TITLE: A Phase II Randomized Study of Induction Chemotherapy followed by Concurrent Chemo-radiotherapy in Locally Advanced Pancreatic Cancer

Coordinating Center： Taiwan Cooperative Oncology Group, National Health Research Institutes, Taipei, Taiwan

Coordinating Center Chief：劉滄梧主任

Study Chairperson： ✓陳立宗醫師 陳立宗 2013.11.12

Principal Investigator： ✓常慧如醫師、沈延盛醫師
台南市勝利路 367 號 2 樓
Telephone: (06) 2083422ext 65111
E-mail address: hjmc@nhri.org.tw
常慧如 2013/11/13

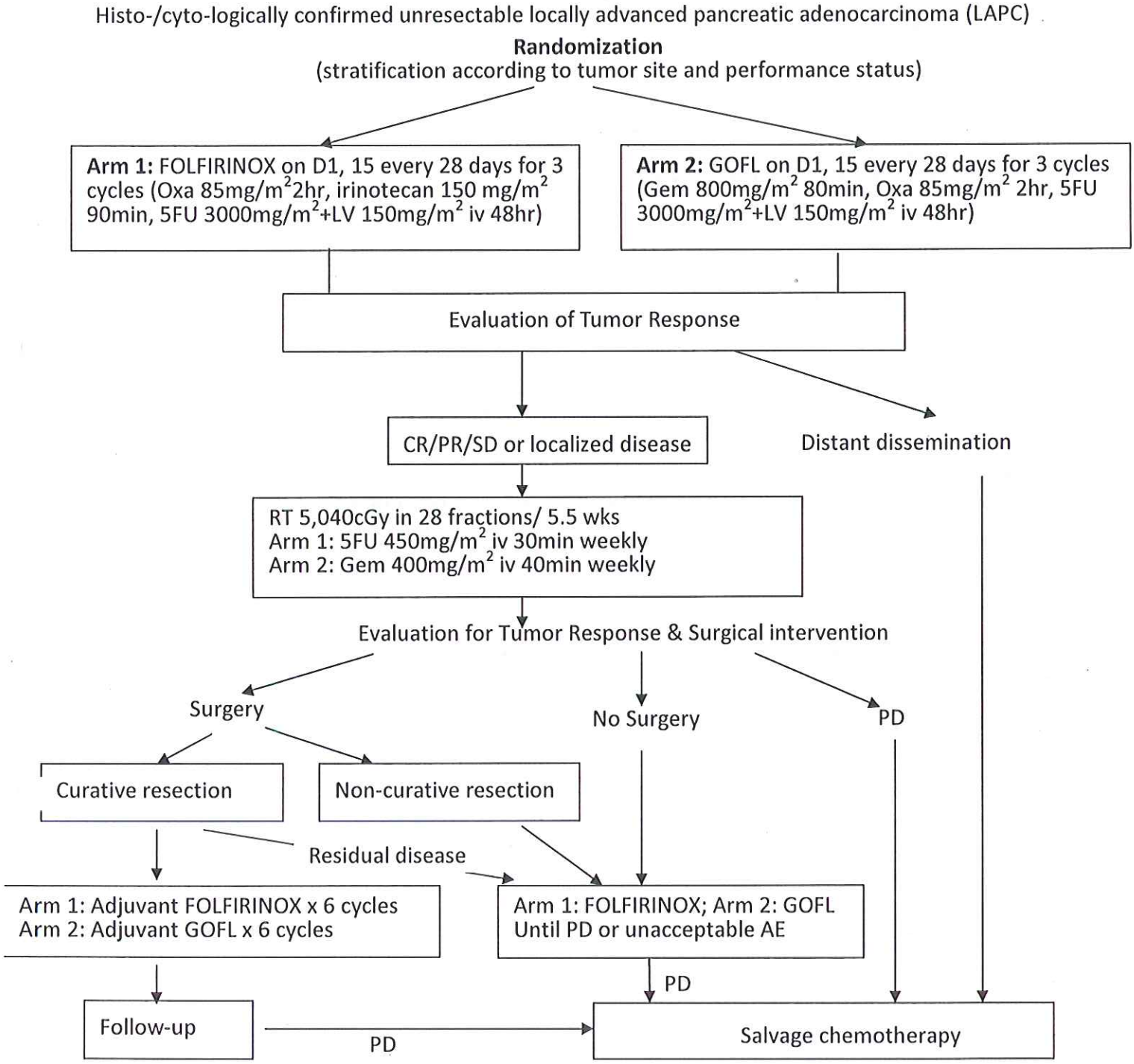
Statistician： 邱燕楓博士
苗栗縣 35053 竹南鎮科研路 35 號
Telephone: (037) 246166 ext 36107
E-mail address: ytchiu@nhri.org.tw

Co-Investigators：

台灣大學附設醫院	徐志宏醫師、許　駿醫師、章明珠醫師、林育麟醫師 田郁文醫師、王秀伯醫師、成佳憲醫師、蔡巧琳醫師 楊士弘醫師、劉高郎醫師
台南成大附設醫院	沈延盛醫師、蔡宏名醫師、蘇五洲醫師、顏家瑞醫師
林口長庚醫院	陳仁熙醫師、黃燦龍醫師、曾雁明醫師、徐鴻智醫師 周文其醫師、沈雯琪醫師
國衛院 癌研所	蔡坤志醫師、張光裕醫師、蔡慧珍醫師、姜乃榕醫師、 王韋淯醫師
馬偕醫院	謝瑞坤醫師、林炯森醫師、王蒼恩醫師、吳孟浩醫師 蘇迺文醫師
三軍總醫院	何景良醫師、陳宇欽醫師、戴明燊醫師、黃子權醫師 張平穎醫師、謝財源醫師、任益民醫師、詹德全醫師 吳宜穎醫師、陳佳宏醫師
高雄榮民總醫院	余明生醫師、林世哲醫師、陳建勳醫師
高醫附設醫院	李金德醫師、郭功楷醫師、蕭惠樺醫師、楊文祺醫師 黃志仁醫師、莊世昌醫師
高雄長庚紀念醫院	饒坤銘醫師、陳彥仰醫師、劉建廷醫師、蘇祐立醫師 吳佳哲醫師、陳彥豪醫師
萬芳醫院	彭汪嘉康、周志銘、張家崙
北醫附設醫院	邱仲峯、夏和雄
雙和醫院	陳明堯、黃銘德、謝燿宇

SCHEMA

This is a phase II randomized clinical trial assessing the efficacy of two triplet-agent induction chemotherapies (ICT) followed by concurrent chemoradiotherapy (CCRT) in locally advanced unresectable pancreatic cancer patients.



Objective:

To compare median 9 month progression free survival rate and safety profile of FOLFIRINOX vs GOFL as ICT followed by CCRT for LAPC patients.

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2. BACKGROUND

2.1 Pancreatic Cancer

According to the Cancer Registry Annual Report by Department of Health, 1380 patients were newly diagnosed to have pancreatic cancer and 1354 patients died of this disease in Taiwan in the year of 2007. It accounted for the 8th and the 7th leading causes of cancer-related death in men and women, respectively. [1] Patients who undergo surgical resection for localized nonmetastatic adenocarcinoma of the pancreas have a median survival of 13 to 20 months. However, less than 25% of patients are able to undergo complete resection.[2] The majority of pancreatic cancers are diagnosed at advanced stage. The survival of patients with inoperable pancreatic cancer is dismal, averaging only 3 - 4 months. For nonmetastatic, unresectable locally advanced, pancreatic cancer (LAPC), the median survival ranges from 6 to 10 months.

Concurrent chemoradiotherapy (CCRT) has been the mainstay of treatment for patients with unresectable LAPC. The Gastrointestinal Tumor Study Group (GITSG) performed a three-arm study in which 194 patients with LAPC were randomized to receive high-dose radiation (6,000cGy given in 2 week, split courses) with or without bolus 5-FU or moderate-dose radiation (4000cGy) with 5-FU.[3] Both combined-modality arms were superior to the radiation-alone arm in terms of overall survival at 1 year (40% vs. 10%, $p<0.05$) and median survival (41 *versus* 23 weeks, $p<0.05$). In a later study involving 43 patients, the GITSG compared chemotherapy alone, using the combination of streptozocin, mitomycin, and 5-FU, to radiation with concurrent 5-FU followed by chemotherapy with streptozocin, mitomycin and 5-FU.[4] Patients in the combined-modality arm had statistically significant improvements in 1-year survival (41 *versus* 19%, $p<0.02$) and median survival (42 *versus* 32 weeks). Conversely, an Eastern Cooperative Oncology Group study also compared chemotherapy alone (5-FU) to 5-FU based CCRT followed by 5-FU chemotherapy, and demonstrated no difference between the two arms in terms of either median time to failure (4.4 *versus* 4.2 months) or median survival (8.2 *versus* 8.3 months) in patients with LAPC. [5]

There are more questions raised after the introduction of gemcitabine, which is considered as the standard of care for advanced pancreatic cancer, including LAPC.

2.1.1 Should LAPC be treated as systemic diseases or localized malignancy?

Studies evaluating staging laparoscopy in pancreatic cancer revealed more than 30% of patients without radiographic evidence of metastases at presentation were found to have metastatic disease on laparoscopic evaluation.[6-8] In patients who receive CCRT before planned pancreaticoduodenectomy, repeat staging CT after CCRT reveals liver metastases in approximately 25%. [9,10] If these patients had undergone pancreaticoduodenectomy at the time of diagnosis, it is probable that the subclinical liver metastases would have already presented. Recent studies of induction chemotherapy (ICT) in LAPC consistently revealed that more than one quarter of patients did develop metastatic disease at the end of ICT.[11] The median survival of patients whose tumor progressed distantly during ICT had a median survival of only 7-8 months. The avoidance of prolonged recovery and morbidity associated with abdominal radiation in patients with such a short expected survival represents a distinct advantage of ICT in allowing disease biology to select patients for treatment. The recent FFCD/SFRO randomized study, which compared gemcitabine alone vs. induction CCRT followed by maintenance gemcitabine, showed that induction CCRT arm was associated with significantly inferior survival [median survival 8.4 vs 14.3 months of gemcitabine alone arm, p =0.014 (log-rank test)].[12] This negative impact of inductional CCRT could be partially attributed to systemic nature of LAPC, which required systemic treatment from the beginning.

2.1.2 Role of consolidation CCRT in the management of LAPC

Recent retrospective analysis of 181 LAPC enrolled to GERCOR studies revealed that 128 patients (70.3%) who had no disease progression after 3-month ICT were eligible for CCRT. Seventy-two (56%) received CRT (group A), whereas 56 (44%) continued CT (group B). The median survival times were 15.0 and 11.7 months, respectively (p=0.0009). [13] Theses results suggest that, after control of disease by initial CT, CCRT could significantly improve survival in patients with LAPC compared with CT alone. The advantage of the "ICT followed by consolidation CCRT" strategy is that this approach can provide patients with full doses of systemic therapy up-front and allow them an adequate period to " declare" themselves as having overt metastatic disease or not. Only those patients without disseminated disease after a predefined treatment period (2 to 6 months) will then receive consolidative CCRT, thus to avoid unnecessary CCRT to those who are going to have rapid systemic disseminated diseases.

Our earlier, prospective phase II study of inductional triplet chemotherapy (GOFL, consisting of gemcitabine 800 mg/m^2 (10 mg/m^2/min) followed by oxaliplatin 85 mg/m^2 and 48-hour infusion of 5-FU/LV 3,000 and 150 mg/m^2 Q 2 weeks) followed by CCRT could also achieve similar exciting survival results in LAPC. In that study, patients who did not experience disease progression (PD) after 6 cycles (3 months) of GOFL would had CCRT consisting of weekly gemcitabine 400mg/m^2 plus 50.4Gy/28 fractions of radiation 4-6 weeks later.[14] Among the 50 enrolled patients, 48 had definitively unresectable diseases. The best response after ICT were partial response(PR) in 9, stable disease in 26, and progressive disease or not evaluable in 15. Among the former 35 patients, 2 had disease progression before CCRT, and 3 declined to have CCRT. Of the 30 patients receiving

CCRT, an additional 4 and 1 patient(s) achieved PR at the end of CCRT and during maintenance chemotherapy, respectively. On intent-to-treat analysis, the overall best response was PR in 14 patients and stable disease in 21. The overall response rate and disease control rate were 28% and 70%, respectively. The median time to progression and overall survival of the intent-to-treat population was 9.3 months and 14.5 months, respectively. The time to progression (TTP) and overall survival of the 30 patients who had CCRT after ICT and the 20 patients who did not have CCRT were 14.7, 18.3 vs 2.4, 8.6 months, respectively. Neutropenia was the most common grade 3/4 toxicity of both ICT and CCRT, with a frequency of 28% and 26.7%, respectively. Significant sensory neuropathy occurred in 9 patients (18%).

Therefore, we are convinced that ICT followed by CCRT should be considered as the optimal treatment strategy for LAPC.

2.1.3 What do we need for inductional chemotherapy, gemcitabine-based *versus* non-gemcitabine based triplet chemotherapy

Gemcitabine became the reference regimen for advanced pancreatic cancer after a randomized trial showing significant improvement in the median overall survival as compared with fluorouracil administered as an intravenous bolus (5.6 vs 4.4 months, p=0.002).[15] The combination of gemcitabine with a variety of cytotoxic and targeted agents has generally shown no significant survival advantage as compared with gemcitabine alone. [16] Some studies have suggested a significant benefit associated with gemcitabine-based cytotoxic combinations in patients with good performance status. [17-19]

We had developed a triplet regimen consisting of biweekly fixed-dose rate (10 mg/m^2/minute) infusion of 800 mg/m^2 gemcitabine followed by 2-hour infusion of 85 mg/m^2 oxaliplatin and then 48-hour infusion of fluorouracil and leucovorin (3,000 and 150 mg/m^2, respectively) every 2 weeks, the GOFL regimen, for advanced pancreatic cancer. [20,21] Our phase II study showed that the overall-response and disease-control rates were 33.3% and 68.9%, respectively. Clinical benefit response was observed in 46.2% of initially symptomatic patients. The median time-to-tumor progression and overall survival were 5.1 (95% CI, 4.0–6.3) months and 8.7 (95% CI, 6.1–11.3) months, respectively. Major grade 3-4 toxicities were neutropenia (28.9%, with 4.4% complicated with fever), peripheral sensory neuropathy (15.6%), nausea/vomiting (13.3%), and diarrhea (6.7%).

We subsequently applied 6 cycles of GOFL as inductional chemotherapy followed gemcitabine-based CCRT in LAPC patients, which result in a median PFS and OS of 9.3 and 14.5 months, respectively.[14] Four (8%) out of 50 patients with LAPC underwent margin-free resection. The results are similar to the 6 to 10% resection rate of initially unresectable pancreatic cancer patients receiving inductional chemo-radiotherapy.[22,23]

However, a recent randomized phase III study evaluating gemcitabine alone vs a non-gemcitabine based triplet combination, FOLFIRINOX (oxapliplatin, 85mg/m^2; irinotecan, 180mg/m^2; leucovorin, 400mg/m^2; and fluorouracil, 400mg/m^2 given as a bolus followed by 2400mg/m^2 given as a 46-hour continuous infusion, every 2 weeks), in 342 metastatic pancreatic cancer patients revealed a significant difference of response rate (31.6% vs 9.4%), progression-free

(6.4 vs 3.3 months) as well as overall survival (11.1 vs 6.8 months) in favor of FOLFIRINOX. [24]As compared with gemcitabine, FOLFIRINOX was associated with a survival advantage and had increased toxicity. The author concluded that FOLFIRINOX is an option for the treatment of patients with advanced pancreatic cancer with good performance status. The trial by Conroy et al suggest that we should be moving beyond gemcitabine as the reference standard in randomized clinical trial design, especially in patients with good performance status. In the setting of LAPC, it would be appropriate to consider use of FOLFIRINOX as part of ICT, especially as one might expect a higher proportion of candidates to be fit enough to receive more aggressive chemotherapy. However, as many patients in this context receive multimodality therapy, we need greater experience to define the optimal duration that FOLFIRINOX can and should be given before consolidative CCRT is administered.[25]

To address the issue of optimal triplet ICT for LAPC, we design this prospective phase II randomized trial to compare the clinical outcomes of LAPC receiving standard FOLFIRINOX *versus* GOFL for 3 months as ICT followed by CCRT.

2.1.4 Successful pancreatic resection after chemoradiotherapy

Because surgical resection of the primary tumor remains the only potentially curative treatment for pancreatic cancer, preoperative irradiation has been studied to assess its ability to render unresectable LAPC into resectable disease. Radiographic response after CCRT generally ranged from 20 to 40%. Surgical resection rate was around 7 to 20%.[2] The recent report from Snady H. et al [26]demonstrated that survival of patients who had surgical resection of inductional CCRT downgraded unresectable LAPC was significantly greater than the survival of patients with a resectable carcinoma receiving primary segmental or total pancreatectomy. Therefore, despite the low resection rate in our previous "inductional GOFL followed by CCRT"-treated LAPC patients, we still recommend patients to be evaluated for surgical intervention after completion of CCRT in current study.

On the other hand, curative surgical resection after CCRT is mostly possible in patients with initial stage of "borderline" unresectable rather than those with "definitive" unresectable LAPC diseases. [22,23]That is the reason we include "borderline versus definitive unresectable disease" as one of the stratification criteria in current study.

2.2 Study Agents

2.2.1 Gemcitabine and 5-FU combination

Preclinical study demonstrated synergistic interaction between 5-FU and gemcitabine[27]. While gemcitabine increases 5-FU activity by depletion of cellular deoxyuridine monophosphate (dUMP) pools and inhibition of thymidylate synthase, 5-FU prevents inactivation of gemcitabine monophosphate by deamination. Because of the single-agent activity of 5-FU and gemcitabine in pancreatic cancer and the non-overlapping toxicity profiles of these two drugs, combination of

standard-dose or high-dose 5-FU plus gemcitabine in treating advanced pancreatic cancer has been studied in several phase II trials.[28,29] They achieved response rates of 3.7 – 43% and a median survival of 5.5 – 13 months. Clinical benefit response ranged from 45 to 57%. We conducted a phase II trial using weekly 30-minute infusion of gemcitabine (800mg/m^2) followed 2 hours later by 24-hour infusion of high dose 5-FU (3000mg/m^2) and leucovorin (300mg/m^2) in advanced pancreatic cancer. [30]An objective response rate of 22% (95% confidence interval: 9-35%) including one complete response and eight partial responses in 41 treated patients was observed. The median time to progression and median overall survival were 4.1 months (95% CI: 3.6-4.6 months) and 6.9 months (95%CI: 6.0-7.8 months) respectively, with 21% of patients surviving at one year. Twenty patients (48%; 95%CI: 32-63%) experienced clinical benefit response in 41 assessable patients. Myelosuppression was the main toxicity in this study.

2.2.2 Gemcitabine and oxaliplatin combination

Preclinical data support an optimal synergistic effect using the sequence gemcitabine followed by oxaliplatin.[31] A multicenter phase II trial [32] using biweekly gemcitabine (1000mg/m^2 in 10mg/m^2/min infusion, D1) and oxaliplatin (100mg/m^2 in 2-hour infusion, D2) to treat advanced pancreatic carcinoma showed a response rate of 28.6% (95% confidence interval 17.2 – 40%) and a median progression-free survival of 21 weeks. Overall, 29.7% of patients experienced a grade 3 – 4 toxicity, which included neutropenia (10.9%), thrombocytopenia (9.4%), nausea/vomiting (10.9%), diarrhea (4.7%), and peripheral neuropathy (7.8%).

2.2.3 Oxaliplatin and 5-FU combination

As stated above, both 5-FU and oxaliplatin have synergistic effect with gemcitabine. Furthermore, oxaliplatin was synergistic with 5-FU in preclinical studies [33-35]. The combinations of oxaliplatin with various schedules of 5-FU have been evaluated in several clinical trials for colorectal cancer, all suggesting a beneficial effect of the combination. [36,37] A phase II trial using biweekly oxaliplatin 80mg/m^2 intravenous infusion followed by 400mg/m^2 of 5-FU given by bolus injection and then 48-hour continuous infusion of 5-FU (3000mg/m2) and leucovorin (150mg/m^2) in treating 5-FU-resistant advanced colorectal cancer was conducted by Hsieh et al. [38]They reported an overall response rate of 33%. The regimen was well tolerable. Toxicities including grade 3 neurotoxicity in 10%, grade 2 neurotoxicity in 27.3%, grade 3-4 vomiting in 10%, grade 3 stomatitis in 3.3%, grade 3-4 neutropenia in 10%, and grade 4 thrombocytopenia in 3% of patients were observed.

We had conducted a phase I/II study to evaluate the feasibility of a triplet regimen consisting of biweekly fixed-dose rate (10 mg/m^2/minute) infusion of 800 mg/m^2 gemcitabine followed by 2-hour infusion of 85 mg/m^2 oxaliplatin and then 48-hour infusion of fluorouracil and leucovorin (3,000 and 150 mg/m^2, respectively) every 2 weeks, the GOFL regimen, in advanced pancreatic cancer patients. [20,21] On intent-to-treat analysis, the overall-response and disease-control rates were 33.3% and 68.9%, respectively. Clinical benefit response was observed in 46.2% of initially symptomatic patients. The median time-to-tumor progression and overall survival were 5.1 (95% CI,

4.0–6.3) months and 8.7 (95% CI, 6.1–11.3) months, respectively. Major grade 3-4 toxicities were neutropenia (28.9%, with 4.4% complicated with fever), peripheral sensory neuropathy (15.6%), nausea/vomiting (13.3%), and diarrhea (6.7%).

2.2.4 Irinotecan and 5-FU/Oxaliplatin combination

Irinotecan has some clinical activity against advanced pancreatic cancer.[39,40] Preclinical studies have indicated that irinotecan has synergistic activity when it is administered before fluorouracil and leucovorin. [41-44] Oxaliplatin and irinotecan show synergistic activity in vitro.[45] Given the relative absence of overlapping toxic effects among fluorouracil, leucovorin, irinotecan , and oxaliplatin, a regimen combining these agents was studied by Conroy T et al.[24] In 171 metastatic pancreatic cancer patients enrolled to the phase III study, FOFIRINOX revealed a response rate of 31.6% and disease control rate of 70.2%. At 6 months, 31% of the patients had a definitive decrease in the scores on Quality of Life scale. The progression-free survival and overall survival were 6.4 months (95% CI, 5.5 to 7.2) and 11.1 months (95% CI, 9.0 to 13.1), respectively. Major grade 3-4 toxicities were neutropenia (45.7% with 5.4% complicated with fever), vomiting (14.5%), diarrhea (12.7%) and sensory neuropathy (9%).

2.3 Radiotherapy and Radiosensitizer

2.3.1 Radiosensitizer

Combined-modality treatment most commonly consists of radiation and fluorouracil (5-FU), based on a single study that demonstrated improved median survival with the combination as compared with radiation therapy alone.[3] The delivery of 5-FU as a protracted venous infusion has been investigated more recently, in an attempt to optimize radiosensitization.[46,47] The impact of this change in the schedule of 5-FU administration is not apparent, and as yet there are no data to indicate improved survival.

The use of gemcitabine with concurrent radiotherapy represents an approach to improve the outcome of pancreatic cancer patients. The integration is prompted further by laboratory studies that have demonstrated potent radiosensitization in human cancer cell lines.[48] In these studies, exposure to noncytotoxic concentrations of gemcitabine produced radiation enhancement ratios of 1.7 to 1.8. Radiosensitization was also noted to persist for 24 to 48 hours after a brief (2-hour) exposure to gemcitabine. Advances in the technical delivery of radiation therapy have further stimulated the renewed interest in concurrent chemoradiotherpy regimens for patients with pancreatic cancer.

However, the toxicity regarding gemcitabine in combination with radiation is notoriously high. The multicenter Phase I trial attempted to determine the maximum tolerable dose of gemcitabine when delivered once weekly, concurrent with 50.4Gy showed hematologic and gastrointestinal toxicity to be dose limiting at 700mg/m^2.[49] Late toxicity remains a concern in patients treated at 600mg/m^2. Objective partial responses were not observed at doses ranging from 300-500mg/m^2. In a recent ECOG trial, the use of gemcitabine with concurrent protracted venous infusion (PVI)

5-FU and radiation therapy was investigated, with weekly gemcitabine doses ranging from 50-100mg/m^2. Three of seven patients on the trial experienced gastrointestinal dose limiting toxicity (DLT) at low weekly doses of gemcitabine. In two patients, this occurred following completion of radiotherapy (59.4Gy in 1.8 fractions). [50] Blackstock et al have investigated twice-weekly gemcitabine during a course of conventional radiotherapy (50.4Gy) in an attempt to maximize radiosensitization. [51]Hematologic and gastrointestinal toxicity were noted at 60 mg/m^2, nearly one-tenth of full dose for systemic therapy. A dose of 40mg/m^2 concurrent with 50.4Gy has been investigated in a Phase II CALGB 89850 trial based on this work. Only 26% of patients completed therapy without treatment breaks or dose reductions.[52]

A retrospective study from MDACC compares the toxicity and efficacy of concurrent gemcitaine-based chemoradiation with that of concurrent 5-FU-based chemoradiation in patients with unresectable pancreatic cancer. [53]Patients receiving weekly gemcitabine (250-500mg/m^2) developed significantly more severe acute toxicity during treatment (23% vs 2%) than did those receiving continuous-infusion 5-FU (200-300mg/m^2). Patients treated with gemcitabine had a similar local progression rate (62% vs 61%) and median survival (11mo vs 9 mo) to patients treated with 5-FU.

Despite the acute toxicity of combining gemcitabine with radiation, the significant clinical benefit from gemcitabine and equivalent local effect compared to that of 5-FU explain the trend of combining gemcitabine with radiation in pancreatic cancer patients. It is apparent hat RT volumes will need to be critically assessed and controlled in order to provide maximally tolerated gemcitabine. Our previous experience revealed minimal toxicity of limited radiation volume up to 5040cGy /28 fractions and weekly gemcitabine 400mg/m^2 in LAPC [14]and curatively resected [unpublished result] pancreatic cancer patients. In this study, we would like to use weekly 5FU versus weekly gemcitabine with RT after ICT with FOLFIRINOX or GOFL, respectively.

2.3.2 Radiation Volume

Radiation treatment volume is perhaps the most critical variable influencing gastrointestinal toxicity in chemoradiotherapy regimens for pancreatic cancer patients.[54]One obvious way to widen the therapeutic ratio in concurrent chemoradiotherapy is to omit elective nodal irradiation. Investigators at the University of Michigan have championed this principle in patients with unresectable disease.[55]The assumption was based on that the majority of the benefit from radiation would result from control of the primary tumor, rather than control of subclinical disease in these nodes. The goal of this effort is to maximize the systemic drug effect while providing local control through sensitization of a modest radiation dose. The standard dose of gemcitabine (1000mg/m^2/wk) was combined with three-week duration of RT with increasing fraction size. Thirty-seven patients with unresectable pancreatic cancer were treated using this approach. The dose-limiting toxicity was noted in 2 of 6 patients at the dose level of 42Gy in 2.8 fractions. Application of the linear quadratic model indicates that 42Gy in 2.8 Gy fractions is biologically equivalent to 50.4Gy in 1.8Gy fractions, a relatively standard dose and fractionation schedule used in the treatment of patients with unresectable pancreatic cancer. Loco-regional progression was

noted in 10 and distant progression in 25 of 37 patients. Only one patient developed local or regional progression in the absence of distant progression. The patterns of failure suggest that the reduction in the radiation dose and field size did not result in excess locoregional failure.

Regional nodes could potentially be controlled by standard doses of chemotherapy as would more distant sites. This strategy required more accurate identification of the primary tumor and three-dimensional conformal radiation treatment. The data on local and regional control suggest that the reduction in radiation field size in the regimen has not resulted in excess failures at these sites.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas.

3.1.2 Patients must have locally advanced pancreatic cancer (LAPC).

3.1.3 Patients must have LAPC evaluated by radiologist and/or surgeon according to either abdominal CT or MRI, or intra-operative findings.

* Locally advanced unresectable disease was defined by CT or MRI images as low-density tumor (primary and/or lymphadenopathy) with
  1) extension to the celiac axis or superior mesenteric artery,
  2) occlusion of the superior mesenteric-portal venous confluence
  3) aortic, inferior vena cava (IVC) invasion or encasement
  4) invasion of SMV below transverse mesocolon

  or unresectable after surgical exploration.

Those who had superior mesenteric vein impingement, superior mesenteric artery abutment were defined as **borderline resectable.**
Those who had superior mesenteric vein occlusion, superior mesenteric artery encasement were defined as **unresectable.**

3.1.4 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See section 8.2 for the evaluation of measurable disease.

3.1.5 Age ≥20 years and ≦70 years.

3.1.6 ECOG performance score of 0 or 1; see Appendix A.

3.1.7 Patients must have normal organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mL
- platelets ≥100,000/mL
- total bilirubin ≤1.5X institutional upper limit of normal

- ALT(SGPT) ≤5 X institutional upper limit of normal
- creatinine within normal institutional limits or
  creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

3.1.8 Patients who present with jaundice will be allowed to enroll after control with temporary or permanent internal/external drainage.

3.1.9 The effects of study agents on the developing human fetus at the recommended therapeutic dose are unknown. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients with distant metastases are not eligible.

3.2.2 Patients with endocrine or acinar pancreatic carcinoma.

3.2.3 Patients may be receiving any steroid, immunologic or other investigational agents within 4 weeks prior to enrollment.

3.2.4 Patients who have had prior chemotherapy or radiotherapy are not eligible.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agents used in the study.

3.2.6 Patients who have above grade II peripheral neuropathy.

3.2.7 Patients who had non-curable second primary malignancy within five years, except for non-melanoma skin cancer.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant women are excluded from this study because the study agents has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with study agents, breastfeeding should be discontinued if the mother is treated with the study agents.

3.2.10 Those who are immuno-compromised or receiving immuno-suppressive therapy are excluded from the study because of increased risk of lethal infections and possible pharmacokinetic interactions with study agent administered during the study.

3.2.11 Those who have chronic diarrhea.

4. TREATMENT PLAN

Patients should be randomized to two study arms stratified by performance status (ECOG 0 or 1) and tumor sites (head and body/tail) after enrollment. Eligible patients will be randomly assigned on a 1:1 basis to either of two study groups, using a central randomization procedure.

Randomization will be performed at the TCOG coordination center using a computer-generated procedure.

After randomization, ICT will be administered for 3 cycles (3 months). Patients who have radiological evidence of distant dissemination will be shifted to salvage chemotherapy. Patients who have responsive, stable disease as well as those with localized progressive disease after ICT will receive concurrent CCRT at least 4 weeks after the last dose of ICT. Surgical evaluation will be performed 4-6 weeks after the completion of CCRT. Patients who have resectable disease will undergo surgical resection. Postoperative adjuvant chemotherapy for 6 cycles (6 months) will be given for those who are considered to have curative resection. Patients who still have unresectable disease or non-curative resection will receive systemic chemotherapy till disease progression or unacceptable toxicity.

4.1 Agents Administration during Induction Chemotherapy

For Arm 1, ICT with FOLFIRINOX will be administered biweekly. For Arm 2, ICT with GOFL will be given biweekly. Reported adverse events and potential risks for gemcitabine, oxaliplatin, irinotecan, 5-FU and leucovorin are described in Section 6. Appropriate dose modifications are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

4.1.1 Treatment schedule of induction chemotherapy

For Arm I: Each dose of **FOLFIRINOX** will be administered as intravenous infusion of oxaliplatin at a dose of 85 mg/m^2, given as a 2-hour infusion, with the addition, after 30 minutes, of irinotecan at a dose of 150mg/m^2, given as a 90-minute infusion. The treatment was immediately followed by a continuous intravenous infusion via central venous catheter of 3000mg/m^2 plus leucovorin 150mg/m^2 over a 48-hour period on day 1 and 15 every 28 days/cycle. For Arm II: Each dose of **GOFL** chemotherapy will be administered as intravenous infusion of 800mg/m^2 gemcitabine at a fixed rate of 10 mg/m^2/min followed by a 2-hour intravenous infusion of oxaliplatin and then a 48-hour intravenous infusion via central venous catheter of 5-FU 3000mg/m^2 and leucovorin 150mg/m^2 on day 1 and 15 every 28 days/cycle.

4.1.2 Premedication before chemotherapy

Patients will receive 4mg of dexamethasone and anti-histamine(optional) and appropriate anti-emetics (serotonine antagonists) before each dose of chemotherapy. Atropine sulfate 0.25mg

iv push prior to Irinotecan. Calcium gluconate and magnesium sulfate supply pre and post oxaliplatin were decided by attending physician.

4.1.3 Study Agents

4.1.3.1 Gemcitabine administration:

Gemcitabine 800 mg/m^2 in Arm 2 will be dissolved in 250 ml of normal saline and infused intravenously at a fixed rate of 10 mg/m^2/min for 80 min. After the administration of gemcitabine, the infusion line should be flushed with 20 ml of normal saline and then 50 ml of 5% glucose solution before the administration of oxaliplatin.

4.1.3.2 Oxaliplatin administration:

For both arms, Oxaliplatin 85 mg/m^2 will be dissolved in 250 ml of 5% glucose solution and administered intravenously within 120 minutes. After the administration of oxaliplatin, the infusion line should be flushed with 50 ml of 5% glucose solution before the infusion of 5-FU or irinotecan.

4.1.3.3 Infusion of Irinotecan

For Arm 1, irinotecan should be administered 30 minutes after the complete of oxaliplatin infusion. The infusion line should be flushed with 50ml of 5% glucose water before irinotecan of 150mg/m^2 in 250ml 5% D/W, given as a 90-minute infusion. The infusion line should be flushed with 50ml of 5% glucose water before the administration of 5-FU.

4.1.3.4 Infusion of 5-FU / leucovorin:

For both arms, 3000 mg/m^2 of 5-FU and 150 mg/m^2 of LV will be admixed in saline with a total volume of 500 ml and infused with the aid of a single infusion pump over a period of 48 hours. (Alternatively, 3000 mg/m^2 of 5-FU and 150 mg/m^2 of LV will be admixed in 2.5% G/W saline with a total volume of 250 ml and infused with the aid of a disposable infusion bag over a period of 48 hours, or 5ml/hr Infusor admixed in 0.9% NaCl total volume 240ml, infusion 48 hours.)

4.2 Supportive Care Guidelines

Prophylactic G-CSF will not be routinely used in this study. In case of febrile neutropenia, patients should be treated with appropriate antibiotics. Therapeutic G-CSF may be used at the discretion of attending physicians for high risk patients.

Cholinergic syndrome related to irinotecan can be controlled by giving Atropine 0.25mg subcutaneously at time of irinotecan administration. Should the syndrome develop, a further dose of atropine may be given.

Diarrhea may occur within 30-90 min of irinotecan infusion, or may be delayed. Once a liquid stool occurs, loperamide 4mg should be taken immediately followed by 2mg 2 hourly for at least 12 hours, and for 12 hours following the last liquid stool. Patients should be instructed to drink large volumes of water/electrolytes. Concomitant fever or vomiting will

require hospitalization for iv hydration. If diarrhea persists for 24 hours despite the loperamide, a prophylactic course of ciprofloxacin 250mg po bid for 7 days should be started. After 48 hours of persistent diarrhea, the patient should be hospitalized for parenteral support and review of treatment. Prophylactic ciprofloxacin should also be commenced in patients with neutrophils $<0.5x10^9/l$, even in the absence of diarrhea. Patients who develop severe neutropenia are especially at risk of infection if they are also suffering from diarrhea.

For acute cold related dysaesthesia due to oxaliplatin, many patients experience transient paraesthesia of hands and feet and some experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patient should be well advised on precautions to be taken. Does not require treatment or dose reduction. For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium +1gm of Calcium Gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made.

For cumulative dose related peripheral sensory neuropathy, it usually occurs after a cumulative dose of $800mg/m^2$. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3-5 months to recovery.

For allergic reactions to oxaliplatin during infusion, immediate intervention is to stop the infusion and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU. The patient may be re-challenged with oxaliplatin on the next cycle, with steroid and antihistamine cover eg. dexamethasone 8mg iv and chlorphenamine 10mg iv and ranitidine 50mg iv 30 min pre-dose. Oxaliplatin infusion should also be started slowly, with a gradual increase in infusion rate as tolerated.

Coronary artery spasm is a recognized complication of 5FU although the evidence base regarding etiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.

4.3 Duration of ICT

In the absence of treatment delays due to adverse events, treatment may continue for 3cycles (28 days as one cycle) or until one of the following criteria applies:

- X Radiographic documented disease progression,
- X Inter-current illness that prevents further administration of treatment,
- X Unacceptable adverse events(s),
- X Patient decides to withdraw from the study, or
- X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.4 Agents and Radiation Administration during Concurrent Chemoradiotherapy

4.4.1 Treatment schedule during CCRT

4.4.1.1 Patient selection

Patients were evaluated after 3 cycles of ICT. Patients who have progressive disease due to distant metastasis or patients who have local progression which can not be encompassed within radiation fields will be given salvage systemic chemotherapy and will not be enrolled into CCRT. Patients who have only local progressive disease but still maybe encompassed within radiation field, and patients who achieve complete remission, partial remission or stable disease will be enrolled into 2nd phase of the study, CCRT, at least 4 weeks after the last dose of ICT.

4.4.1.2 Treatment schedule

For Arm 1, 5FU 450mg/m^2 in 250ml normal saline will be infused for 30 mins weekly 2hrs before RT on day 1, 8, 15, 22, 29, 36.
For Arm 2, Gemcitabine 400mg/m^2 in 250ml normal saline will be iv infused for 40mins, 2hrs before RT on day 1, 8, 15, 22, 29, 36.
Radiation will be given 180cGy per day, 5 days a week for 28 fractions to totally 5040cGy.

4.4.1.3 Premedication for CCRT

Patients were suggested to be given dexamethasone 2mg orally three times a day (tid) from the morning of their first radiotherapy fraction. The prophylactic dexamethasone will be continued until after they had received their fifth radiation treatment. Therefore, depending on the day of the week the patients started treatment, dexamethasone will be taken for 5 to 7 days. All patients will be issued with rescue medication, prochlorperazine 10mg every 6 hours orally if they develop nausea and vomiting. If patients still have nausea and/or vomiting during treatment of dexamethasone and prochlorperazine or after the fifth day of radiotherapy, ondansetron 8mg orally or iv one to three times per day or granisetron 1mg per po or iv once everyday 30mins before radiotherapy should be given.

4.4.2 Study Agents

5-FU 450mg/m^2 will be dissolved in 250ml normal saline and infused intravenously for 30 mins.
Gemictabine 400mg/m^2 will be dissolved in 250ml normal saline and infused intravenously at a fixed rate of 10mg/m2/min for 40 mins.

4.4.3 Radiation

4.4.3.1 Radiation technique

Radiation should be performed by high-energy linear accelerators. Techniques of at least three-dimensional conformal radiation treatment planning should be used in all cases. Patients will be immobilized in a foam cradle in a supine position, and the treatment planning CT was obtained. Tumor mapping should be performed according to treatment planning CT and the diagnostic CT before induction chemotherapy. Treatment planning was performed with the isocenter calculated at 100% and the 95% line encompassing the planning target volume. The spinal cord was limited to 4600cGy. If one kidney was to receive more than 20Gy then more than 90% of the remaining kidney was excluded from the primary beam. Generally, a three to four-field beam arrangement (opposed laterals with posterior with or without anterior) was used.

4.4.3.2 Radiation volume

The gross tumor volume is the primary tumor identifiable on CT scan before induction chemotherapy. The clinical target volume was defined as the gross tumor volume plus 1.0 cm. The planning target volume was the clinical target volume plus 0.5cm for daily patient set-up variation. No prophylactic nodal irradiation will be given.

4.4.3.3 Radiation dosage

A total dose of 5,040cGy in 28 fractions, 180cGy per fraction, one fraction per day, 5 days per week, will be given.

4.5 Surgery

4.5.1 Surgical evaluation

Patients completed induction chemotherapy and concurrent chemoradiotherapy will be evaluated for surgical resection. If there is evidence of distant metastasis, consultation for surgical intervention will not be arranged. The feasibility of surgical resection will be evaluated by qualified surgeon according to contrast-enhanced abdominal CT or MRI. Laparoscope is optional for pre-surgical evaluation.

4.5.1.1 Resectable

- No distant metastases
- Clear fat plane around celiac and superior mesenteric arteries (SMA)
- Patent superior mesenteric vein (SMV)/portal vein

4.5.1.2 Borderline resectable

- Severe unilateral SMV/portal impingement
- Tumor abutment on SMA
- Gastroduodenal artery (GDA) encasement up to origin at hepatic artery
- Colon or mesocolon invasion
- Adrenal, colon or mesocolon, or kidney invasion

4.5.1.3 Unresectable

- Distant metastases
- SMA, celiac encasement
- SMV/portal occlusion
- Aortic, inferior vena cava (IVC) invasion or encasement
- Invasion of SMV below transverse mesocolon
- Rib, vertebral invasion

4.5.2 Treatment schedule of surgery

Surgery will be performed within 4-6 weeks after CCRT complete.

4.5.3 Surgical technique

Patients whose tumor is considered to be resectable will undergo laparotomy. If complete surgical resection is feasible, optimal surgery will be performed. If complete surgical resection is impossible, biopsy with or without palliative surgery (eg. bypass surgery) may be performed.

4.6 Adjuvant/Maintenance Chemotherapy

4.6.1 Treatment schedule

Patients who have curative surgical resection will receive additional 6 cycles (6 months) of adjuvant chemotherapy (Arm 1, FOLFIRINOX; Arm 2, GOFL) within 6-8 weeks after surgery and then followed up until tumor progression. Patients who are not feasible for curative resection, will receive continued chemotherapy (Arm 1, FOLFIRINOX; Arm 2, GOFL) at least 4 weeks after CCRT complete. The regimen will continue till disease progression.

Patients who develop progressive disease during systemic chemotherapy will shift to salvage chemotherapy. Salvage chemotherapy for Arm 1 includes GOFL, ADI-PEG etc.; for Arm 2 includes PEP02, ADI-PEG etc.

5 DOSING DELAYS/DOSE MODIFICATIONS

5.1 Dose modifications and delays for ICT of GOFL

5.1.1 Dose modification and delays according to hematologic toxicity

Hemogram and WBC classification within 36 hours prior to each dose of chemotherapy should be taken to make sure that ANC is no less than $1.5x10^9$/L and platelet count no less than 100×10^9/L. Patients will receive a dose of chemotherapy every 2 weeks if they have adequate ANC and platelet counts as stated above. If patients' ANC or platelet count is not adequate, the scheduled dose of chemotherapy should be delayed for one week. After a one-week delay of chemotherapy, if patients' hemogram does not recover to ANC count not less than $1.5x10^9$/L and platelet count not less than 100×10^9/L, the scheduled dose of chemotherapy should be delayed for another week. If patients' hemogram does not recover to ANC count not less than $1.5x10^9$/L and platelet count not less than 100×10^9/L before day 28, they should be off the study.

5.1.2 Dose modification and delays for oxaliplatin

In the event of Grade 2, Grade 3, or Grade 4 neuropathy, oxaliplatin should be discontinued. Dosing or continuation of gemcitabine, 5-FU, and leucovorin will not be affected by neuropathy (except hyper-ammonemic encephalopathy).
With any of the conditions described in sections 5.1.2.1 ~ 5.1.2.5, the dose of oxaliplatin should be reduced by 20 %.

5.1.2.1 Platelet count < 25×10^9/L

5.1.2.2 Platelet count < 50×10^9/L associated with bleeding

5.1.2.3 ANC of < 0.5×10^9/L associated with fever of > 38.5℃ or documented infection

5.1.2.4 Delay of chemotherapy for two consecutive doses of chemotherapy

5.1.2.5 Any non-hematologic toxicity of Grade 3 or 4 with the exception of nausea,

vomiting, alopecia, neuropathy, mucositis, diarrhea and hyper-ammonemic encephalopathy.

5.1.2.6 In the presence of grade 3/4 mucositis or diarrhea, the dose of oxaliplatin will be reduced only after 5-FU being modified firstly (as defined at section 5.1.3.2).

5.1.3 Dose modification and delays for 5-FU

5.1.3.1 In the presence of 5-FU associated hyper-ammonemic syndrome (occurrence of severe nausea/vomiting, irritable and / or conscious disturbance in association with hyperammonemia at or near the end of 5-FU infusion), the next dose of 5-FU will be reduced to 2400 mg/m^2. If symptomatic hyper-ammonia still presence, the dose will be further decreased to 1600 mg/m^2 in subsequent cycles of treatment.

5.1.3.2 In the presence of grade 3/4 mucositis and/or diarrhea, the dose of 5-FU will be firstly reduced to 2400 mg/m^2. If grade 3/4 mucositis/diarrhea persist after 5-FU dose reduction, the dose of oxaliplatin will be reduced by 20 % in subsequent cycle treatment.

5.1.3.3 After the dose reduction of oxaliplatin described in section 5.1.2 has been applied, if any of the conditions described in sections 5.1.2.1~5.1.2.5 is still observed, the dose of 5-FU will be reduced to 2400 mg/m^2 in subsequent cycles of treatment.

5.1.4 If the conditions described in sections5.1.2.1~5.1.2.5 can still be observed after the dose modification of oxaliplatin and 5-FU, (described in sections 5.1.1and 5.1.2), patients should be off the study. These patients may be treated with single agent gemcitabine or with the regimen at the discretion of in-charged physician.

5.1.5 Patients who experience grade 3-4 allergic reaction or anaphylaxis to oxaliplatin will continue the treatment protocol with the omission of oxaliplatin in his/her subsequent treatment.

5.1.6 Patients who experience grade 3-4 allergic reaction or anaphylaxis to gemcitabine will continue the treatment protocol with the omission of gemcitabine in his/her subsequent treatment. (5-FU will be used as radiosensitizer in the part of chemoradiotherapy).

5.2 Dose modifications and delays for ICT of FOFIRINOX

5.2.1 Dose modifications and delays for hematologic toxicities

Hemogram and WBC classification within 36 hours prior to each dose of chemotherapy should be taken to make sure that ANC is no less than 1.5x10^9/L and platelet count no less than 100 × 10^9/L. Patients will receive a dose of chemotherapy every 2 weeks if they have

adequate ANC and platelet counts as stated above. If patients' ANC or platelet count is not adequate, the scheduled dose of chemotherapy should be delayed for one week. After a one-week delay of chemotherapy, if patients' hemogram does not recover to ANC count not less than $1.5x10^9$/L and platelet count not less than 100×10^9/L, the scheduled dose of chemotherapy should be delayed for another week. If patients' hemogram does not recover to ANC count not less than $1.5x10^9$/L and platelet count not less than 100×10^9/L before day 28, they should be off the study.

5.2.1.1 Dose modifications and delays due to neutropenia

5.2.1.1.1 First occurrence of low neutrophils (ANC<$1.5x10^9$/L), febrile neuropenia for >7 days, reduce irinotecan to 120mg/m^2.

5.2.1.1.2 Second occurrence of the above mentioned hematologic toxicities, reduce oxaliplatin to 60mg/m^2.

5.2.1.1.3 Third occurrence of the above mentioned hematologic toxicities, stop treatment and off patient from the study.

5.2.1.2 Dose modifications and delays due to thrombocytopenia

5.2.1.2.1 First occurrence of low platelets (plat <100×10^9/L), reduce oxaliplatin to 60mg/m^2 and reduce 5FU to 75% of original dose.

5.2.1.2.2 Second occurrence of the above mentioned hematologic toxicity, reduce irinotecan to 120mg/m^2.

5.2.1.2.3 Third occurrence of the above mentioned hematologic toxicity, stop treatment and off patient from the study.

5.2.2 Dose modifications and delays for non-hematologic toxicities

5.2.2.1 renal impairment

Cockcroft & Gault formula (GFR=(140-age)*(Wt in kg)*(0.85 if female) /(72*serum Cr in ug/dL) may be used to predict creatinine clearance. If borderline.

5.2.2.1.1 If CrCl(ml/min)<30, omit oxaliplatin, give irinotecan at 50% dose and 5FU at 80% dose.

5.2.2.2 hepatic impairment

5.2.2.2.1 If Bilirubin 1.5-3x ULN or ALP>5x ULN, give irinotecan at 50% dose.

5.2.2.2.2 If Bilirubin>3xULN, give oxaliplatin 50% dose, omit irinotecan and give 5FU at 50% dose.

5.2.2.2.3 Significant impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment. Always discuss deteriorating organ function with consultant.

5.2.2.3 diarrhea

For management of diarrhea, see section 4.2.

If diarrhea from the previous cycle, even if not severe, has not resolved (without loperamide for at least 24 hours) by the time the next cycle is due, delay 1 week.

5.2.2.3.1 First occurrence of grade 3/4 diarrhea or diarrhea with fever, reduce

irinotecan to 120mg/m^2.

5.2.2.3.2 Second occurrence of the above symptoms, reduce oxaliplatin to 60mg/m^2 and reduce the infusion 5FU to 75% of previous dose.

5.2.2.3.3 Third occurrence of the above sysmptoms, stop treatment and off patients from the study.

5.2.2.4 neurological toxicity

5.2.2.4.1 If neurological symptoms occur lasting >7 days and troublesome, reduce oxaliplatin dose to 65mg/m2.

5.2.2.4.2 If paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose to 65mg/m2.

5.2.2.4.3 If paraesthesia with functional impairment persisting until the next cycle, oxaliplatin should be discontinued.

5.2.2.5 stomatitis

If mouth ulcers ≧ grade 2 develop, reduce the 5FU doses by 25% for subsequent cycles unless further toxicity occurs.

5.2.2.6 palmar/plantar erythema

Treat symptomatically, initially with pyridoxine 50mg po tid. If symptoms continues to be a problem (grad 3.4), reduce 5FU by 25% for subsequent cycles.

Dose modification for FOFIRINOX:

Toxicity	1st occurrence	2nd occurrence	3rd occurrence
Neutropenia	Reduce irinotecan to 120mg/m2	Reduce oxaliplatin to 60mg/m2	Off study
Thrombocytopenia	Reduce oxaliplatin to 60mg/m2 and 5FU to 75%	Reduce irinotecan to 120mg/m2	Off study
Renal impairment	Omit oxaliplatin, give irinotecan at 50% and 5FU at 80%		
Hepatic impairment	Bil 1.5-3x, ALP>5x irinotecan 50% Bil>3x Omit irinotecan, give oxaliplatin and 5FU at 50%		
Diarrhea	Irinotecan to 120 mg/m2	Oxaliplatin to 60mg/m2 and 5FU to 75%	off
Neurological	Without functional impairment, reduce oxaliplatin to 65mg/m2 Functional impairment, DC oxaliplatin		
Stomatitis	5FU to 75%		
Palmar/plantar erythema	5FU to 75%		

5.2.3 Adjustment of starting dose of irinotecan

5.2.3.1 If more than 50% of the first twelve patients enrolled to Arm 1 (FOLFIRINOX) experienced adverse effects that required dose modification during the first

two cycles of induction chemotherapy, the starting dose of irinotecan will be decreased to 120mg/m2 in the following patients enrolled to Arm 1. Dose modification of irinotecan, with starting dose of 120mg/m2, will be revised proportionally to 96mg/m2.

5.3 Dose modifications and delays for concurrent chemoradiotherapy

5.3.1 Dose modifications and delays according to hematologic toxicity

Hemogram and WBC classification within 36 hours prior to each dose of Gemcitabine or each week for 5FU should be taken to make sure that ANC is no less than 1.0×10^9/L and platelet count no less than 80×10^9/L. Patients will receive a dose of gemcitabine chemotherapy every week or 5FU infusion if they have adequate ANC and platelet counts as stated above. If patients' ANC or platelet count is not adequate, the dose of weekly gemcitabine or 5FU chemotherapy should delayed for one week. After one week rest, if patients' hemogram does not recover to ANC count not less than 1.0×10^9/L and platelet count not less than 80×10^9/L, the scheduled dose of gemcitabine or 5FU should be delayed for another one week. If patients' hemogram does not recover to ANC not less than 1.0×10^9/L and platelet count not less than 80×10^9/L after 2 week's rest, chemotherapy will be discontinued for the rest of time during radiotherapy. Radiotherapy will be delayed only after chemotherapy was delayed for two weeks or Grade 4 hematologic toxicity occurred.

5.3.2 Dose modification and delays according to non-hematologic toxicity

In the event of Grade 3 GI toxicity despite adequate antiemetics, gemcitabine or 5FU will be discontinued first. If the GI toxicity persisted during radiation, radiotherapy will be discontinued for one week. Radiation and gemcitabine/or 5FU will be resumed after GI toxicity relieved to less than Grade 3 but no later than two weeks. In the event of Grade 4 GI toxicity, radiation therapy will be discontinued. Patient will be evaluated for systemic chemotherapy after recovery from GI toxicity.

5.4 Criteria to Off-Study

5.4.1 Presence of NCI grade 4 nausea, vomiting that refractory to appropriate anti-emetics management.
5.4.2 Progressively worsening of NCI $\geq$ grade 2 of peripheral neuropathy after the omission of oxaliplatin.
5.4.3 Repeat occurrence of $\geq$ grade 3 infection.
5.4.4 Presence of severe allergic reaction or anaphylaxis to gemcitabine and / or oxaliplatin.
5.4.5 Presence of other unmanageable NCI $\geq$ grade 3 non-hematologic toxicity after dose reduction.

5.4.6 Presence of prolonged (> 7days) NCI grade 3 hematologic toxicity and/or the presence of neutropenic fever at lower than 50% dosage of investigational agent.
5.4.7 Refusal of treatment
5.4.8 Disease progression
5.4.9 Inadequate compliance to the request of protocol
5.4.10 Patients death

6. AGENT FORMULATION AND PROCUREMENT

6.1 Irinotecan

6.1.1 Irinotecan (CPT-11, Irino®) produced by TTY Biopharm Company, Taipei, Taiwan will be used in the current trial. The Irinotecan used in this trial is not liposomal encapsulated.

6.1.2 Mechanism of action:

The hydrochloride salt of a semisynthetic derivative of camptothecin, a cytotoxic, quinoline-based alkaloid extracted from the Asian tree Camptotheca acuminate. Irinotecan is activated by hydrolysis to 7-ethyl-10-hydroxy-camptothecin (SN-38), an inhibitor of topoisomerase I. This is then inactivated by glucuronidation by uridine diphosphate glucoronosyltransferase 1A1 (UGT1A1). The inhibition of topoisomerase I by the active metabolite SN-38 eventually leads to inhibition of both DNA replication and transcription.Becuase ongoing DNA synthesis is necessary for irinotecan to exert its cytotoxic effect, it is classified as an S-phase –specific agent.

6.1.3 Adverse Effect

6.1.3.1 Diarrhea

Irinotecan-associated diarrhea is severe and clinically significant, sometimes leading to severe dehydration requiring hospitalization or intensive care unit admission

6.1.3.2 Immunosuppression

The immune system is adversely impacted by irinotecan.

6.1.4 Pharmacogenomics

Irinotecan is converted by an enzyme into its active metabolite SN-38, which is in turn inactivated by the enzyme UGT1A1 by glucuronidation. People with variants of the UGT1A1 called TA_7, also known as the "*28 variant", express fewer UGT1A1 enzymes in their liver and often suffer from Gilbert's syndrome.[56] In 2005, the FDA made changes to the labeling of irinotecan to add pharmacogenomics recommendations, such that irinotecan recipients with a homozygous polymorphism in UGT1A1 gene, to be specific, the*28variant, should be considered for reduced drug doses.[Camptosar®, irinotecan hydrochloride injection August 2010, http://labeling.pfizer.com/ShowLabeling.aspx?id=533]

6.1.5 Clinical Formulation

Irinotecan is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2ml-fill vials contain 40mg irinotecan hydrochloride and 5ml-fill vials contain 100mg irinotecan hydrochloride. Irinotecan is intended for dilution with 5% dextrose injection, USP(D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluents is 5% Dextrose Injection, USP.

6.2 Gemcitabine

6.2.1 Gemcitabine hydrocloride will be used in the current trial. The drug is available as vials containing 200mg or 1000mg sterile lyophilized material.

6.2.1.1 Chemical information:

Gemcitabine hydrocloride is 2'-deoxy-2',2'-difluorocytidine monohydro-chloride (β-isomer). The empirical formula is $C_9H_{11}F_2N_3O_4$-HCl with a calculated molecular weight of 299.66.

6.2.1.2 Mechanism of action:

Gemcitabine (dFdC) is metabolized intracellularly by nucleoside kinase to active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP.

6.2.1.3 Metabolism:

Following a single 1,000 mg/m^2/30 minutes infusion of radiolabeled gemcitabine, 92% to 98% of the dose is recovered within one week after gemcitabine administration. Gemcitabine is rapidly metabolized by cytidine deaminase in the liver, kidney, blood and other tissue to form dFdU. The metabolite dFdU is extensively distrubuted into tissues and is excreted in urine without further biotransformation.

6.2.1.4 Pharmacokinetics:

The pharmacokinetics of gemcitabine appears to be linear over the doses examined. Peak gemcitabine plasma concentrations obtained immediately after the end of a single 1,000 mg/m^2/30 minutes infusion range from 10 to 40 *u*g/mL with a terminal half-life of 17 minutes. Plasma concentration of gemcitabine obtained following a single 1,000 mg/m2/30 minutes infusion is > 5 *u*g/mL for approximately 30 min after the end of infusion and > 0.4 *u*g/mL for an additional hour.

6.2.2 Adverse effects

6.2.2.1 Hematological toxicity:
Gemcitabine is a bone marrow suppressant. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count.

6.2.2.2 Gastrointestinal toxicity:
Mild, transient impairment of liver function tests were relatively common, but rarely necessitate stopping treatment. Nausea and vomiting occurred in 1/3 of patients, and most of them were manageable with standard anti-emetics. Transient diarrhea was reported by 7% of patients but none of the patients discontinued therapy because of diarrhea.

6.2.2.3 Renal toxicity:
Mild proteinuria and hematuria are reported in approximately half of treated patients, but are rarely clinically significant. However, 0.6% of renal failure of uncertain etiology have been reported hence gemcitabine should be used with caution in patients with impaired renal function.

6.2.2.4 Pulmonary toxicity:
Approximately, 10% of patients experienced dyspnea which usually abated spontaneously without any specific therapy. Only 0.6% of patients discontinued due to dyspnea and only 0.1% of these believed to be drug-related.

6.2.2.5 Allergic toxicity:
Mild skin rash is seen in 25% of patients and is associated with pruritus in 10% of them.

6.2.2.6 Neurotoxicity:
Mild to moderate somnolence occurs in 10% of patients, but only 0.1% of patients discontinued therapy for somnolence. Severe asthenia and paresthesias occur in 1.4% and 0.2%, respectively.

6.2.2.7 Flu-like syndrome:
Approximately 20% of patients experienced flu-like symptoms.

6.2.2.8 Edema/ peripheral edema:
Edema / peripheral edema is reported by 30% of patients.

6.2.3 Clinical formulation:
Gemcitabine hydrochloride is commercially available in a sterile form for intravenous use only. Vials of gemcitabine hydrochloride contain 200 mg (expressed as free base) in the form of a sterile lyophilized material. After reconstituted in 0.9% sodium chloride, the preparation

is suitable for intravenous injection. Due to solubility consideration, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentration greater than 40 mg/mL (less than 5 mL 0.9% sodium chloride injection solution to the 200 mg vial) may result in incomplete dissolution, and should be avoided. Solutions of reconstituted gemcitabine should be stored at room temperature (15 to 30℃) and should be administered within 24 hours. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

6.3 Oxaliplatin

6.3.1 Oxaliplatin (Oxalip) produced by TTY Biopharm Company, Taipei, Taiwan will be used in the current trial. It is available in the form of vials of sterile solution. Each vial contains 50mg of oxliplatin in 10ml solution. The concentration of oxaliplatin in the solution is 5mg/ml.

6.3.2 Mechanism of action:
Oxaliplatin is a diaminocyclohexane (DACH) carrier ligand-based platinum compound that inhibits DNA synthesis. The major cytotoxic lesions are intrastrand platinum-DNA adducts. Interstrand cross-link may also be formed, although that account for < 5% of the total platinum-DNA adducts.

6.3.3 Adverse effects:

6.3.3.1 Neurotoxicity:
The dose-limiting toxicity of oxaliplatin is sensory neuropathy. Oxaliplatin-induced sensory neuropathy takes two forms. The first is tingling of the extremities, which may also involve the perioral region, and occurs early in treatment and usually resolves within a few days. With repeated dosing, symptoms may last longer between cycles, but do not appear to be of long duration or cumulative. Laryngopharyngeal spasm and cold dysesthesia may be observed after infusion of oxaliplatin in 1 to 2% of patients. The resulting feeling of difficulty in breathing or swallowing is distressing to the patient, but symptoms resolve within hours of onset and can be prevented by prolonging the duration of infusion. A second neuropathy, more typical of that seen with cisplatin, affects the extremities and increases with repeated doses. Functional impairment, which includes difficulty in executing activities requiring fine sensory-motor coordination such as writing and buttoning clothing, may necessitate dosage reduction. In an analysis of data from 682 patients enrolled in 9 clinical trials, the risk of developing functional impairment was estimated to occur in 10% of patients receiving a cumulative oxaliplatin dose of 780 mg/m2, and in 50% of patients at a cumulative dose of 1170 mg/m2.

6.3.3.2 Nephrotoxicity:

Unlike cisplatin, oxaliplatin dose not appear to be nephrotoxic.

6.3.3.3 Ototoxicity:

Oxaliplatin has not been associated with ototoxicity.

6.3.3.4 Hepatic toxicity:

Transient elevation in liver function parameters may occur on patients treated with oxaliplatin.

6.3.3.5 Gastrointestinal toxicity:

Nausea and vomiting were commonly observed but were easily controlled using standard antiemetic regimens including 5-HT3 antagonists. Diarrhea was reported in 41% of patients but reached grade 3 – 4 in fewer than 5% of them. Mucositis occurred in only 4% of patients and was of mild intensity in most cases.

6.3.3.6 Hematologic toxicity:

Myelosuppression is uncommon and is not severe with oxaliplatin as a single agent, but is a feature of combination regimens involving this drug.

6.3.3.7 Cardiac toxicity:

Oxaliplatin does not induce cardiac toxicity.

6.3.3.8 Allergic reactions:

Infrequent allergic reactions have been described. Anaphylactic type reactions were reported in around 0.5% of patients treated with oxaliplatin.

6.3.3.9 Vesicant reactions:

Oxaliplatin has demonstrated minimal or no vesicant potential.

6.3.3.10 Alopecia:

Oxaliplatin does not induce clinically significant alopecia.

6.3.4 Clinical formulation:

It is recommended that Oxaliplatin should be diluted for infusion in 250 ml to 500 ml of 5% glucose solution. Oxaliplatin should not be mixed or administered with saline or other chloride-containing solutions or alkaline media such as basic solutions of 5-FU. These media should not be administered via the same infusion line and the line should be flushed after oxaliplatin infusion. Furthermore, any equipment containing aluminum should not be used for the administration of oxaliplatin.

6.4 5-FU

6.4.1 Mechanism of action:

5-Fluorouracil is an analog of uracil, and can be metaboilzed intracellularly to both the ribonucleotide level and to the deoxyribonucleotide level. Fluoro-uridine triphosphate can be incorporated into RNA by RNA polymerase, and consequently interferes with RNA processing and function. Fluoro-deoxyuridine monophosphate is a potent inhibitor of TS. FdUTP can also be incorporated into DNA.

6.4.2 Clinical toxicity:

5-Fluorouracil functions as an antimetabolite, and its main toxic effects are exerted on rapidly dividing tissues, primarily the gastrointestinal tract (manifested by mucositis, diarrhea, nausea/vomiting) and bone marrow (leukopenia and granulocytopenia, thrombocytopenia). Dermatologic toxicity (dermatitis, alopecia, pigmentation abnormalities) may also occur. Less frequently obersved toxicities include neurologic toxicity (central), and ocular toxicity; isolated case reports of chest pain in temporal association with 5-FU administration suggest that 5-FUmay produce cardiac toxicity in rare circemstances.

6.4.3 Clinical formulation:

5-FU is commercially available in 10 ml ampules as a colorless aqueous solution containing 500 mg/10 ml. Fluorouracil should be stored at room temperature. This undiluted preparation is suitable for direct intravenous injection or for infusion in sodium chloride solution.

6.5 Calcium leucovorin

6.5.1 Mechanism of action:

Leucovorin is the formyl derivative and active form of folinic acid used to counter the hematologic and other toxicities associated with methotrexate and other antifolates.

6.5.2 Clinical toxicity:

Allergic sensitization has been reported following both oral and parenteral administration of folinic acid. The administration of LV with 5-FU augments the severity of toxicity typically associated with 5-FU.

6.5.3 Clinical formulation:

Leucovorin calcium injection is a sterile solution of folinic acid (as calcium salt) in water for injections. Sodium chloride is included for isotonicity. The vial of 50 mg / 5 ml contains sodium methyldroxy-benzoate 0.09% w/v and sodium propylhydroxybenzoate 0.02% w/v as bactericides. When required for intravenous infusion, it may be diluted in 1 litre of 5%w/v glucose in water for injection or normal saline.

7. STUDY CALENDAR and Translational Studies

7.1 Study Calendar

Baseline blood evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Wk 1	Wk 3	Wk 5	Wk 7	Wk 9	Wk 11	Wk 13-16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Surgical evaluation Wk 26-28	Regularly every 8 wks till off study
ICT Arm1 FOLFIRINOX Arm 2 GOFL		X X	X X	X X	X X	X X	X X									
Arm 1 5FU Arm 2 Gem CCRT									xxxxxxx X xxxxx	xxxxxxx X xxxxx	xxxxxxx X xxxxx	xxxxxxx X xxxxx	xxxxxxx X xxxxx	xxx X xxx		
Informed consent	X															
Weight	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Performance Status	X		X		X		X			X		X		X	X	X
Quality of Life [6]	X						X					X			X	X
CBC, W/diff	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Serum chemistry [5]	X	X		X		X	X		X			X			X	X
CEA , CA19-9	X					X	X		X			X			X	X
CXR	X					X	X								X	X
Abd CT or MRI	X					X		X[1]							X[2]	X
PES (optional)	X															
Tissue collection [3] (optional)	X															
Translational study [4] (optional)	X					X			X						X	X

1. First imaging evaluation will be performed (during wk 9 or later) after 2 cycles of induction chemotherapy ; Second imaging study to confirm the tumor status (if not PD at wk 9) will be performed (during wk 13-16 or later) after 3 cycles of ICT and before the start of CCRT.

2. At least 4 weeks after CCRT complete, abdominal CT should be performed to evaluate post-CCRT response as well as for surgical evaluation. If no surgery will be performed, confirmation of post-CCRT response should be done 8 weeks later.
3. Biopsy or surgical pathology tissue of pancreas tumor and/or non-tumor part pancreas before ICT may be collected. Any biopsy or surgical pathology tissue during or after treatment may also be collected depend on attending physician's discretion and patient's approval.
4. Blood sampling 8cc in heparinized glass tube. Time schedule of collection: Before ICT and every 8 weeks thereafter till off study.
5. Serum chemistry include Bil T/D, AST, ALT, ALP, LDH, rGT ,Na, K, Cl,BUN, Cr, Sugar AC and other items according to attending physician's decision.
6. The patient's quality of life during this study will be evaluated before treatment, and every 8-10 weeks.

7.2 Translational study

7.2.1 Objectives:

1) The primary end point is to measure drug resistance, cancer progression and metastasis associated biomarkers from blood sample and tumor tissue of pancreatic cancer patients before and after primary treatment.
2) The secondary end point is to correlate biomarkers with clinical outcomes of pancreatic cancer patients.

7.2.2 Introduction and Rationale

1) Heterogenous progression pattern in locally advanced pancreatic cancer patients

As previously mentioned in section 2.1.1, We believe that most locally advanced pancreatic cancer should be treated as systemic disease. Radical local therapy such as surgery and radiotherapy should be reserved for patients with low metastatic potential or patients who had responsive or stable disease after systemic chemotherapy.

On the other hand, there are 8 (16%) patients developed local progression during ICT of T1204 trial. Two (4%) of them progressed over local only without distant disease.(unpublished data) An autopsy study in pancreatic cancer patients revealed 8 to 15% of pancreatic cancer patients died from local destructive disease without distant metastasis.[57] In this group of patients, upfront radical surgery or aggressive local radiation might provide beneficial effect to patients not only for survival time but also for quality of life.

Before the development of effective systemic therapy, it is urgent to develop biomarkers to differentiate between high risk of local destructive disease or distant metastasis in patients presented initially with localized pancreatic cancer.

2) Treatment resistance of pancreatic cancer

Despite intensive efforts, the prognosis for patients with pancreatic adenocarcinoma remains very grave. The benefits of systemic chemotherapy combined with radiation are even more limited. The reason for relative treatment resistance could be the low perfusion found in pancreatic cancer lesions compared with the normal pancreas, already indicated by early angiographic studies [58] and recent combine functional imaging studies. [59]

The angiogenesis of tumors is important in predicting the growth and metastasis of pancreatic cancer. Therefore, drugs targeting the inhibition of oncogenic signaling pathways to block angiogenesis have recently been developed. [60] The fact that antiangiogenic drugs have not consistently provided significant benefit in pancreatic cancer [61] could be due to the large variability in perfusion found in untreated lesions. Furthermore, inadequate blood supply that is unable to meet energy demands results in metabolic stress and low oxygen levels. [62]

Current issues to be addressed are the optimal treatment strategy for tumors with flow-metabolism mismatch; the appropriate dosing schedule of antiangiogenic therapy to normalize the delivery of oxygen and nutrients to the tumor and possibly render it

more sensitive to systemic or radiation therapy; and the role of targeting tumor vasculature in regard to the imbalance between metabolism and perfusion. Besides functional imaging studies and in vivo studies, the molecular mechanism that regulates tumor blood perfusion, metabolism and sensitivity to therapy should be investigated. In addition to tumor itself, the mechanical tumor microenvironement contributes significantly for tumor blood perfusion and interstitial pressure which lead to tumor phenotypes of resistance, progression and metastasis.

3) Tumor-stroma interaction in pancreatic cancer

The host stromal response to an invasive epithelial carcinoma is frequently called a desmoplastic reaction and is a universal feature of pancreatic ductal adenocarcinoma. [63] The complex interplay between the normal host epithelial cells, invading tumor cells, stromal fibroblasts, inflammatory cells, proliferating endothelial cells, an altered extracellular matrix, and growth factors activating oncogenic signaling pathways by autocrine and paracrine mechanisms are responsible of progressive tumor growth and invasion through mechanisms include anoikis resistance, genomic instability, and drug resistance. [63] Several key molecules have been identified such as collagen type I, fibronectin, laminin, matrix metalloproteinases(MMPs), and their inhibitors, growth factors (transforming growth factor β, platelet-derived growth factor, connective tissue growth factor, and hepatocyte growth factor), chemokines and integrins as constituents of the desmoplastic reaction.[64] Despite these findings, it is unclear which molecular cellular events initiate and drive desmoplasia in pancreatic cancer. Accumulating evidence indicates that pancreatic stellate cells when activated switch to a myofibroblast phenotype that produces components of the extracellular matrix, MMPs and tissue inhibitors of MMPs by activating the mitogen-activated protein kinase (extracellular signal regulated kinase 1/2) pathway. [65]

Based on current evidence, we would like to develop prognostic biomarker and therapeutic targets focusing on tumor-stromal interaction of pancreatic cancer.

4) The role of TGFβ signaling pathway in pancreatic cancer

The TGFβ plays a dual role in carcinogenesis, acting early as a tumor suppressor but promoting tumor progression in later stages. During tumor development, many tumor cells lose their growth inhibitory responses to TGFβ. This results from low expression levels of TGFβ receptors, mutations of Smad proteins, or the induction of TGFβ resistance by oncogenes.[66] Smad 4 mutations [67] or loss of Smad 4 immunostaining [57] have been correlated with poor prognosis and metastatic phenotype of pancreatic cancer. It is now apparent that TGFβ signaling is tightly controlled by an increasing number of cytoplasmic (eg. Smad 7) and nuclear (eg. coproteins) mechanisms that integrate the TGFβ signal within a regulatory network of the cell. Furthermore, TFGβ activates a distinct pattern of signaling pathways (eg . PI3K, JNK) and transcription factors such as the TGFβ-inducible early response gene (TIEG, also named Klf10) proteins, which may work

concurrently or independently of the Smads in TGFβ mediated pancreatic growth control. In addition, there is an increasing number of cellular mechanisms affecting the final response of a cell to TGFβ. This includes crosstalk with other signaling pathways (eg. Ras) and the induction of transcription factors.

Development of the knowledge of TGFβ signal transduction in pancreatic cancer will provide the theoretical framework for future studies aimed at developing candidate biomarker and effective therapeutic strategies to treat this dismal disease.

5) The role of extracellular matrix/integrin signaling pathway in pancreatic cancer

The integrin family of cell adhesion receptors regulates a diverse array of cellular functions crucial to the initiation, progression and metastasis of solid tumors. Integrins directly bind components of the extracellular matrix (ECM) and provide the traction necessary for cell motility and invasion. ECM remodeling is also controlled by integrins, which regulate the localization and activity of proteases. In addition to migration and invasion, integrins can regulate tumor proliferation and drug resistance.[68] Depending on environmental cues, integrins have the ability to either enhance cell survival or initiate apoptosis. In vitro studies revealed that down regulation of integrins beta 1, alpha 5 and alpha 6 increased pancreatic cancer cell motility, invasion and decreased adhesion. [69] From 25 resection specimen of pancreatic cancer, overexpression of integrin-linked kinase (ILK) correlated with the increase in expression of the E-cadherin repressor Snail.[70] Furthermore, increased intrinsic chemoresistance to gemcitabine in pancreatic cancer was correlated with focal adhesion kinase (FAK) phosphorylation. [71]

Preclinical studies revealed that integrin antagonists inhibit tumor growth by affecting both tumor cells and tumor associated host cells, most notably the angiogenic endothelium. Integrin antagonists currently in clinical trials include monoclonal antibodies and RGD peptide mimetics. Years of preclinical and early clinical trials have now culminated in the initiation of a Phase III clinical trial in glioblastoma with the RGD peptide mimetic cilengitide. [68]

Besides developing biomarkers and therapeutic target, investigation of ECM/integrin signaling in pancreatic cancer may elucidate the factors responsible for tumor susceptibility to integrin inhibitors and ultimately influence how effective these agents are as cancer therapeutics.

7) Conclusion

Pancreatic cancers are represented by distinct genetic subtypes with significantly different patterns of failure. Determination of candidate biomarker status at initial diagnosis may be of value in stratifying patients into treatment regimens related to local control versus systemic therapy. Development of candidate therapeutic targets to reverse chemotherapy and radiation resistance is another promising strategy.

Genetic profiling of tumor cells has already revealed important regulators of the drug resistance, metastatic process and suggested novel targets for cancer

therapeutics. However, examining the resistance/metastatic signature at the tumor stroma will prove useful in more completely preventing tumor spread. Targeting the tumor cell alone may not be sufficient. Multi-modality therapy against tumor cells, their growth factors and the essential accessory cells with which cancer cells interact is imperative if the prognosis of resistance/metastasis is to be improved.

This study may provide essential information for optimizing multimodality treatment strategy in pancreatic cancer patients. Exploring the fundamental events promoting tumor-stroma interaction may expose new targets for diagnostic and therapeutic strategies and reduce the morbidity and mortality from resistant and metastatic disease.

7.2.3 Sample collection

Collection of tissue and blood sample is base on no disturbance of patients' regular diagnostic and therapeutic procedure. If there is no adequate tissue or blood sample to collect, patients will not be exclude from the trial.

a. Tissue

Formalin fixed or fresh tissue specimens/slides from patients enrolled onto this study will be obtained after patients' approval.

1) Only biopsy or surgical specimens will be collection. Aspiration cytology specimens will not be qualified for collection.
2) Specimens before primary treatment will be collected. Specimens during or after treatment will also be collected.
3) Formalin fixed pancreas tumor, non-tumor part pancreas tissue/ or slides will be obtained from Departments of Surgery and/or Pathology. For each sample, at least two biopsy specimens (in formalin) or ten 4 μm plus three 10μm thick blank pathology slides should be collected.
4) Fresh frozen tissue of pancreas tumor, non-tumor part pancreas tissue will be obtained from Department of Surgery. For each sample, at least two biopsy specimens (in at least -80°C) or ten 4 μm plus three 10μm thick blank pathology slides should be collected.
5) The tissue specimen will be evaluated for collagen type I, laminin, MMPs and their inhibitors, CTGF, TGFβ, TGFβ receptors, Smads, Klf10, Ras, HGF, integrins, MAPK, ERK, ILK, FAK, E-Cadherin,ZO-1, Snail, S100, fibronectin, DNMT-1.

b. Blood

Blood samples from patients enrolled onto this study will be obtained after patients' approval.

1) Amount of blood sampling each time: 8cc in heparinized green head glass tube.
2) Time schedule of collection: Before ICT and every 8 weeks thereafter till off study.
3) The blood sample will be evaluated for TGFβ, CTGF, HGF, GLUT2, GLUT4 and promising secreting markers from the candidate genes obtained from differential expression of Klf10 knockout and wild type mice, including Aacs, Acly, Acot3, Acss2, Angptl3, Cd36, Chpt1, Cpt1a, Cyb5r3, Cyp4a14, Cyp7a1, Dak, Elovl2, Elovl5, Elovl6, Fas, Gpd1, Hdlbp, Hpgd, Lpl, Mttp, Me1, Pctp, Pltp,

Ppap2b, Sc5d, Scd1, Serinc1, Spot14, Ugt2b38, Gbe1, Gpam, Pepck, L-Pk, Rdh12, Slc2a2, Sord, Ugt3a1.

c. Clinical information

Clinical information of initial disease status, treatment outcome including time to disease progression and pattern of progression will be collected.

d. Specimen Delivery

Tissue/blood collected by research nurses of participating hospitals will be send to central lab of NICR over Tainan (ext 65132). Blood sample should be delivered within 24 hr in room temperature. Pathology tissue samples may be collected in optimal condition (in formalin, in room temp., in -80°C, in nitrogen tank depending on the status of specimen) and be delivered within one month.

7.2.4 Laboratory evaluation

Immunohistochemical studies will be quantified by at least two pathologists independently without knowing clinical information. Previously mentioned secreted proteins within blood will be evaluated. DNA/RNA extraction for gene expression of previously mentioned molecules will be evaluated.

7.2.5 Statistical analysis

All analyses were performed using Statview software (version 5.0.1; SAS Institute Inc., Cary, NC). The Cox model was used to perform uni-variate analyses to determine the relative risk of each variable. Correlations between markers and clinico-pathologic parameters were determined using chi-square analysis. Survival curves were calculated using Kaplan-Meier analysis with assessment of statistical significance using the Mantel-Cox log-rank test.

7.3 Pharmacogenetics study

For study on the polymorphisms of cytochrome p450, UDP-glucuronosyltransferase, ATP-bidning cassette transporter, carboxylesterase and methylenetetrahydrofolate reductase, heparinized blood samples will be taken before enrollment. Genomic DNA will be prepared from peripheral leukocytes of theose heparinized blood samples. Polymerase chain reaction products of genomic DNA will be sequenced and analyzed for variant gene alleles.

8. MEASUREMENT OF EFFECT

For the purposes of this study, response rate should be evaluated for patients who complete ICT, CCRT with or without surgery. Patients should be evaluated for response to each stage of treatment in order to make decision of subsequent treatment strategy.

Evaluation for response to ICT at 13 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks (week 18) following initial documentation of objective response. Patients should be also evaluated for response to CCRT at 4 weeks after radiotherapy completed. If patients are going to receive surgical intervention, the response will be evaluated radiologically and surgically. If patients are not feasible for surgical intervention, confirmatory scans should be obtained not less than 4 weeks following initial documentation of objective response.

8.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee [72]Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below.

8.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with conventional techniques (CT, MRI, x-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Malignant lymph nodes must be≥15mm in short axis when assessed by CT scan.

8.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

8.1.3 Target lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

8.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

8.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Abdominal CT or MRI. These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously with reconstruction algorithm. Contrast enhanced as well as T1WI, T2 WI should all be performed in order to provide detailed information.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they should be followed regularly during treatment and must be normalized for a patient to be considered in complete clinical response.

8.3 Response Criteria

8.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive Disease (PD): At least a 20% increaseand an absolute increase of at least 5mm in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

8.3.2 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/
Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

8.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

8.3.4 Quality of Life

8.3.4.1 EORTC-QLQ-C-30 Questionnaire (Appendix C)

8.3.4.2 The patient's quality of life during this study will be evaluated by the questionnaire developed by Quality of Life Study Group of European Organization for Research and Treatment of Cancer (EORTC-QLQ-C30).

8.3.4.3 Patients will fill out or be asked the questionnaire by him-/herself before treatment, and every 8-10 weeks.

8.4 Confirmatory Measurement/Duration of Response

8.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 wks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks (see section 9.3.3).

8.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented.

8.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.5 Time to Tumor Progression, Progression-Free Survival and Overall Survival.

Time to tumor progression (TTP) is defined as the duration of time from start of treatment to time of progression.

Progression–Free survival (PFS) is defined as the time elapsed between treatment initiation and tumor progression or death from any cause.

Overall survival is defined as the duration of time from start of treatment to patient's death.

8.6 Distant Metastasis Rate

Distant metastasis rate is defined as the incidence of metastasis after the start of treatments. The treatment includes induction chemotherapy, concurrent chemoradiotherapy with or without surgery.

8.7 Response Rate

The response rate for the completion of individual chemotherapies is defined as the proportion of the number of patients having a complete response (CR) or a partial response (PR)

to the induction, concurrent, or combined chemotherapy, respectively. The denominator of the response rate for the induction chemotherapy is the number of patients treated by induction therapy. The denominator of the response rate for the concurrent chemotherapy is the number of patients treated by concurrent therapy. The denominator of the response rate for the combined chemotherapy is the number of patients enrolled in this study. The responses refer to the best overall responses defined in 8.3.3.

8.8 Disease Control Rate

The disease control rate is defined as objective response plus stable disease rate.

9. ADVERSE EVENTS

The descriptions and grading scales found in the revised NCI Common Terminology criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.[73] It is the responsibility of the investigators to detect and to document all adverse events (AEs) which occur during the study and which fulfill the definitions and criteria outlines in this protocol.

9.1 Definitions

9.1.1 Definition of Adverse Events (AE)

Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.1.2 Definition of Serious Adverse Events (SAE)

A serious adverse events is any untoward medical occurrence that at any dose, which fulfils the definition for an AE and in addition:

X results in death
X is life threatening
X requires inpatient hospitalization or prolongation of existing hospitalization but not caused by the nature course of disease nor regular check.
X results in persistent or significant disability /incapacity
X results in a congenital anomaly/birth defect

To assist with the above definitions, the following information is provided for clarification/ interpretation:

- *Life Threatening*: The patient was at immediate risk of death from the event. This term dose not refer to an event, which hypothetically might have caused death if it were more severe.
- *Disability/Incapacity*: The event results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.
- *Hospitalization:* Hospitalization signifies that the patients has been detained (usually involving at least an overnight stay) at the hospital or emergency ward

for observation and/or received treatment.

9.1.3 Definition of Unexpected Adverse Events

An adverse event, the nature of severity of which is not consistent with the Investigator's Brochure or summary of product characteristics.

9.2 Guidelines for adverse event reporting

Adverse event collection and reporting is a routine part of every clinical trial. The first step is to identify the event using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The severity of the event should then be graded using the CTCAE4.0 criteria. (http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx) All adverse events reported spontaneously by the patients or observations by the Investigator must be recorded on the CRF. The obligation of recording the adverse event will be continued until one month after completion of protocol treatment.

9.3 Serious Adverse Event Reporting

According to CTEP: NCI AE reporting guideline, for Phase III study, serious adverse events must be reported, when the severity is increased or unexpected adverse events causing inpatient hospitalization or prolongation of existing hospitalization but not caused by the nature course of disease, to the Sponsor by telephone (Tel:) or facsimile (Fax:) and to TCOG center, Tel: 037-246166 ext 35118 or Fax 037-580702; and the Principal Investigator, Hui-Ju Chang Tel: 06-2083422 ext 65111 or Fax: 06-2083427, as soon as possible and not later than one working day following the discovery of the event. A written report should follow the oral report within 7 working days to the Sponsor. The Sponsor will advise the Investigator of any further information or documentation that is required.

The Investigator should also report any serious/unexpected adverse events to the Ethics Committee, head of Institute, IRB (Institutional Review Board) and DOH (Department of Health in Taiwan).

9.4 Adverse Follow-up

Any serious adverse events that are still continuing at the time of a patient's final visit must be followed-up until resolution, stabilization or until that event has been determined to be caused by an etiology other than trial drug or trial participation.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design and Endpoints

This is a randomized phase II trial of ICT followed by CCRT with radiotherapy in LAPC. The efficacy will be primarily measured by progression free survival (PFS) as defined in Section 8.5.Other measurements include the response rate, disease control rate, overall survival, and patients' quality of life as described in Section 8. The secondary endpoint is to compare the

survival time.

10.2 Sample Size and Study Duration

In the proposed randomized phase II study for LAPC, ICT with FOFIRNOX arm will be the control arm. ICT with GOFL will be the experiment arm. Both ICT will be followed by CCRT if patients still have a localized disease. The primary endpoint of the present study is the progression free survival (PFS).

With a 2-year accrual period and 2 years follow-up after accrual, the 9-month median PFS rates of the two arms are assumed to be 45% vs. 55% with a difference of 0.1 (or a ratio of 0.22 (0.1/0.45)). The Selection Designs[74] using the Cox regression model to select a best treatment based on survival was used to determine the sample size required for this randomized phase II study. In such designs, sample size requirements are established so that when the true PFS rate of the actual best treatment is higher than all the others by a specified amount, it will be selected with a high probability, P. Equivalently, the chance of selecting a treatment actually inferior by the specified amount is 1-P. The probability P, also called "the correct selection probability" was set to be 0.8 in the present study.

Assuming Arm 1 is the treatment with the higher median PFS rate than the other, which can be either FOLFIRINOX or GOFL, the ratio between the median PFS of Arm 1 and Arm 2 is estimated to be 1.22 (0.55/0.45). Assuming exponential survival distributions with a correct selection probability of 0.8, the total sample size required for an improvement of 1.22, quantified by the ratio of the median PFS rates between these two arms, is 39.

We anticipate that the attrition rate is about 10%, hence, roughly 43 patients will be needed per regimen arm. As about 20 patients will be recruited per year, we anticipate that the recruitment will be completed in 4.5 years.

10.3 Statistical Analysis

10.3.1 Population for Analysis

A summary table for patient disposition will be provided. Patients will be categorized into an evaluable and/or intent-to-treat (ITT) patients population according to their termination status.

1. Intent-to-Treat Population

   The ITT population is defined to be all patients who are exposed to at least one dose of the ICT .

10.3.2 Demographic and Baseline Characteristics

The baselines for clinical findings, laboratory evaluations and performance status will be those evaluated at the beginning of the study. Demographic data and baseline characteristics will be summarized according to their data types.

10.3.3 Evaluation of the Response Rate

The overall response rates for the ICT, ICT+CCRT will be evaluated respectively. The response of ICT+CCRT will be evaluated at least 4 wk after the complete of CCRT and every 8 wks thereafter.

The response rates and their 95% confidence intervals will be calculated.

10.3.4 Evaluation of the Distant Metastasis Rate

Patients will be evaluated for distant metastasis after the completion of ICT and after the completion of CCRT with or without surgery. The evaluation to patients who complete the combined treatment will be followed at least once every 3 months during the subsequent years. The metastasis rates and their 95% confidence intervals will be calculated.

10.3.4 Evaluation of Time to Tumor Progression and Overall Survival

Upon completion of the study, the Kaplan-Meier [75] curves of time to progression, progression free and overall survival will be produced with 95 confidence intervals. The influence of prognostic factors on survival will be explored by Cox's proportional hazards regression model[76].

10.3.5 Evaluation of Quality of Life Scores

Patients will fill out or be asked the questionnaire before the start of the treatment and every 4 weeks afterward. Wilcoxon signed rank tests will be applied to assess the change of each score from the baseline to a specified time point. The pattern of changes over time for each score will be explored using GEE (Generalized Estimating Equation) approach [77].

10.4 General Statistical Consideration

10.4.1 Premature Termination and Missing Values

All available data will be displayed. Listings of patients with premature termination will be provided with the dates and reasons for termination. Missing data will not be replaced by any estimated or imputed values.

10.4.2 Multi-center Study

This is a multi-institutional study in Taiwan. The number of patients enrolled at each center will be small. As a result, the data from all centers will be pooled for statistical analysis.

10.4.3 Presentation of the Results

Kaplan-Meier estimates for progression-free survivals and overall survival will be plotted. Other analysis results will be presented in tables or figures. Point estimates of clinical endpoints will be provided with their corresponding 95% confidence intervals.

11. ETHICAL CONSIDERATIONS

11.1 Good Clinical Practice (GCP)

The trial will be carried out in accordance with the World Medical Association's Declaration of Helsinki as amended 1996 and in accordance with the GCP principles as defined in the International Conference on Harmonization of Technical Requirements for

Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice.

11.2 Ethics Committee Approval

The Investigator must submit a copy of the protocol to the local Ethics Committee for consideration. The study will not start until written approval of the protocol has been given by Institutional Review Board (IRB) and then by Department of Health (DOH) in Taiwan.

11.3 Regulatory Requirements

The Sponsor is responsible for ensuring that the protocol and any supporting documentation are submitted to the relevant regulatory authorities and the necessary approval obtained, prior to the start of the trial (where applicable) according to local regulations.

11.4 Information for Participants

The investigator must explain to each participant before hand the objectives and requirements imposed by the study, as well as the nature of the test medication and potential adverse drug reactions. A patient information sheet drafted in simple language should be given to each participant.

11.5. Informed Consent

The Investigator is responsible for providing written (patient information sheets) and verbal information to the patient and obtaining written informed consent prior to participation in the trial. A copy of the completed consent form will be given to the patient. The Investigator will confirm in writing that informed consent has been obtained. The written information must be approved by the Sponsor.

11.6 Premature Termination of Trial

The Investigator as well as the Sponsor has the right to terminate the trial at any time for reasonable medical and/or administrative reasons. Reasons for termination must be documented appropriately.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

NCI Toxicity Criteria

Appendix C

QLQ-C30