Center (Ann Arbor, MI), to determine MDT of cisplatin to be added to full dose gemcitabine and RT, 19 patients with in PDAC, were treated with gemcitabine (1,000 mg/m^2), administered over 30 minutes on days 1, 8, and 15, of a 28-day cycle, followed by cisplatin on days 1 and 15, at an initial dose level of 30 mg/m^2, escalated to a targeted dose of 50 mg/m^2. RT was added on cycle 1, day 1, in 2.4 Gy fractions for a total dose of 36 Gy. A second cycle of chemotherapy was planned following a 1-week rest. Acute DLT was seen in 4/8 patients at the 50 mg/m^2 cisplatin dose level. Cisplatin dose levels of 30 and

40 mg/m² were well tolerated without DLT. MST was 10.7 months overall, and 12.9 months for those without metastasis. In this trial, cisplatin at doses up to 40 mg/m² was safely added to full dose gemcitabine and conformal RT. Local and systemic disease control and survival in this study cohort supports further investigation of this regimen in this setting (Muler JH, etal, J Clin Oncol, 15 Jan 2004;22(2):238-43; Epub 9 Dec 2003).

In a prospective randomized trial of gemcitabine monotherapy versus gemcitabine plus cisplatin in the treatment of metastatic pancreatic cancer, the two approaches produced comparable modest response rates, but gemcitabine monotherapy was less toxic than the combination. In this trial, between January 1998 and June 2002, 46 patients with metastatic pancreatic cancer were enrolled with 25 treated with gemcitabine (1000 mg/m²), and 21 with gemcitabine and cisplatin (25 mg/m²), weekly, for 3 weeks, every 4 weeks. MST and median TTP were 4.6 months and 2.8 months, respectively, for gemcitabine and 5.6 months and 2.8 months with the combination. Clinical benefit, including pain control, improved performance status, and body weight gain, was seen in 36% patients treated with gemcitabine alone and in 29 % with the combination. Quality-adjusted-life-months survival was 5.6 ± 0.3 months for gemcitabine and 3.8 ± 0.2 months for the combination. There were 3 (12%) PR in the gemcitabine monotherapy group, and 2 (10%) in the combined treatment group. Toxicity, including Grade 3/4 neutropenia (8% versus 19%), anemia (8% versus 10%) or hospitalization days per month of survival (6.8 ± 2.2 versus 6.2 ± 1.6 days) were not significantly different between the two groups, but the combination resulted in a higher rate (24% versus 4%) of thrombocytopenia (Li C and Chao Y, ASCOGI04, Abs. 140).

Docetaxel (Taxotere; Aventis) has been evaluated in pancreatic cancer in combination with gemcitabine, or as part of a gemcitabine-based CRT regimen (Exhibit 1). Docetaxel is also being combined with novel agents for the treatment of pancreatic cancer, as described in part III of this report.

Worldwide sales of Taxotere were €1,362 ($1,539 million) in 2003, up 22.5%, while USA sales were €733 million ($828.3 million) in 2003, up 25.0% from 2002 levels.

Gemcitabine (Gemzar; Lilly) is a synthetic pyrimidine nucleoside with cytotoxic and randiosensitizing properties. The mechanism of gemcitabine radiosensitization is not completely understood, but it is thought to involve inhibition of ribonucleotide reductase, which, in turn, causes cell-cycle redistribution into S phase, and lowers the threshold for radiation-induced apoptosis. Gemcitabine has been shown to be a potent radiosensitizer in colorectal, pancreatic, and other solid tumor human cell lines. Gemcitabine produces radiation enhancement ratios that are higher than those of other established radiosensitizing agents, and this radiation enhancement occurs at low non-cytotoxic concentrations. Radiosensitization increases with dose and with duration of exposure to gemcitabine, and is greatest when exposure to gemcitabine precedes radiation. The primary radiosensitizing effect of gemcitabine seems to be associated with depletion of endogenous nucleotide pools; deoxyadenosine triphosphate reduction is particularly striking, even at the lowest concentrations of gemcitabine (Shewach DS and Lawrence TS, Semin Oncol, Oct 1996;23(5 Suppl 10):65-71).

Recent studies suggest that further improvement in patient outcomes may be achievable by optimizing drug delivery using pharmacokinetic principles such as fixed dose rate (FDR) infusion. It appears that FDR infusion increases intracellular triphosphate gemcitabine, which may result in a higher treatment benefit compared to standard infusion.

Gemzar was approved for the treatment of pancreatic cancer in May 1996, on the basis of two trials, a phase II clinical trial in patients with 5-FU-refractory disease, and a randomized, phase III clinical trial in chemotherapy-naive patients, in comparison with 5-FU. In both these trials, Gemzar (1000 mg/m²) was administered by a 30-minute IV infusion, weekly, for 7 weeks, followed by a week of rest. Subsequent treatment cycles consisted of weekly infusions for three weeks, followed by 1 week of rest.

In the multicenter, phase III clinical trial of gemcitabine, among 126 patients with >70% having metastatic PDAC (gemcitabine=71% and 5-FU=76%), 63 were treated with gemcitabine and 63 with 5-FU. MST with gemcitabine was 5.7 months compared with 4.2 months for 5-FU, an increase of 1.5 months, representing a relative improvement of 36%. In this trial, 23.8% of previously untreated patients experienced a clinical benefit response with gemcitabine, compared with 4.8% of those treated with 5-FU. There were no confirmed objective tumor responses with either treatment. Clinical benefit response as a primary study endpoint was incorporated in this trial because pancreatic tumor growth is extremely difficult to measure. This difference was statistically significant. The survival probability estimate for gemcitabine was 46% (n=30) and 5-FU 29% (n=19), for 6-months, and 18% (n=9) and 2% (n=2), respectively, for 1 year. Survival probability estimates project results from the clinical trials to the larger population of patients with PDAC.

In the phase II trial of gemcitabine monotherapy, conducted among 63 patients (metastatic disease=87%) refractory to 5-FU, MST was 3.9 months; 31% of patients survived for 6 months, and 4% for 1 year. In addition, clinical benefit response was observed in 27% of patients.

Gemcitabine monotherapy is used as a palliative in advanced PDAC. In a phase II clinical trial conducted in Germany between June 1995 and June 2000, in 4 community-based oncology group practices, 127 patients with advanced PDAC were treated on an outpatient basis to evaluate the feasibility, efficacy and toxicity of palliative chemotherapy/supportive care in this setting. A total of 94

(75%) patients underwent cytotoxic treatment, while 33 (25%) were treated with best supportive care (BSC) only. First line treatment consisted of gemcitabine (1000 mg/m^2) on days 1, 8, 15, every 29 days, in 81 (86%) patients, 5-FU in 8 (9%), CRT in 4 (4%) and RT only in 1 (1%) patient. Among 94 patients, 30 (5-FU=21, gemcitabine=6, various=3) were administered second line therapy. Based on a total of 1501 gemcitabine applications, toxicity was mild. Reversible Grade 3 and 4 hematotoxicity was seen in only 20 of the applications. Grade 3/4 asthenia syndrome occurred in 1% of all patients. Therapy-associated hospitalization was necessary in 4 patients (3%). A total of 111 (88%) patients (61 at home, 50 in hospital) died during the observation time. MST of all patients was 35 (range=4-238) weeks. MST of patients undergoing cytotoxic treatment was 41 (range=7-238) weeks. MST of patients managed by BSC was 21 (range=4-88) weeks. The 6-, 12-, 24, 36-month survival rate was 65%, 32%, 14% and 7%, respectively (Koeppler H, etal, ASCO02, Abs. 2620:200b).

Gemcitabine remains the standard of care for the treatment of advanced PDAC. In a systematic review and meta-analysis of all randomized trials, conducted by Eli Lilly investigators to explore if there is a survival benefit of chemotherapy treatment in advanced PDAC, data was gathered from 29 randomized trials involving 3,458 patients. In 9 trials, comparing 434 patients managed with BSC to 262 treated with a 5-FU-based combination regimen, average MST was 3.87 months with BSC compared to 6.38 months with 5-FU combinations, illustrating the relative superiority of chemotherapy. However, trials comparing 5-FU or other cytotoxics alone versus 5 FU-based combinations did not show any statistical differences and neither did various 5 FU-combinations when compared among themselves, with MST hovering at 4.38 to 5.23 months. However, one randomized single agent clinical trial comparing gemcitabine versus 5-FU, showed a hazard ratio (HR) of 0.56 favoring gemcitabine. Also, various new agents under development were inferior to gemcitabine, and gemcitabine-based combinations failed to demonstrate any additional benefit over gemcitabine monotherapy. Generally, gemcitabine appears to improve survival over 5-FU and other new agents (Fung MC, etal, ASCO03, Abs. 1155:288).

Worldwide sales of Gemzar were $1,021.7 million in 2003, up 17% from $874.6 million in 2002. The patent of Gemzar expires in May 2010.

Irinotecan, in combination with gemcitabine, was shown to be an active regimen in clinical trials in pancreatic cancer (Exhibit 1). In a randomized, multicenter, phase III clinical trial comparing efficacy and safety of gemcitabine and irinotecan (Camptosar; Pfizer), to gemcitabine alone in chemotherapy-naïve patients with locally advanced or metastatic PDAC, although there was no improvement in long-term outcome with the combination, it was well tolerated and more active in inducing tumor regression than gemcitabine alone. In this trial, in arm 1, gemcitabine (1000 mg/m^2) infused over 30 minutes was immediately followed by irinotecan (100 mg/m^2) on days 1 and 8 of 3-week cycles, while in arm 2, gemcitabine was administered for 7 out of 8 consecutive weeks in cycle 1 and on days 1, 8, and 15 of 4-week cycles thereafter. A total of 360 patients were randomized, 180 in each arm, stratified by performance status, extent of disease, and prior RT. Main patient characteristics were comparable with advanced/metastatic disease (arm 1=15%/82% and arm 2=13%/81%) and prior RT (arm 1=6% and arm2=7%).

Although the overall response rate was 16.1% in arm 1 compared to 4.4% in arm 2, time-to-treatment failure (2.9 months versus 2.7 months), TTP (3.4 months versus 3.0 months), MST (6.3 months versus 6.6 months), and 1-year survival (21% versus 22%) were all comparable in the two arms. Among 342 patients (arm 1=173, arm 2=169), adverse events included Grade 3/4 neutropenia (37.6% versus 32%), diarrhea (18.5% versus 1.8%), and vomiting (13.9% versus 8.3%); thromboembolic events were 15% versus 13.6%. The 60-day, all cause mortality was 17.9% versus 16% (Rocha Lima CMS, etal, ASCO03, Abs. 1005:251).

Ocreotide acetate, in combination with gemcitabine, is effective not only in controlling hormonally related tumor symptoms, but also in prolonging survival of patients with neuroendocrine cancer. According to investigators at LSU Health Sciences Center (New Orleans, LA) and Vanderbilt University (Nashville, TN), in *in vitro* studies, gemcitabine, in the presence of octreotide, resulted in enhanced cell killing (Theodossiou C, etal, ASCO02, Abs. 2208).

In November 1998, the FDA approved Sandostatin Lar Depot (octreotide acetate for injectable suspension) manufactured by Novartis, to control the symptoms, such as severe diarrhea and flushing, of metastatic carcinoid tumors, and the profuse, watery diarrhea associated with vasoactive intestinal peptide secreting tumors (VIPomas). Sandostatin Lar Depot works by imitating the action of somatostatin, a hormone found naturally in the body, which inhibits the release of growth hormone and other substances, including insulin growth factor 1 (IGF-1). Sandostatin Lar Depot helps reduce and normalize levels of IGF-1 and growth hormone. Using a microsphere delivery system, this new formulation provides a slow release of octreotide acetate from the site of injection over the course of a month.

The indication of Sandostatin Lar Depot for the treatment of carcinoid syndrome was based upon one 6-month trial, which compared intragluteal injections of Sandostatin Lar Depot (10, 20 or 30 mg), administered every 28 days, to 3 daily subcutaneous injections of Sandostatin. Sandostatin Lar Depot effectively controlled diarrhea and flushing in most patients with carcinoid syndrome. The recommended starting dose is 20 mg. For patients with carcinoid tumors or VIPoma, concomitant subcutaneous injections of Sandostatin are administered

for at least the first two weeks of Sandostatin Lar Depot therapy. Toxicity in patients with carcinoid syndrome included nausea, abdominal pain, headache, dizziness, fatigue, gas, vomiting, pain at injection site and low blood sugar levels. Some patients developed gallstones, although few required treatment.

Worldwide sales of Sandostatin were $695 million in 2003, up 14% from 2002 levels. USA sales were $318 million in 2003, up 13%, and offshore sales were $377 million in 2003, up 3% from 2002 levels.

Oxaliplatin (Eloxatin/Eloxatine; Sanofi-Synthelabo) is a novel platinum compound with activity in gastrointestinal malignancies. In January 2004, oxaliplatin for injection was approved by the FDA, in combination with 5-FU and leucovorin, for first line treatment of advanced colorectal cancer. In August 2002, the same combination had been granted accelerated approval by the FDA for treatment of patients with advanced colorectal cancer that recurs or progresses following bolus 5-FU, leucovorin and irinotecan therapy. Oxaliplatin has also been approved for these indications in Europe and many other world markets. Worldwide sales of Eloxatin were €824 million ($931.1 million) in 2003, up 111.8% from 2002 levels. USA sales were €460 million ($520 million) in 2003 while offshore sales were €364 million ($411 million).

Oxaliplatin is being evaluated in various combination regimens in pancreatic cancer (Exhibit 1). Two multicenter, randomized phase III clinical trials are investigating the combination of oxaliplatin and gemcitabine in treating locally advanced or metastatic PDAC.

A multicenter, randomized phase III clinical trial (protocol ID: FRE-GERCOR-GEM-GEMOX/D00-3, EU-20324) was initiated in France and Italy, under Christophe Louvet, MD, of Hôpital Saint Antoine (Paris, France) as Study Coordinator, to compare treatment with gemcitabine monotherapy or gemcitabine plus oxaliplatin (GEMOX) in chemotherapy- and radiotherapy-naive patients with inoperable locally advanced or metastatic PDAC. Between March 2001 and February 2003, 326 patients were enrolled in this trial with 313 eligible patients randomized 156 (locally advanced disease=30%, and metastatic disease=70%) to the gemcitabine arm, and 157 (locally advanced disease=32%, and metastatic disease=68%) to the GEMOX arm. The primary objective was to compare overall survival by showing an MST increase of 2 months from 6 to 8 months. Secondary objectives include comparison of response rate, PFS, clinical tolerance and benefit, and QoL.

Patients were stratified according to participating center, ECOG performance status (0 or 1 versus 2), and extent of disease (locally advanced versus metastatic), and randomized to 1 of 2 treatment arms. According to the protocol, in arm 1 patients were treated with gemcitabine IV over 30 minutes once weekly on weeks 1-7 and 9-11 in the absence of disease progression or unacceptable toxicity. In arm 2, patients are treated with IV gemcitabine (1000 mg/m^2) IV over 100 minutes on day 1 and IV oxaliplatin (100 mg/m^2), over 2 hours, on day 2, every 2 weeks. Courses repeated every 14 days for up to 3 months in the absence of disease progression or unacceptable toxicity. After the completion of chemotherapy, patients with locally advanced disease were also treated with CRT. QoL was assessed at baseline and then every 2 months.

Median number of cycles was 7 with gemcitabine and 6 with GEMOX. As of May 2003, 55.5% of the patients expired and disease progressed in 81% treated with gemcitabine alone, and 73% treated with GEMOX. Overall response was 16.1% (locally advanced disease=13%, and metastatic disease=17.4%) in the gemcitabine arm and 25.8% (locally advanced disease=25%, and metastatic disease=26.7%) in the GEMOX arm. However, despite of improved response in the GEMOX arm, the median duration of response was identical in both arms (42 weeks versus 41 weeks). Grade 3/4 toxicity was mainly neutropenia (gemcitabine arm=26.3% and GEMOX=18.5%). Neurological Grade 3/4 toxicity was seen in 15.3% of patients treated with oxaliplatin. Subsequently, CRT, consisting of 55 Gy for 5 weeks and 5-FU (250 mg/m^2), daily, was administered to 45 patients in the gemcitabine monotherapy arm and 49 patients in the GEMOX arm (Louvet C, etal, ASCO03, Abs. 1004:250).

An NCI-sponsored, multicenter, randomized, phase III clinical trial (protocol ID: ECOG-6201) was initiated in the USA by ECOG in March 2003, to evaluate prolonged infusion gemcitabine with or without oxaliplatin versus standard infusion gemcitabine in patients with locally advanced or metastatic PDAC. This trial was designed to compare survival, toxicity, objective response, patterns of failure, PFS, frequency of deep vein thrombosis (DVT) and pulmonary embolism (PE), and QoL, including improved symptom control and/or additional side effects, in patients treated in this setting. A total of 666 patients (222 per treatment arm) will be accrued for this study, stratified according to ECOG performance status (0 or 1 versus 2) and disease stage (locally advanced versus metastatic) and randomized to 1 of 3 treatment arms. In arm 1 (standard treatment), patients are treated with gemcitabine IV over 30 minutes once weekly for 7 weeks followed by 1 week of rest for course 1 only. In all subsequent courses, patients are treated with gemcitabine IV over 30 minutes on days 1, 8, and 15, with courses repeating every 4 weeks in the absence of disease progression or unacceptable toxicity. In arm 2, patients are treated with gemcitabine IV over 150 minutes on days 1, 8, and 15, with courses repeating every 4 weeks in the absence of disease progression or unacceptable toxicity. In arm 3, patients are treated with gemcitabine IV over 100 minutes on day 1 and oxaliplatin IV over 120 minutes on day 2, with courses repeating every 2 weeks in the absence of disease progression or unacceptable toxicity. QoL is assessed at baseline and then at 8 and 16 weeks. Patients are followed for 3 years. Elizabeth Poplin, MD, with ECOG is Protocol Chair.

Virulizin, under development by Lorus Therapeutics (Toronto, Canada), is a biological response modifier that inhibits tumor growth via stimulation of macrophages. Treatment with Virulizin was not effective against tumors in mice deficient in macrophages, providing strong support that macrophages play a major role in Virulizin-mediated antitumor activity. Cytotoxic activity of macrophages was increased approximately 5-fold in cultures containing 2.5% of Virulizin compared to that of controls (Du C, etal, Int J Oncol, Nov 2003; 23(5):1341-6). Virulizin has also been associated with increases in natural killer (NK) cell activity in clinical trials. In October 1997, the Mexico Ministry of Health approved Virulizin for the treatment of malignant melanoma.

In June 2002, the FDA granted 'fast track' designation for Virulizin in the treatment of pancreatic cancer. In early clinical trials Virulizin was shown to have clinical activity comparable to gemcitabine in advanced PDAC but with a much more favorable safety profile. A phase I/II clinical trial, completed in December 1998, enrolled 26 patients with advanced PDAC who failed standard therapies; 19 evaluable patients were treated with different dose levels of Virulizin (1.5, 3.0, 6.0 ml) 3-times per week, and with 3.0 ml 5-times per week for at least 4 weeks. MDT was well tolerated. There was 1 CR in the last cohort and disease stabilized in 7 (37%). MST was 6.7 months with a 6-month survival rate of 58%. Also, there was significant improvement in QoL (Liu C, etal, AACR99, Abs. 3793).

A randomized, multinational, double-blind, phase III clinical trial (protocol ID: LORUS-LOR-VIR-P03-002) of Virulizin was initiated in September 2002 to compare gemcitabine with or without Virulizin in treating patients with Stage II, III, or IV pancreatic cancer. A total of 350 patients are to be randomized to 1 of 2 treatment arms. Arm 1 treatment consists of IV gemcitabine over 30 minutes weekly for 7 weeks followed by 1-week rest. Then IV gemcitabine is administered over 30 minutes on days 1, 8, and 15, with courses repeated every 28 days. Virulizin is administered intramuscularly (IM) for 3 days each week. Arm 2 treatment consists of gemcitabine, as in arm 1, and placebo. Treatment is continued in both arms in the absence of disease progression or unacceptable toxicity. The regimen may be followed by second line therapy with Virulizin or placebo with or without 5-FU, whereby patients are randomized to 1 of 3 treatment arms. In arm 1, either Virulizin IM or placebo IM is administered for 3 days each week with 5-FU. If 5-FU is discontinued for any reason, Virulizin or placebo may continue. In arm 2 either Virulizin or placebo is administered as in arm 1. In arm 3 patients undergo observation only and are followed for survival. The primary efficacy endpoint of this trial is survival while secondary endpoints include TTP, and the effect of Virulizin on key clinical benefit parameters such as pain, analgesic consumption, changes in weight, and performance status. In addition, the trial is correlating immune parameters with clinical outcome.

In September 2003, Lorus expanded this phase III clinical trial in PDAC to encompass over 100 clinical sites in the USA, Russia, Ukraine, Romania, Poland, the Czech Republic, Hungary, Spain, Brazil, Canada and Mexico.

Hyperthermia

In hyperthermia, tissue temperature is elevated artificially in order to either treat cancer as monotherapy or as an adjunct to enhance the effectiveness of chemotherapy. Hyperthermia is sometimes referred to as 'fever therapy'. The role of hyperthermia in cancer treatment is based on the observation that cancer cells are more sensitive to heat than normal cells. Raising the temperature of the tumor may thus selectively kill cancer cells.

Hyperthermia may be delivered either externally, using such devices as heating rods, microwaves, radiofrequency, ultrasound, thermal blankets or lasers, or internally, using pyrogens administered systemically to patients to induce fever. In the USA, the most common approach is use of external devices. Hyperthermia is usually classified as local, regional or whole body. In pancreatic cancer, hyperthermia is being evaluated as a adjunct to chemotherapy in both PDAC and neuroendocrine tumors, and intraperitoneally to treat peritoneal carcinomatosis resulting from GI and ovarian malignancies.

Combination of gemcitabine, cisplatin, interferon α (IFN-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), and fever-range, long-duration whole-body hyperthermia (FR-WBH), was safe, well tolerated, and resulted in clinical benefit to patients with pancreatic or neuroendocrine cancer (see Exhibit 1). Investigators at the University of Texas Medical School (Houston, TX) have initiated a phase II clinical trial with this combination with a cisplatin dose of 60 mg/m^2.

A new integrated system, BSD-2000/3D/MR, developed by Siemens Medical Systems (Malvern, PA) and BSD Medical (Salt Lake City, UT), uses progressive magnetic resonance (MR) images to monitor tumor temperatures during treatment. Tumor hyperthermia is accomplished by a microwave phased-array system, developed by BSD. Major funding for this project was provided by the German Federal Research Council, under leadership of the Charite Medical School of Humboldt University (Berlin, Germany). This approach is being applied to various types of cancer, including PDAC.

Photodynamic Therapy (PDT)

PDT produces local tissue necrosis with light after prior administration of a photosensitising agent. In experimental studies it was shown to be tolerated by the pancreas and surrounding normal tissue. The approach uses systemic photosensitizers and percutaneously placed light catheters. Although PDT kills pancreatic cancer *in vitro* and *in vivo*, the difficulty in using PDT in the clinic lies in providing adequate light dosimetry to the tumor. Also, care is required for pancreatic tumors invading the duodenal wall or involving the gastroduodenal artery.

Various photosensitizers and light sources have been investigated. Interstitial hypericin and laser phototherapy significantly decreased growth of pancreatic cancer both *in vitro* and *in vivo* in mice (Liu CD, etal, J Surg Res, Sep 2000;93(1):137-43). PDT with pheophorbide A, a chlorophyll derivative, in culture and after grafting into athymic mice, destroyed human PDAC at low photosensitizer and energy application. It exerted this tumoricidal effect via apoptosis induction with a gentle protocol, and apoptosis and/or necrosis with a stronger protocol (Hajri A, etal, Br J Surg, Jul 1999;86(7) 899-906).

The safety and efficacy of the photosensitizer meso-tetrahydroxyphenyl chlorin (mTHPC), marketed as Foscan by biolitec Pharma (Edinburgh, Scotland), was investigated in a phase I clinical trial conducted at the National Medical Laser Centre, University College Hospital, Royal Free and University College Medical School (London, UK). According to the protocol, 16 patients with inoperable PDAC (2.5-6 cm in diameter) localized to the head of the pancreas, were administered IV mTHPC (0.15 mg/kg) and 3 days later, up to six needles carrying laser fibers delivering light, were inserted through the skin and directly into the tumor under CT guidance. Subsequently, 3 patients were also treated with chemotherapy. After treatment, substantial tumor necrosis was observed on scans. In terms of complications, 2 patients with tumors involving the gastroduodenal artery experienced significant GI bleeding that was controlled without surgery. There was no treatment-related mortality. Patients were able to start eating and drinking within 48 hours of the procedure, and left the hospital 10 days later. MST after PDT was 9.5 (range=4-30) months. Compared with the expected 6 to 10 months survival, 7/16 (44%) patients were alive one year after PDT; 2 patients survived for 2 years and 1 for 30 months. Further studies are indicated to assess its influence on the course of the disease, alone or in combination with CRT (Bown SG, etal, Gut 2002;50:549-557).

Investigators at Massachusetts General Hospital (Boston, MA) studied EUS-guided PDT of the pancreas in a porcine model. After injection of porfimer sodium (Photofrin; Axcan Pharma), a 19-gauge needle was inserted into the pancreas, the liver, the spleen, and the kidney under EUS guidance. A small diameter quartz optical fiber, passed through the EUS needle, was used to illuminate the tissue with laser light. Localized tissue necrosis was achieved in all organs, without significant complication. There was no significant difference in inflammation induced by PDT within the various organs. EUS-guided PDT is a safe and simple technique that can induce small areas of focal tissue ablation within the liver, the pancreas, the kidney, and the spleen, and may be used to treat a variety of benign and malignant conditions (Chan HH, etal, Gastrointest Endosc, Jan 2004;59(1):95-9).

Electroporation Therapy (EPT)

In EPT electric pulses are delivered to tumors to induce transient permeabilization to anticancer agents. Genetronics Biomedical (San Diego, CA) has developed the MedPulser, an electroporation device that uses a needle array applicator to deliver bleomycin to tumors. EPT allows for intracellular accumulation of cytotoxic drugs without the toxic side effects associated with systemic administration. Bleomycin, a generic chemotherapeutic agent that induces single and double strand DNA breaks in cancer cells, was selected because its size makes its delivery across cell membranes difficult.

In March 1999, Genetronics received approval in Europe to affix the CE Mark to the MedPulser electroporation device used for EPT of solid tumors with bleomycin, permitting its sales throughout the European Union.

To investigate EPT as a treatment of pancreatic cancer, human pancreatic tumors were implanted subcutaneously in 8 mice. Treatment consisted of a single intratumoral injection of bleomycin, mitomycin C or carboplatin followed 5 to 10 minutes later by electrical pulsing. On day 89 after treatment, there were 6 (75%) CR in mice treated with bleomycin and EPT, a significantly better response rate compared to mice treated with mitomycin C and carboplatin and EPT, which resulted in 1/8 (12.5%) CR and 2/9 (22%) CR, respectively. In all of the control groups, which were treated with one of the drugs alone or with the electric pulse alone, tumor volumes increased after treatment, indicating progressive disease (Nanda GS, etal, Anticancer Res, May-Jun 1998;18(3A):1361-6).

Treatment by Stage

Treatment of pancreatic cancer is extremely challenging. In early disease the treatment of choice is surgery with adjuvant chemotherapy or CRT employed in high-risk cases. However, because a high percentage of patients present with either inoperable locally advanced or metastatic disease, prevailing nonsurgical management strategies include RT, chemotherapy or CRT. Most of the discussion here refers to the treatment of PDAC.

None of the currently practiced strategies in the management of PDAC provide satisfactory solutions. Therefore, clinical trials are used to advance the state-of-the-art in the management of pancreatic cancer. However, it takes several years for results from these trials, particularly large randomized trials, to become available, often making their conclusions obsolete because of major advances in science and technology.

RT represents one of the foundations of current practice in the treatment of PDAC, for both resectable and inoperable disease. However, there is no clear evidence as to the best RT approach in this setting. Investigators at Kyoto University, in Japan, compared IORT and/or EBRT in both resectable and inoperable PDAC in 332 (resected disease=157 and inoperable disease=175) patients, treated with surgery and/or RT between 1980 and 1995. Survival rates were significantly higher with EBRT and IORT ± EBRT than with no RT for noncuratively resected PDAC. The 2-year survival probability of the IORT ± EBRT group

in this setting was 16% compared with 0% in the EBRT group. For inoperable pancreatic cancer, MST of 52 patients without distant metastases was 6.7 months for palliative surgery alone, 7.6 months for EBRT alone, and 8.2 months for IORT ± EBRT. The 2-year survival probability for the IORT ± EBRT group was 14%, while it was 0% in the no RT or EBRT groups. Tumor size, stage, and curability of resection were significant variables in the outcome of resectable pancreatic cancer, while distant metastases and IORT treatment were significant variables in inoperable pancreatic cancer. EBRT dose was a marginally significant factor for all tumors. In terms of complications, ulcers of the GI tract were noted in 14% of the 126 patients treated with IORT. Although prolongation of the MST by IORT was not remarkable, long-term survival (>2 years) was attained with IORT ± EBRT for noncuratively resected and inoperable PDAC. Therefore, IORT combined with EBRT is indicated for noncuratively resected or inoperable PDAC without distant metastases (Nishimura Y, etal, Int J Radiat Oncol Biol Phys, 1 Aug 1997;39(1):39-49).

Generally, chemotherapy is used for local control and to combat metastases. Although, a large percent of patients with pancreatic cancer are diagnosed with locally advanced nonmetastatic disease at first presentation, the tumor is inoperable in most because of the extent or nature of involvement of local organs. In addition, many patients diagnosed with Stage II or III disease, harbor micrometastases. A new strategy is to incorporate a chemotherapeutic regimen to target micrometastases in the liver and the peritoneal cavity that are common sites of progression. Use of chemotherapy in the adjuvant, neoadjuvant and palliative setting has increased the number of regimens administered significantly (Exhibit 2) despite the fact these regimens have not been shown to lengthen life expectancy. A unique endpoint, clinical benefit, is being used to describe treatment-related improvements in QoL, such as less pain, better appetite, etc., to justify treatment.

Most often, RT and chemotherapy are used in combination, making CRT the most common and, perhaps, the most controversial treatment approach in all stages of PDAC.

Resectable Locally Advanced Disease

Resectable disease is treated with surgery and adjuvant chemotherapy and/or CRT. Generally, resection of PDAC is resource-intensive with a limited impact on survival. Postoperative treatment of patients with PDAC is controversial, because of contradictory findings reported from phase III clinical trials. No management option, which spans from observation, to bolus 5-FU monotherapy, to CRT followed by bolus 5-FU, has yielded satisfactory results and most patients die within 2 years from surgery. Lack of a survival benefit may result from use of an inactive schedule of a poorly active drug, an outdated RT schedule, and the wrong sequence of treatment modalities.

Adjuvant chemotherapy/CRT is being investigated in the postoperative setting because the prevalent pattern of failure is local recurrence and metastatic disease. With surgery, even when macroscopically complete resection is achieved, local recurrence rates are unacceptably high (30% to 70%), which is usually attributed to the difficulty of obtaining microscopically free surgical margins. Such margins are difficult to achieve because pancreatic tumors frequently extend into the peripancreatic tissues, abut or invade the adjacent large vessels (the portal vein and superior mesenteric artery), and have a propensity to invade the lymphovascular and perineural space. Another common reason of failure after attempted curative resection is metastasis to the liver and the peritoneal cavity.

One of the limitations of adjuvant treatment lies in the inability to deliver adequate RT doses without causing severe radiotoxicity. Newer techniques such as 3D-CRT and IMRT that precisely localize the dose to the target volume, may reduce radiotoxicity in the postoperative setting to such critical structures such as the kidney, liver, small intestines, stomach, and spinal cord (Penberthy DR, etal, Semin Surg Oncol 2003;21(4):256-60).

Major trials such as ESPAC-1 and ESPAC-3, initiated in Europe, have set new standards for patient recruitment and development in the adjuvant treatment of PDAC (Raraty MG, etal, Acta Oncol 2002; 41(7-8): 582-95). ESPAC-1 compared adjuvant 5-FU and folinic acid chemotherapy with or without RT in locally advanced resectable pancreatic cancer, and ESPAC-3 is comparing adjuvant 5-FU/folinic acid chemotherapy with gemcitabine monotherapy. Previously, smaller trials in this setting were undertaken by the Gastrointestinal Tumor Study Group (GITSG) that showed a survival benefit for CRT (40Gy + 5-FU) in 43 patients, while an European Organization for Research and Treatment of Cancer (EORTC)-sponsored trial showed no advantage for postoperative CRT (40Gy + 5-FU) in 114 patients, and a trial sponsored by the Norwegian Pancreatic Cancer Trials Group showed no overall survival benefit for CRT in 47 patients. Results from these trials confirm that, in the adjuvant setting, there is little or no overall benefit for CRT but a small benefit for chemotherapy.

ESPAC-1, the largest randomized, multinational, clinical trial of its time, was designed to assess the role of adjuvant CRT or chemotherapy in the treatment of resected PDAC. The trial randomized 550 patients with resected pancreatic cancer to either CRT (40 Gy plus 5-FU/folinic acid) or chemotherapy (5-FU/folinic acid). Unlike earlier trials that were underpowered and often excluded patients with positive resection margins, ESPAC-1 included 111 (20%) patients with positive resection margins (R1 tumors) as recognition of the natural behavior of the disease. The trial's primary endpoint was 2-year survival. The last ESPAC-1 patient was randomized in April 2000. A total of 434 (79%) deaths were recorded in ESPAC-1 at a median follow-up of 44 (range=27–63) months. The final analysis

Exhibit 2
Worldwide Incidence of Pancreatic Cancer in 2002

AJCC Staging*	AJCC Staging Description*	UICCC TNM Staging Equivalent	Standard Treatment	Novel Approaches	Patients/ Regimens (#)
Stage I/0	The tumor is limited to the pancreas itself and has not spread to other organs	Tis, N0, M0 or T1, N0, M0; T2, N0, M0	Resection or radiosurgery; disease monitoring using CA19-9 every 3 to 6 months; some patients are also administered adjuvant RT, chemotherapy or CRT		3,070/1,000
Stage II	The tumor has spread to nearby organs such as the duodenum and/or bile duct, but has not spread to the lymph nodes	T3, N0, M0	Resection; adjuvant/neo-adjuvant chemotherapy or CRT	IORT/IEORT; hyperthermia; PDT; radiosurgery	8,596/17,192
Stage III	The tumor has spread to the lymph nodes near the pancreas and may or may not have spread to nearby organs	T1, N1, M0; T2, N1, M0; T2, N1, M0;	Chemotherapy; RT/IORT; palliative surgery	Clinical trials with novel agents	19,034/28,551
Stage IVa	The tumor has metastasized to organs near the pancreas such as the stomach, spleen and/or colon but not to distant organs like the liver or lungs	T1, N1, M0; T2, N1, M0; T3, N1, M0	Chemotherapy (intra-arterial or systemic combination of mitomycin/cisplatin or single agent gemcitabine, or mitomycin, with or without leucovorin and FUDR); CRT; analgesia; surgical bypass/ stent placement		
Stage IVb	Metastases present in distant organs such as the liver and lungs	Any T, any N, M1	Chemotherapy (as above); analgesia; CRT		
Total					30,700/46,743

Source: American Joint Committee on Cancer

confirmed no survival benefit with CRT. MST with CRT was 15.5 months versus 16.7 months without CRT. However, MST in the chemotherapy arm was 19.7 months, which is as good or superior to multimodality treatments including IORT, adjuvant CRT and neoadjuvant approaches (Neoptolemos JP, etal, Pancreatology 2003; 3:209–269, and Neoptolemos JP, etal, Ann Oncol, May 2003;14(5):675-92).

ESPAC-3, a multicenter, randomized, controlled, phase III clinical trial, was initiated in July 2000 to investigate the benefit of adjuvant chemotherapy with either 5-FU and folinic acid or gemcitabine versus no treatment in resected PDAC. Endpoints include PFS, 2-year and 5-year survival rate, toxicity and QoL. This 3-arm trial is testing two hypotheses, that adjuvant chemotherapy improves survival compared to no additional treatment following resection of pancreatic cancer, and that there is a difference in survival between gemcitabine and 5-FU plus folinic acid when used as adjuvant therapy following resection for pancreatic cancer. Approximately 990 patients are expected to enroll in ESPAC-3, in Europe, Canada and Australasia.

Various prognostic factors may determine the efficacy of adjuvant CRT. One such factor involves the status of surgical margins. In ESPAC-1, resection margin status was confirmed as an influential prognostic factor, with a MST of 10.9 months for R1 versus 16.9 months for R0 margins. Among 541 patients followed-up for a median of 10 months, 101 (19%) underwent R1 resections. Resection margin status remained an independent factor only in the absence of tumor grade and nodal status. There was a survival benefit for chemotherapy but not CRT irrespective of R0/R1 status. For patients with R0 margins, chemotherapy produced longer survival compared to no chemotherapy. This difference was less apparent for the smaller subgroup of R1 patients, but there was no significant heterogeneity between the R0 and R1 groups. Patients with margin-positive pancreatic tumors, a biologically more aggressive malignancy, benefited from resection and adjuvant chemotherapy but not CRT. The magnitude of benefit for chemotherapy is reduced for patients with R1 margins versus those with R0 margins. Patients with R1 tumors should be included in future trials of adjuvant treatments

and randomization and analysis should be stratified by this significant prognostic factor (Neoptolemos JP, etal, Ann Surg, Dec 2001;234(6):758-68; comment in Ann Surg, Nov 2002;236(5):694; author reply 694-6).

Another factor, i.e. narrowing of the superior mesenteric vein, has been considered a contraindication to surgical treatment. The impact on survival of a trimodality regimen was investigated at Fox Chase Cancer Center (Philadelphia, PA) in locally advanced PDAC with image-detected superior mesenteric vein narrowing. This trial correlated preoperative imaging of pancreatic cancer with patient outcomes. Preoperative imaging studies identified 51 patients, undergoing curative resections, with involvement of the SMV or portal vein (PV), or of the non-circumferential superior mesenteric artery or celiac axis (including encasement). Of these, 28 patients were treated with preoperative CRT, 19 with postoperative CRT, and 4 were not treated at all. Among surgeries, 41 were Whipple procedures and 10 total pancreaticoduodenectomies. There was one inhospital death. MST was 18 months for the entire group at a median follow-up of 17 months. MST for those treated preoperatively, those treated postoperatively and those without further treatment was 20, 14 and 6.5 months, respectively. The 1-, 2- and 3-year survival rates at 79%, 42% and 23% for the preoperatively treated group and 68%, 42% and 12% for the postoperative therapy group, were not statistically significant. MST was 19 months among those with a positive resection margin, and 22 months in those with negative margins. There were 5 patients alive with disease at 70, 42, 35, 31, 27 months, and 5 with no evidence of disease at 23, 21, 17, 13, 12 months. These results suggest there may be a survival benefit in patients with locally advanced PDAC treated with surgery, in conjunction with CRT, when compared to previously reported series of patients treated without resection with MST in the 8-12 month range. Aggressive surgical therapy for PDAC involving the SMV/PV with CRT may be appropriate in selected patients, with the understanding that long-term cure is unlikely (Meyers MO, etal, ASCO03, Abs. 1166:290).

Inoperable Locally Advanced Disease

Locally advanced pancreatic cancer is inoperable because of tumor spread in adjacent tissues and organs. In some cases, neoadjuvant chemotherapy and CRT may be used to downstage the disease and permit resection. Also, for patients with localized but inoperable malignancy, RT combined with 5-FU, gemcitabine, or paclitaxel (Exhibit 1) has shown symptom palliation, and modest improvements in survival.

In October 2003, at the Clinical Congress of the American College of Surgeons, Howard Reber, MD, reported that in a small clinical trial, conducted at the University of California Los Angeles (UCLA), a 4-drug chemotherapy regimen plus surgical resection increased survival significantly in 12 patients with locally advanced, inoperable pancreatic cancer. Although patients enrolled in this trial were considered surgical candidates at diagnosis, during an exploratory procedure, surgeons discovered that the pancreatic tumors were too extensive to be excised. Therefore, patients were treated with chemotherapy in an attempt to shrink the tumors to a resectable size. Patients were treated with a daily continuous infusion of 5-FU (200 mg/m^2), IV bolus calcium leucovorin (30 mg/m^2), every week, IV mitomycin-C (10 mg/m^2), every six weeks, and daily oral dipyridamole (75 mg). After chemotherapy, pancreatic tumors in all but one patient were small enough to be removed surgically.

MST from the time of diagnosis was 35 months in patients who underwent surgical resection, over 3 times the expected MST of 10 months for historic controls. Patients with resected disease lived for at least 1 year after treatment; 82% lived for 2 years, 41% for 3 years, and 27% for 4 years. Although 7/12 patients died of recurrent disease, 5 were alive and disease free between 10 and 117 months after diagnosis.

The treatment approach used in this trial departs from standard therapy for pancreatic cancer, which focuses predominantly on treating localized disease in the pancreas. Because at the time of diagnosis, as many as 85% to 90% of patients with pancreatic cancer have microscopic metastases that are too small to detect by current scanning techniques, within 3 months after the completion of RT many patients present with liver metastases. Obviously these metastases were already there, too small to be detected. In order to deal with micrometastases, patients must be exposed to effective systemic treatment. Rather than high dose chemotherapy for a fixed number of treatment cycles over 2 to 4 months, physicians in this trial treated patients with low dose chemotherapy continuously for as long as the patient continued to respond.

Chemoradiotherapy (CRT) is used in the treatment of inoperable locally advanced pancreatic cancer as a neoadjuvant approach, and as a palliative to improve QoL. Potential benefits of CRT include local control, palliation of symptoms, and the possibility of long-term survival for approximately 10% of patients. Thus, although there may be small improvements in survival, the palliative effects of CRT are taken into account when deciding on the management of these patients. In the preoperative setting it is doubtful that CRT offers a significant downstaging effect, but a small percentage of patients initially deemed to have inoperable disease, may become candidates for surgery on staging studies done after CRT. Given the relative success of CRT for treatment of patients with locally advanced pancreatic cancer, novel combinations of chemotherapy are being studied to improve on both local and systemic disease control (Exhibit 1).

Various RT approaches, including EBRT, IORT and stereotactic radiosurgery, combined with chemotherapy regimens, have been deployed in an effort to deliver a more effective tumor-killing treatment. Over the past 30 years, there has been modest improvement in palliation and sur-

vival for patients with locally advanced PDAC using CRT. Although ESPAC-1 concluded that CRT does not appear to be beneficial in the adjuvant setting in resectable disease, other investigations have shown benefit. Often, improvements in therapeutic modalities negate results from clinical trials because technology advances far more rapidly than medical practice. Results from randomized trials usually take at least 3 and usually more than 5 years to be reported. In that time span technology makes significant progress often rendering treatments under evaluation obsolete. Therefore, new combinations of chemotherapy and advanced RT approaches, such as 3D-CRT, IMRT and the development of novel agents and combinations, may benefit patients with PDAC.

Investigators at Memorial Sloan-Kettering Cancer Center, concluded that, although CRT is associated with improved overall survival in locally advanced disease, it rarely leads to surgical downstaging allowing for potentially curative pancreatic resections. Among 163 patients admitted between January 1993 and March 1999 with locally advanced PDAC, CRT based on various regimens from standard 5-FU/gemcitabine-based therapies to experimental protocols, was administered to 87 (53.3%) patients. Only 3/87 (3.4%) experienced a sufficient clinical response on restaging to warrant re-exploration. Of these, on subsequent laparoscopy, disease was inoperable in 2 because of extensive vascular involvement or metastatic disease. Only 1 patient without nodal involvement underwent a potentially curative resection, and survived 18 months despite negative margins. Overall MST for all patients with locally advanced disease treated with CRT was 11 months compared to 6.5 months without multimodal therapy (Kim HJ, etal, J Gastrointest Surg, Sep-Oct 2002;6(5):763-9).

An outcomes trial was conducted at Mt. Sinai Medical Center (New York, NY), to examine whether preoperative CRT as the initial treatment improves survival of patients with regional PDAC with a minimal chance of being resected successfully. Patients with radiologically regional tumors were staged by laparotomy and/or CT followed by endoscopic ultrasonography, angiography, and/or laparoscopy. Those with locally invasive, inoperable, regional PDAC initially were treated with simultaneous split-course RT plus 5-FU, streptozotocin, and cisplatin (RT-FSP), followed by selective surgery (group 1). Patients determined to have a resectable tumor initially underwent resection without preoperative CRT, or with/without postoperative CRT (group 2). Over 8 years, 159 patients presenting with nonmetastatic, PDAC were administered RT-FSP or underwent surgery. There was 0% mortality within 30 days of entry in group 1, comprised of 68 patients initially treated with RT-FSP. In 20/30 patients undergoing surgery after RT-FSP, tumors were downstaged and resected. A 5% mortality within 30 days of entry was seen in group 2, comprised of 91 patients who initially underwent successful resection. Postoperatively, 63 of these patients were treated with chemotherapy with or without RT. MST for group 1 was 23.6 months compared with 14.0 months for group 2, despite more advanced disease cases in group 1. Survival favored RT-FSP regardless of whether lymph nodes were malignant. Based on a reversal of the expected trend that patients with earlier stage resectable carcinoma (T1,2, N0,1, M0) who undergo tumor removal survive longer than patients with more advanced regional disease (T3, N0,1, M0), survival was found to improve significantly in patients reliably staged as having locally invasive, inoperable, nonmetastatic PDAC when initially treated with RT-FSP (Snady H, etal, Cancer, 15 Jul 2000; 89(2):314-27).

EBRT with concurrent continuous 5-FU infusion increased survival length and improved QoL compared to no CRT, and provided a definite palliative benefit for patients with inoperable pancreatic cancer. According to the protocol, 31 patients with histologically proven locally advanced, inoperable PDAC without distant metastases were evaluated in a prospective randomized trial at the Kagoshima University School of Medicine, in Japan. EBRT (50.4 Gy/28 fractions) with concurrent continuous infusion of 5-FU (200 mg/m^2/day), was administered to 16 patients, whereas 15 patients were not treated with CRT. MST of 13.2 months and 1-year survival rate of 53.3% in the CRT group were significantly better than MST of 6.4 months and 0% 1-year survival in the group without CRT. The average monthly Karnofsky score was 77.1 in the CRT group, which was significantly higher than the 65.5 in the group without CRT. The number of hospital days per month of survival was significantly fewer in the CRT group than in the no-therapy group (12.3 versus 19.0 days). In the CRT group, there were 5 (31%) PR, and disease stabilized in 9 (56%) for a median duration of 6.1 months. Patients treated with CRT had a lower rate of liver and peritoneal metastases than those not treated (31% versus. 64%). Of 10 patients who experienced pain before CRT, 8 (80%) achieved pain relief that lasted a median of 5.2 months (Shinchi H, etal, Int J Radiat Oncol Biol Phys, 1 May 2002;53(1):146-50).

CRT with more intensive RT, based on a combination of IORT and conformal EBRT, and protracted 5-FU, was investigated in a phase II clinical trial at the National Cancer Center Hospital East (Chiba, Japan) in 30 patients with inoperable, locally advanced PDAC. Treatment consisted of IORT (25 Gy), followed by EBRT (40 Gy) in 20 fractions, 5 times per week, and concurrent protracted infusion of 5-FU (200 mg/m^2), beginning 2 to 4 weeks after IORT. The full EBRT dose was administered in 28/30 patients; EBRT was terminated in 1 patient at 8 Gy because of progression of brain metastasis and another patient was not treated with EBRT or chemotherapy because of massive ascites after IORT. Within a follow-up period of 12.0-28.1 months, metastatic spread was detected in the abdominal cavity at laparotomy in 11/30 patients. There were 7 (23.3%) PR in primary pancreatic tumor on

dynamic CT scans. Grade 3/4 toxicity, including anorexia, nausea, emesis, fatigue, leukopenia, and/or elevation of transaminase levels, was observed in 15/28 (53.6%) patients treated with the full RT dose. There were no treatment-related deaths, but 1 patient died 25.6 months after treatment of hepatic failure related to late effects of RT. MST of the 30 patients was 7.8 months and the 2-year survival rate was 8.1%. MST of the 19 patients without metastatic spread in the abdominal cavity was 12.9 months, and that of the 11 patients with metastatic spread was 5.8 months. This regimen of CRT was not superior to conventional CRT with EBRT and 5-FU in this setting (Furuse J, etal, Cancer, 1 Mar 2003;97(5):1346-52).

Survival after neoadjuvant CRT and resection appears to be at least comparable to survival after resection and adjuvant (postoperative) CRT. Since 1995, investigators at Duke University Medical Center (Durham, NC) treated 111 patients with radiographically localized, pathologically confirmed PDAC, with neoadjuvant CRT, consisting of EBRT (median 45 Gy) and 5-FU. Tumors were defined as potentially resectable (n=53) in the absence of arterial involvement and venous occlusion, and locally advanced (n=58) with arterial involvement or venous occlusion by CT. Restaging was not possible in 5 (4.5%) patients; 3 died and 2 became intolerant to therapy. Distant metastatic disease on restaging CT was detected in 21 (19%) patients. After CRT, surgery was performed in 28 (53%) patients with initially potentially resectable tumors, and in 11 (19%) patients with initially locally advanced tumors. Histologic examination revealed 2 CR and significant fibrosis in all resected specimens. Surgical margins were negative in 72%, and lymph nodes were negative in 70% of cases of resected disease. At a median follow-up of 16 months, MST had not been reached in those treated surgically. Neoadjuvant CRT provided an opportunity for patients with occult metastatic disease to avoid the morbidity of resection, and resulted in tumor downstaging in a minority of patients with locally advanced tumors (White R, etal, Ann Surg Oncol, Dec 2001; 8(10):758-65; comment in Ann Surg Oncol, Dec 2001;8(10):747-8).

Between January 1992 and June 1999, 31 patients with locally advanced PDAC were treated at the Istituto di Radiologia, Cattedra di Radioterapia Oncologica (Rome, Italy) to evaluate the efficacy of combined RT and continuous infusion 5-FU. In 20 (65%) patients, the tumor was located in the head of the pancreas and in 11 (35%) in the body or tail; nodes were involved in 13 patients. RT consisted of a median dose of 63 Gy in 33-36 fractions applied to the tumor and regional lymph nodes. Chemotherapy with 5-FU (250 mg/m^2), daily, by continuous infusion, was administered in the first and fifth week of RT. Thereafter, 22 patients were treated with 3-10 cycles of adjuvant chemotherapy at the same dose. At a median follow-up of 20 months, MST was 15.2 (range=4-42) months. At restaging, there were 14 (45%) PR, and there was no change in 17 (55%) cases. At the end of CRT, 8 (26%) were considered resectable with surgery performed in 4 patients. There were 2 (6.4%) surgical cases proven to be disease free, and enlarged lymph nodes disappeared in 11/13 (85%) cases with node involvement. Among survivors, 19 (61%) patients were alive with clinical evidence of disease, and 2 were alive with liver metastases; 8 (26%) patients died of PDAC. Complete pain control was achieved in 74% of cases. Treatment was well tolerated. Nutritional assistance correlated with survival. In this trial, tumor downstaging and resectability rates were high, together with prolonged survival and good QoL (Osti MF, etal, Tumori, Nov-Dec 2001;87(6):398-401).

Combination of different protocols of preoperative RT and chemotherapy in patients with inoperable pancreatic cancer is feasible with acceptable toxicity. From November 1991 to September 1998, 47 patients with inoperable PDAC were treated at the University of Navarre (Pamplona, Spain) with simultaneous preoperative RT (45 Gy) and chemotherapy using 3 different protocols, cisplatin, 5-FU ± paclitaxel; cisplatin and protracted infusion of 5-FU; and docetaxel plus gemcitabine. In patients selected for resection, Whipple pancreatoduodenectomy was performed 1 month after the end of radiation. After preoperative treatment, 23 (47%) inoperable tumors were treated with an additional dose (10-12 Gy) of RT, either by IORT or EBRT. After preoperative treatment, 12 (26%) patients were considered to have clinically resectable tumors. Of the 9 (19%) patients who underwent Whipple pancreatoduodenectomy one month after completion of RT, 2 had complete pathologic response. After CRT, one patient died of pneumonia and another of GI bleeding, and 2 others died in the postoperative period. Distant metastases occurred in 57% of patients, and local recurrence in 22%. The 3-year survival rate was 0% (MST=10 months) for patients with inoperable tumors and 48% (MST=23 months) for patients with resectable tumors. Preoperative treatment with chemotherapy and RT in patients with inoperable pancreatic cancer is feasible, and in some cases may lead to a complete pathologic response. Tumor resection resulted in long term survival. However, more effective chemotherapy regimens are needed because the majority of the patients died of metastatic disease (Aristu J, etal, Am J Clin Oncol, Feb 2003;26(1):30-6).

Stereotactic radiosurgery, may play a role in the treatment of inoperable locally advanced pancreatic cancer. A total of 23 patients with locally advanced (no Stage IV disease) pancreatic carcinoma (advanced primary tumors=21 and recurrence =2) whose tumors were considered inoperable because of invasion of adjacent structures, were treated with stereotactic RT at Copenhagen University Hospital and Aarhus University Hospital in Denmark. Patients were either immobilized by use of the Stereotactic Body Frame (Elekta) or by a custom-made whole body fixation system. Stereotactic RT of a central dose of 45 Gy was administered in 3 fractions over 5 to 8 days. All patients were administered prophylactic ondansetron

(Zofran; GlaxoSmithKline) during the treatment period and pantoprazol for at least 4 weeks.

Within a median follow-up time of 24 months, only 18 patients were evaluable for toxicity at day 14, and 12 patients at day 56 because of deterioration; for the same reason, evaluation by CT was only performed in 15 patients. Disease progressed locally in 3 patients and distantly in 11, with only 1 patient surviving without progression 24 months after treatment. Mean PFS was 5 months and MST was 6.5 months. Toxicity was pronounced with a significant worsening of performance status, nausea, and pain at 14 days after treatment compared to baseline. In conclusion, this study shows unacceptable toxicity and low efficacy of high dose hypofractionated RT in PDAC (Roed H, etal, ASCO03, Abs. 1513).

Intraoperative radiation therapy (IORT) is attempted as a means of achieving local control in inoperable disease. Despite IORT, however, overall survival of patients with locally advanced PDAC remains unchanged because rapid appearance of metastatic disease in these patients offsets any benefit from improved local control. For instance, collectively, clinical trials of CRT with IOERT reported MST ranging between 8 and 16 months, and a 2-year survival rate between 6% and 27%.

The possible advantages of high-dose IORT, in combination with EBRT, were evaluated in 115 patients with inoperable PDAC (nonmetastatic=53 and Stage IV=62), treated between 1983 and 1993, at Kyoto University, in Japan, with EBRT + IORT (n=55), EBRT alone (n=44), or IORT alone (n=16). In nonmetastatic disease, EBRT alone was used because of unavailability of IORT and IORT alone was used because of refusal of EBRT. The IORT dose was 30-33 Gy and the EBRT dose was 40-60 Gy. A historical control group comprised of 101 patients undergoing palliative surgery alone was also analyzed.

Prognosis of patients treated with EBRT with or without IORT was better than that of nonirradiated historical controls. Among patients without metastases, MST of the EBRT + IORT group (8.5 months) and the EBRT group (8 months) was similar, although survival of 38% versus 10% at 12 months and 19% versus 0% at 18 months was higher among patients treated with EBRT + IORT. In patients with Stage IV disease, prognosis was not influenced by the type of RT. Multivariate analysis revealed that a pretreatment carbohydrate antigen CA 19-9 level <1000 U/ml was associated with better survival. In patients without metastases and a CA 19-9 level <1000 U/ml, EBRT + IORT appeared to produce a better survival than EBRT alone. This observation was supported by multivariate analysis. Therefore, high dose IORT + EBRT may be more effective than EBRT alone in patients with inoperable but localized PDAC and a low CA 19-9 level (Shibamoto Y, etal, Int J Radiat Oncol Biol Phys, 1 Jan 1996; 34(1): 57-63).

Metastatic Disease

There is no effective treatment for metastatic pancreatic cancer. Various combinations of approved chemotherapeutics have been used as palliatives but none so far has shown significant benefit. Hope in this area rests with novel agents in development, mostly in combination with approved agents. Development of novel agents in the treatment of pancreatic cancer is the topic of Part III of this series.

Gemcitabine, alone or in combination with cisplatin, is the current standard treatment for metastatic PDAC. A novel regimen is being evaluated in a phase II clinical trial that involves administration of gemcitabine as a fixed-dose rate (FDR) infusion, in combination with low dose cisplatin, for treatment of chemotherapy-naive patients with histologically confirmed PDAC and documented extrapancreatic metastases. Patients are treated with a combination of gemcitabine (1000 mg/m^2) infused at 10 mg/m^2/minute, together with cisplatin (20 mg/m^2), both administered on days 1 and 8 of a 21-day cycle. CT scans are performed after every 2 cycles and CA19-9 levels measured at the start of each cycle. Treatment continues until evidence of disease progression or unacceptable toxicity.

As of September 2003, 42 patients had been enrolled, in this trial with a median follow-up time of 198 (range=20-580) days. Major toxicities have been primarily hematologic, including 24/42 patients (57.1%) experiencing at least one episode of Grade 3 or 4 neutropenia; 7/42 (16.7%) Grade 3 or 4 anemia; and 5/42 (11.9%) Grade 3 or 4 thrombocytopenia. With regard to therapeutic efficacy, in 7/38 (18.4%) patients with measurable disease there was radiographic evidence of minor or partial response. Furthermore, among 32 patients with elevated serum CA19-9 levels at baseline, a >50% biomarker decline during treatment occurred in 15 (46.9%). Preliminary survival analysis on the first 42 patients, shows an estimated median TTP of 3.4 months, and an estimated MST of 8.6 months. The combination of FDR gemcitabine and cisplatin was well tolerated, with Grade 3/4 neutropenia being the most common toxicity. This regimen shows promising activity in previously untreated patients with metastatic PDAC. Completion of accrual goal for this trial (48 patients), and longer follow-up and survival data will show whether this regimen deserves further investigation, either in a randomized phase III trial or as a chemotherapeutic backbone on which to add newer targeted therapies (Ko AH, etal, ASCOGI04, Abs 127).

Pain Management

Tumors pressing on surrounding nerves can cause severe pain, especially in the later stages of PDAC. Although pain is a real concern for people with pancreatic cancer, treatment with morphine or similar medications can provide relief in many cases. Long lasting forms of morphine taken only once or twice a day, provide a baseline degree of round-the-clock pain control, with immediate-acting narcotics used as needed for breakthrough pain.

When medication does not control unremitting pain, other options include cutting some of the nerves that transmit pain signals or injecting alcohol into these nerves

to block the sensation of pain. Palliative chemotherapy can sometimes improve PDAC-related symptoms, such cachexia, pain, and overall poor functional status.

TREATMENT COSTS

Pancreatic cancer is expensive to manage. Medicare payments for treatment of pancreatic cancer are estimated at an average of $30,000 per patient. Inpatient Medicare payment per patient with pancreatic cancer was $17,500 for those with no metastases and $16,800 for those with metastatic disease, while outpatient costs were virtually identical at $12,800 and $12,300, respectively (Zbrozek Arthur S, etal, ASCO02, Abs. 2592).

An estimate of the average cost of treatment was assessed for 53 patients with pancreatic cancer treated between 1997 and 1999 in 4 hospitals in southern Sweden. Average cost was estimated to €18,947, 55% of which was attributable to hospitalization (including surgical procedures), 20% to long-term care and 11% to chemotherapy. Diagnostic work-up and RT accounted for 9% and 4%, respectively. MST was 5.6 (mean=6.3) months. Treatment costs per patient were negatively correlated with age but were higher for patients treated with CRT and surgery than for those on standard supportive care. Disease stage and type of hospital (university versus regional/local hospital) were not significant predictors of cost per se. Based on the assumption that this estimate of average cost is representative for Sweden, the total healthcare cost for PDAC care was €16 million ($14 million), about 2%-3% of the cost of all cancer care in Sweden. Although the overall cost of pancreatic cancer in Sweden accounted for about the same proportion as in the USA, the cost per patient was about half of the USA estimate. The distribution of costs between the different types of treatment services did not differ greatly between Sweden and the USA (Hjelmgren J, etal, Acta Oncol 2003;42(3):218-26).

Introduction of novel agents and combination regimens based on new drugs will undoubtedly increase the cost of PDAC treatment.

Editors note: *Next issue covers novel agents in clinical and preclinical development. Information presented includes protocols and interin or final results of single agent or conbination clinical trials in pancreatic cancer.*

INDEX OF COMPANIES & INSTITUTIONS

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