A Randomized Phase II Study of Hepatic Arterial Infusion with FUDR and Dexamethasone and Intravenous Irinotecan, 5FU and Leucovorin with or without Panitumumab, in Patients with Wild Type RAS who have Resected Hepatic Metastases from Colorectal Cancer

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	All Protocol Activities
Bergen	All Protocol Activities
Commack	All Protocol Activities
Monmouth	All Protocol Activities
Rockville Centre	All Protocol Activities
Westchester	All Protocol Activities
Nassau	All Protocol Activities

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Objective

- The primary objective of the study is to determine if panitumumab with hepatic arterial infusion (HAI) in combination with systemic chemotherapy can increase the recurrence free survival (RFS) for colorectal cancer patients with resected liver metastases.

Study Population

- Eligible patients (metastatic colorectal cancer with no extra-hepatic disease immediately prior to protocol enrollment) who have liver resection and are all-RAS wild type.

Number of Patients

- 78

Study Design

- Randomized phase II trial

Therapeutic Intervention

- All patients receive HAI FUDR (0.12 mg/kg/day X kg X pump volume) / pump flow rate and Dexamethasone flat dose of 25 mg on days 1.
- All patients receive CPT-11 (150 mg/m^2 IV over 30 min to an hour), Leucovorin (400 mg/m^2 IV over 30 min to an hour) and 5FU (1000 mg/m^2/day continuous infusion over two days) on days 15 and 29
- Randomization to panitumumab 6 mg/kg day 15 and 29 (or no panitumumab)
- Each cycle repeats every 36 days for a total of 6 cycles.

This phase II study aims to assess the efficacy of panitumumab with HAI in combination with systemic chemotherapy in patients with completely resected hepatic metastases from colorectal cancer. The protocol includes biological correlative studies. The primary objective of this study is to determine if the RFS increases with the addition of concurrent intravenous Panitumumab to HAI plus systemic chemotherapy after hepatic resection. This study will 1:1 randomize 78 patients who are all-RAS wild type after liver resection to HAI FUDR and dexamethasone with systemic chemotherapy, +/- systemic Panitumumab. The primary endpoint is 15 month RFS.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- The primary objective of the study is to determine if panitumumab with HAI in combination with systemic chemotherapy can increase the 15 month RFS for colorectal cancer patients with resected liver metastases.
- The secondary objectives are (1) to assess toxicity, (2) to determine survival, (3) to analyze tumor tissue for predictive biomarkers (such as NRAS, BRAF, PIK3CA, AKT1 and MEK1), and correlate with patient progression and survival following therapy. Most patients will have had RAS testing performed prior to protocol treatment; RAS will be analyzed at surgery if not performed previously. Frozen and paraffin-fixed tissue from the liver metastases will be available at surgery to measure these values.

3.0 BACKGROUND AND RATIONALE

There are almost 150,000 new cases of colorectal cancer each year in the United States. Approximately 60% of patients develop hepatic metastases, and 15% are suitable for surgical resection. Of those who are able to undergo resection, 5-year survival is approximately 30% to 50%. About 200 patients each year undergo surgery at MSKCC for treatment of hepatic metastases, and approximately 100 undergo resection. Our older single institution experience with liver resection documents the efficacy of this aggressive approach with an actuarial two-year survival of 75%, but a two-year disease-free survival of only 21.2% in the subset of patients who underwent complete resection of colorectal liver metastases. Combined multi-institutional data from the registry of hepatic metastases was similar, with two-year actuarial survival and disease-free survivals of 65% and 35% respectively. These studies were conducted without standardized adjuvant chemotherapy post-surgical resection. Those least likely to be cured by resection of hepatic metastases are patients with node-positive primary, disease free interval ≤ 12 months, > 1 tumor, tumor size ≥ 5 cm, CEA > 200 ng/ml. Giving one point to each risk factor produces a Clinical Risk Score (CRS) between 0-5. Those with a risk score of 0 have a 60 percent five-year survival and those with a score of 5 have a 14 percent five-year survival. Therefore, we will use CRS to stratify patients.

Patients who do not undergo resection do not have favorable outcomes. Scheele et al reported no patient surviving 5 years if complete resection was not performed.

3.1 Rationale for Treatment after Hepatic Resection

3.1.1 Recurrence-Free Survival

RFS greatly depends on patient characteristics such as used in the Fong and Nordlinger scores, and can therefore vary from one study to another.

In data from our institution and in review of the surgical literature, patients who underwent complete resection of hepatic metastases from colorectal cancer were only afforded a 5-year actuarial overall survival of 33-50%, with a 5-year disease-free survival of only 22%. Therefore, approximately 75% of resected patients will recur, with 50% recurring in the liver and 50% recurring elsewhere. Of those patients who do recur, approximately 80% will do so in the first two years.

Our definition of recurrence will be any lesion growing in the liver or extrahepatic sites that is felt by the reference radiologist to be new disease. RFS or disease-free survival (DFS) as seen most recently in studies using systemic therapy or no therapy are listed below.

Publications	DFS/RFS at 15 months	Characteristics

Kornprat (Annals of Surgical Oncology; Vol. 14, No. 3, 2007)	35%	All patients had greater than 4 metastases; largest median size 4.3 cm; 69% of patients were synchronous
Choti (Annals of Surgery; Vol. 235, No. 6, 2002)	40%	Patients with ≤ 3 and > 3 metastases had a median DFS of 16 vs 8 months; Synchronous disease had a median DFS of 13 months
Nordlinger (Cancer; Vol. 77, No. 7, 1996)	40%	40% of patients were synchronous; 86% had 1-3 metastases; 12% had > 4 metastases

3.1.2 Systemic Chemotherapy

Perioperative chemotherapy has shown to increase disease free survival. The EORTC randomized 364 patients with resectable liver metastases (1-4 metastases) to 6 cycles of FOLFOX4 pre-surgery and had 6 cycles post versus surgery alone. The endpoint was an improvement in disease free survival (DFS) which was not significant when all patients were included (7.3%, p=0.058). In eligible patients the DFS increased from 28% to 36% at 3 years with perioperative chemotherapy (p=0.041) which increased further to a 9.2% difference (p=0.025) when only resected patients were analyzed. Median followup time was 39 months.

Recurrence after liver resection is a significant problem with nearly 70% of patients developing recurrence, and the majority of recurrences occur in the first 2-years post resection. A Canadian and European Intergroup (EORTC-NCICTG-GIVO) compared bolus FU/LV to surgery alone in 107 patients after liver resection and showed no increase in overall survival or DFS. The Fédération Francophone de Cancérologie Digestive (FFCD) trial randomized 173 patients after liver resection to bolus FU/FA or no further therapy. The end-point of the study was DFS which was 33.5% and 26.7% at 5 years in the treated and control arms, respectively. After adjusting for negative prognostic factors, there was a significant DFS advantage for the chemotherapy group (p=0.028). Sixty-nine percent of patients in this study had only one metastasis, and 72% had a >12 month time interval from primary to metastases. With a median follow-up of 84.7 months, the median survival was 62 and 46 months for the treated and control patients, respectively (p=0.13).

A meta-analysis of these two studies with a total of 278 patients reported a median PFS of 27.9 and 18.8 months for chemotherapy versus control groups, respectively (p=0.058) and a median survival of 62.2 and 47.3 months, respectively (p=0.95). Patients in this study had very good risk factors; 69 % had only 1 metastasis, 66 % had Duke‘s B carcinoma and 67 % had liver recurrence documented one year after the primary. In their multivariate analysis, adjuvant chemotherapy was independently associated with improved PFS (p=0.026) and overall survival (p=0.046). The number of metastases (≥2) was also associated with decreased PFS (p=0.022) and survival (p=0.023).

A European study randomized 151 patients to bolus/infusional 5FU/LV or FOLFIRI after liver resection. With a median follow-up of 42 months, the median DFS was 21.6 and 24.7 months for

the 5FU/LV and FOLFIRI groups, respectively (p=0.47). On multivariate analysis, adverse factors associated with DFS included prior adjuvant chemotherapy for the primary tumor, diagnosis of liver metastases ≤ 1 year after the primary cancer, and >1 liver lesion. There are currently no randomized trials to support adjuvant FOLFOX after liver resection. A Japanese trial of adjuvant FOLFOX started accrual in 2004 and enrolled only 60 patients, since 62 were excluded because of extrahepatic disease and 20 refused randomization, demonstrating some of the difficulty doing randomized trials in this setting. A newer study is accruing patients to hepatectomy followed by FOLFOX versus no further therapy.

Several retrospective series have shown a benefit for adjuvant treatment after liver resection. Parks and colleagues reported on 792 patients who had liver resections between 1991 and 1998. Multivariate analysis showed that positive margins (HR=1.59), bilateral liver tumors (HR=1.39) and adjuvant chemotherapy (HR=0.75) were independent predictors of outcome. Patients who received adjuvant chemotherapy with a higher CRS had increased chances of surviving (1.3-2 times higher) compared with those patients who did not receive adjuvant treatment. Wang et al using the Seers-Medicare data base found 923 patients >65 years of age who had liver metastases. The 5 year survival was 22%, which was increased with both systemic and HAI + SYS therapy after resection. A retrospective study from Korea compared of 156 patients who were treated after liver resection with FOLFOX, FOLFIRI or fluoropyrimidines alone. After median follow-up of 3.7 years, there was a non-significant difference among the three adjuvant regimens with respect to DFS (p=0.088). [35% (FOLFOX), 25% (FOLFIRI) and 25% (fluoropyrimidines alone).] After adjusting for adverse prognostic variables there was a trend towards a greater benefit with FOLFOX (p=0.068).

In summary, the administration of chemotherapy, with 5FU/LV after resection of liver metastases tends to improve prognosis and DFS. Irinotecan added to FU/LV did not improve results. Newer studies with post-op FOLFOX or XELOX with or without Cetuximab are ongoing by NSABP and European groups.

3.1.3 HAI Therapy after Hepatic Resection

Ackerman has demonstrated that microscopic metastases less than 1mm in size derive their blood supply from the portal circulation. As tumors begin to grow they induce the development of new vessels. Tumors measuring 1 to 2mm are encircled by new vessels derived from both the arterial and portal circulation, which mix freely. Tumors greater than 3mm have a well-developed arterial circulation. Metastases that remain after hepatic resection are probably in the range of 2 to 3mm and are therefore not detectable by the ultrasound scanning technique, which has a resolution of 5mm. Presumably, these metastases derive most of the their blood supply from the arterial circulation. Therefore, adjuvant chemotherapy to the liver for resected hepatic metastases should be given via arterial circulation.

A number of studies randomized patients after liver resection to HAI plus systemic therapy versus no further therapy, or systemic chemotherapy alone. The Eastern Cooperative Oncology Group (ECOG) randomized 109 patients to HAI plus systemic versus no further therapy. The arms were well matched, and all patients had 1-3 resectable liver metastases. This study achieved its primary endpoint of an increase in DFS. The DFS at 4 years was 46% for the HAI group and 25% for surgery alone (p=0.04).

A randomized study at MSKCC compared hepatic arterial infusion (HAI) and systemic therapy versus systemic chemotherapy alone. The study revealed a significant increase in hepatic disease-free survival in those patients who received HAI therapy in addition to systemic.

At 2 years, hepatic progression-free survival was 89% and 37% for the HAI + SYS vs. SYS alone groups. Median PFS was 31 and 17 months, respectively. Updated survival analysis reveals a median survival of 5.6 years for the HAI and 4.7 years for systemic alone. For patients with a poor clinical risk score of 3-5, the 10 year survival was 40% for the HAI + SYS group versus 18% for SYS group.

A study from Greece on 122 patients reported a significant improvement in 5 year DFS, 58% versus 34% (p=0.002), and 5 year survival, 73% versus 60% (p=0.05) for adjuvant HAI plus systemic chemo-immunotherapy versus systemic alone groups, respectively. A randomized study from Germany showed no improvement in DFS.

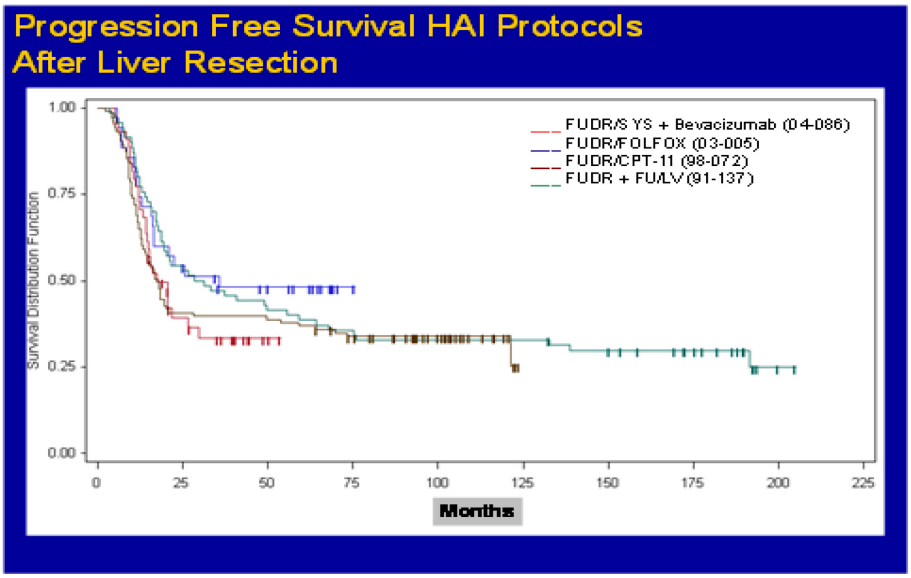
Modern chemotherapy such as irinotecan in combination with HAI FUDR/ Dexamethasone (Dex) in a phase I/II trial after resection of liver metastases yielded a 5 year survival of 59%. In a phase I trial with oxaliplatin + FU/LV added to HAI FUDR/Dex after liver resection, the 4 year overall survival was 88%. Alberts and colleagues reported results from the NSABP study of systemic capecitabine and oxaliplatin alternating with HAI FUDR after resection of liver metastases. The 2 year survival rate was 88% (95% CI 82-98%) with a median follow-up of 4.8 years. The 2 year overall recurrence was 59.7 %.

In a retrospective review, House et al evaluated patients who underwent liver resection between 2001-2005 and compared 125 patients who were treated with HAI plus modern systemic chemotherapy with those who received modern chemotherapy alone. They reported a 5 year survival of 72% and 52% (p=0.004) for the 2 groups, respectively. In a larger retrospective review at MSKCC of over 1,000 patients who underwent liver resection, a multivariate analysis demonstrated that one of the most significant factors leading to improved survival was postoperative HAI therapy. Those who received HAI therapy after hepatic resection had a median survival of 68 months versus 50 months for those who did not (p<0.001).

In our last four adjuvant studies, the patient population has been changing. Our surgeons are resecting patients with more disease. As we accrue patients with worse prognostic factors, the recurrence-free survival is decreasing. The table below reflects these characteristics.

Variables		**HAI + 5FU/LV (n = 74) %**	**HAI + CPT-11 (n = 96) %**	**HAI + FOLFOX (n = 37) %**	**HAI + FOLFOX or FOLFIRI, +/- BEV (n = 73) %**
# lesions (Pathology)	1	36	40	32	23
	2-4	45	47	57	43
	>4	19	13	11	33
Lesion Size	≥ 5cm	30	25	22	18
DFI	< 12 mos	77	74	62	79
Margins	≤ 1 mm	23	11	11	16

+ Margins	0 mm	15	4	5	10
Post-op CEA	> 5 ng/ml	26	33	16	21



Because of the increase in poor patient characteristics, the recurrence-free survival in our most recent study with HAI depicted above by the red line appeared to be inferior to previous adjuvant studies conducted at MSKCC with HAI (RFS was 59 % at 15 months). This is compared with a RFS of approximately 40 % at 15 months from recent studies evaluating systemic therapy (as reflected in the chart in section 2.1.1).

To fairly evaluate our next trial, we feel we should use as historical control a recurrence-free survival that reflects both what is in literature and our most recent trial. Therefore an RFS at 15 months of 50% (which is an average between the estimates in our study and in the other studies), will be considered as an appropriate historical control for the 15 months RFS.

This year at ASCO the N0147 trial (adjuvant cetuximab after stage III colon resection) was presented. Results will show no benefit for patients receiving cetuximab. Our proposed trial is for adjuvant therapy after liver resection. This patient population has a much higher rate of recurrence (especially outside the liver). Because of the good protection of the liver with HAI therapy, one of the common places for recurrence is lung and nodal disease. In my experience, both these areas benefit from anti-EGFR therapy. Therefore, we feel the addition of anti-EGFR agents to systemic therapy and HAI therapy may improve RFS after liver resection.

This trial will evaluate HAI therapy with systemic CPT-11+ 5FU/LV plus or minus panitumumab. Patients will be stratified by clinical risk score (1-3 vs 3 or greater) and previous chemotherapy (oxaliplatin vs irinotecan or no previous therapy).

3.2 Panitumumab

Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). EGFR is a member of the ErbB receptors, a grouping of four closely related receptor tyrosine kinases, namely EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). Panitumumab, a human monoclonal antibody, works

by selectively binding to the EGFR's extracellular domain, thus preventing its activation. Panitumumab arrests the cascade of intracellular signals activated by this receptor, thereby inhibiting tumor cell proliferation. The clinical efficacy of panitumumab appears to be limited to patients with non-mutated (wild type) KRAS tumors. Approximately 65 percent of patients express the non-mutated tumor.

Recent results from Phase II and Phase III clinical trials of metastatic colorectal cancer demonstrate that patients with RAS mutations are unlikely to benefit from monoclonal antibodies (Allegra et al, 2015). Limitation of use: Panitmumab (Vectibix) is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

3.2.1 Phase I/II Efficacy Results

Analyses by KRAS status demonstrated a statistically significant larger panitumumab treatment effect on PFS in the wild-type KRAS stratum versus the mutant KRAS stratum (quantitative interaction test p-value < 0.0001) (Amado et al, 2008). Within the KRAS wild-type group, a 55% reduction in relative risk of disease progression or death was observed between subjects treated with panitumumab compared with those who received BSC alone (hazard ratio = 0.45, 95% CI: 0.34, 0.59) (Amado et al, 2008). In contrast, the hazard ratio for the mutant KRAS analysis set was 0.99 (95% CI: 0.73, 1.36), suggesting no meaningful effect of panitumumab treatment on PFS among subjects with mutant KRAS tumor type (Amado et al, 2008).

A number of studies showed a significant increase in survival and response rate for anti-EGFR agents. A Phase III trial of panitumumab plus best supportive care (BSC) compared with BSC alone showed a significant increase in RFS for patients receiving panitumumab (hazard ratio [HR], 0.54; 95% CI, 0.44 to 0.66, [*P* < .0001]). Median PFS time was 8 weeks (95% CI, 7.9 to 8.4) for panitumumab and 7.3 weeks (95% CI, 7.1 to 7.7) for BSC.

A phase III study randomized patients to second-line therapy with FOLFIRI +/- panitumumab. The study showed a significant increase in RFS when adding panitumumab to FOLFIRI compared with FOLFIRI alone in patients with wild-type KRAS. Median PFS in KRAS wild-type patients was 5.9 months for the FOLFIRI + panitumumab group and 3.9 months for the FOLFIRI alone group (p = 0.004); Median overall survival was 14.5 months versus 12.5 months in the FOLFIRI + panitumumab and FOLFIRI arms, respectively (p = 0.12).

The CRYSTAL trial randomized patients either to FOLFIRI alone or FOLFIRI plus cetuximab. Response rates were significantly increased by the addition of cetuximab (38.7 % for FOLFIRI alone and 46.9 % for cetuximab, FOLFIRI, p= 0.0038). A statistically significant difference in favor of cetuximab was seen in RFS (p=0.0167; hazard ratio [HR] estimate 0.68 [95% CI: 0.051-0.934]) for wild type KRAS patients.

Independent analyses have consistently shown a high positive predictive value (range 80% to 100%) for lack of objective tumor response associated with mutant KRAS status (Benvenuti et al, 2007; De Roock et al, 2007; Di Fiore et al, 2007; Freeman et al, 2008; Liévre et al, 2006).

Additionally, at the 2011 ASCO meeting, a small randomized comparison showed trends for improved DFS and OS with the addition of Cetuximab to FOLFIRI in patients with resected stage III colon cancer patients. Trends were seen regardless of KRAS status.

The PRIME trial, a randomized phase III study of panitumumab with FOLFOX compared to FOLFOX alone as first-line treatment for metastatic colorectal cancer, also showed a significant increase in RFS. In the KRAS wild-type patient group, the median PFS was 9.6 months versus 8.0 months for the FOLFOX + panitumumab group versus FOLFOX only, respectively (p = 0.02). A prospective-retrospective analysis done by Douillard et al on patients treated on the PRIME trial (FOLFOX4-panitumumab versus FOLFOX4 alone) found that in using patients without any RAS mutations, the PFS with panitumumab-FOLFOX4 versus FOLFOX4 alone was 10.1 versus 7.9 months, respectively (p=0.04). There was a slight improvement in PFS when they used all RAS wild type versus KRAS wild type (10.1 versus 9.6 months respectively) (Douillard et al.2013),

3.2.2 Safety of Panitumumab

The below referenced studies reflect the reported adverse events at the time of the last Panitumumab Investigator‘s Brochure (Version 7.0, 10 June 2008). Please refer to the current version of the Panitumumab Investigator‘s Brochure as well as the updated safety information contained in the Investigational New Drug safety letters for further updates.

Safety analyses from 16 clinical studies in subjects with a variety of solid tumors (n = 1599 receiving panitumumab) indicated that panitumumab is generally well tolerated. Among these studies, 11 enrolled subjects with mCRC (n = 1052 receiving panitumumab as a single agent). In these subjects, dermatologic-related toxicities were the most frequently reported adverse events (91% of subjects), with most events being mild to moderate. Relatively few subjects (2%) permanently discontinued panitumumab due to dermatologic adverse events. Infusion reactions to panitumumab (defined as any reported allergic reaction, anaphylactoid reaction, chills, fever, or dyspnea, occurring within 24 hours of the first dose that were not otherwise designated as either anaphylactoid or allergic reaction) were infrequent (3% of subjects; < 1% severe) Panitumumab antigenicity, as measured by enzyme-linked immunosorbent assay (ELISA) and Biacore assay, was very low and was not associated with clinical sequelae.

3.2.3 Panitumumab Monotherapy Studies

An integrated analysis of the safety of panitumumab has been conducted for 1052 subjects with mCRC receiving panitumumab monotherapy (mCRC Monotherapy Set). Subjects primarily received panitumumab doses of 2.5 mg/kg once weekly (15%) or 6.0 mg/kg every 2 weeks (82%).

Consistent with the published data on subjects treated with EGFr inhibitors (i.e., class/target effect) (Perez-Soler and Saltz, 2005), the most commonly reported treatment-related adverse events in subjects treated with panitumumab were associated with the skin, including pruritus (52%), acneiform dermatitis (51%), erythema (50%), and rash (38%). Most subjects (833 of 1052 subjects, 79%) with any dermatologic toxicity had events that were considered to be mild or moderate. Only 3% of subjects permanently discontinued panitumumab administration for dermatologic toxicities. Dermatologic toxicities typically were observed after initiation of panitumumab, with a median time to first integument toxicity (of any severity) of 10 days (95% CI: 8, 11).

Other common treatment-related adverse events (i.e., subject incidence $\geq$ 10%) included fatigue (15%) and diarrhea (13%).

Infusion reactions to panitumumab were infrequent even though premedication was not mandated in the panitumumab clinical program. Overall, 1% of subjects had an infusion reaction reported by the

investigator as an adverse event. Using a definition consistent with the Vectibix USPI (2007), 3% of panitumumab-treated subjects had a potential infusion reaction; < 1% of subjects had a potential infusion reaction by this definition ≥ grade 3.

Please refer to the current Panitumumab Investigator's Brochure for further details.

To date, panitumumab has been evaluated in combination with chemotherapy in subjects with CRC, NSCLC, and SCCHN.

In the mCRC setting in combination with IFL (Study 20025409), the incidence of grade 3 or 4 diarrhea (58%) was notably higher than that historically expected for this already highly GI-toxic chemotherapy regimen, and 1 subject had an episode of grade 4 diarrhea that was also considered serious. Of note, panitumumab in combination with the FOLFIRI regimen using the same agents but different doses/infusion times was better tolerated with an incidence of grade 3 or 4 diarrhea similar to that expected from the literature for this chemotherapy regimen alone (25%) (Andre et al, 1999; Saltz et al, 2000). These data suggest that the potential for additive toxicities in the gastrointestinal tract exists when panitumumab is administered in combination with GI-toxic chemotherapy.

Acute renal failure has been observed in patients who develop severe diarrhea and dehydration.

Infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, have been reported in the clinical trials and post-marketing experience (including fatal outcomes). Fatal reactions have also been observed in patients with a history of prior hypersensitivity reaction to panitumumab including a case of fatal angioedema occurring more than 24 hours following the administration of panitumumab.

3.2.4 Rationale for HAI FUDR + Dex and Systemic Chemotherapy, +/- Panitumumab

In studies analyzing patients with wild-type KRAS, a statistically significant improvement in PFS was observed for the panitumumab group. By combining Panitumumab with HAI and systemic treatment, we seek to obtain better control of hepatic and extrahepatic progression, thereby enhancing patient survival.

This study is based on the hypothesis that the growth and progression of metastatic liver lesions may be associated with mutations affecting the epidermal growth factor receptor (EGFR) pathway. EGFR is a member of the ErbB receptors, a grouping of four closely related receptor tyrosine kinases, namely EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). The clinical efficacy of panitumumab appears to be limited to patients with non-mutated (wild type) KRAS tumors. When Panitumumab binds to EGFR it competitively inhibits the binding of ligands for EGFR. This results in inhibition of cell growth, stimulation of apoptosis, decreased pro-inflammatory cytokine and vascular growth factor production. Panitumumab arrests the cascade of intracellular signals activated by this receptor, thereby inhibiting tumor cell proliferation.

3.2.5 Evaluation of Molecular Markers and Tumor Specimens

Permission from patients entering the study will be obtained for liver biopsy of normal and tumor liver tissue at the time of surgery to be sent to Dr. Solit's lab at Memorial Sloan Kettering. All tumor samples will be reviewed by board certified Gastrointestinal Pathologies for >70% tumor content and for histologic verification. For specimens in which less than 70% of the collected tissue comprises

viable tumor, macrodissection will be performed. Genomic DNA will be obtained by using the DNeasy Tissue Kit (Qiagen, Valencia, CA). For studies using the Sequenom platform, mutations are detected using the iPLEX assay (Sequenom, Inc., San Diego, CA), which is based on a single-base primer extension assay. Briefly, multiplexed PCR and extension primers are designed for a panel of known mutations. After PCR and extension reactions, the resulting extension products are analyzed using a MALDI-TOF mass spectrometer. Our current sequenom assay is an 8 well assay which detects mutations in the *KRAS, NRAS, BRAF, PIK3CA, AKT1* and *MEK1* genes. This assay has been optimized for use with formalin fixed paraffin embedded tissues and validated using a set of 626 colorectal tumors. Mutations detected by Sequenom are further validated by Sanger sequencing. For mutation detection by the Sanger method, intron-based PCR primer sequences are used for exon amplification by PCR. PCR products are sequenced using the Applied Biosystems PRISM dye terminator cycle sequencing method. For detection of the copy number alterations in PTEN, we will use a custom Agilent aCGH array which detects copy number alterations in over 100 genes commonly altered in human cancer. For detection of PTEN methylation, we will use a Sequenom-based assay which has been validated using a retrospective set of human tumors.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

A total of 78 patients whose liver metastases have been completely resected will be randomized 1:1 to two arms: patients in Arm A will receive Panitumumab in addition to HAI FUDR/Dexamethasone plus systemic CPT-11/5FU/LV, and patients randomized to Arm B will receive HAI FUDR/Dex plus systemic CPT-11/5FU/LV alone. Patients in both arms will be treated for a total of 6 cycles (7.5 months).

<table>
<tr><th colspan="4">Cycle Schema q5 weeks</th></tr>
<tr><td>Day 1</td><td>Day 15</td><td>Day 29</td><td>Day 36 (Day 1 of next cycle)</td></tr>
<tr><td rowspan="2">Pump Therapy
FUDR* +
Dexamethasone (14 day infusion)</td><td>Systemic ** +/- Panitumumab***</td><td>Systemic ** +/- Panitumumab***</td><td rowspan="2">Pump Therapy
FUDR +
Dexamethasone (14 day infusion)</td></tr>
<tr><td>Pump Emptied Saline‡</td><td>Pump Emptied Saline</td></tr>
</table>

* *The following pump dose will be used:*

FUDR 0.12 mg/kg * kg * 30 / pump flow rate

Dexamethasone flat dose of 25 mg

** *The following systemic doses will be used (at PI's discretion, lower dose of CPT-11 (150 mg/m^2) can be used if clinically appropriate and can be escalated to 150 mg/m^2):*

CPT-11 150 mg/m^2 IV over 30 min to an hour

5FU 1000 mg/m^2/day cont. infusion over two days (no bolus FU)

Leucovorin 400 mg/m^2 IV over 30 min to an hour

*** *For patients randomized to receive Panitumumab, the dose will be:* ***6 mg/kg IV, over 60 minutes****. Panitumumab will be given on Days 15 and 29 only.*

‡ If clinically appropriate, patients will have pump emptied and filled with glycerol instead of heparin saline. Glycerol will last for 6 to 8 weeks; within that time, patient does not have to have pump filled with heparin and saline. If patients are allergic to heparin, they will receive Fondaparinux in the pump instead along with saline.

4.2 Intervention

- All patients receive HAI FUDR (0.12 mg/kg/day X kg X pump volume) / pump flow rate and Dexamethasone flat dose of 25 mg on days 1.
- All patients receive CPT-11 (150 mg/m^2 IV over 30 min to an hour), Leucovorin (400 mg/m^2 IV over 30 min to an hour) and 5FU (1000 mg/m^2/day continuous infusion over two days) on days 15 and 29
- Randomization to panitumumab 6 mg/kg day 15 and 29 (or no panitumumab)
- Each cycle repeats every 36 days for a total of 6 cycles
- CT C/A/P every 2 cycles during treatment

4.3 Correlative Studies

4.3.1 Liver Biopsy

Permission from patients entering the study will be obtained to take normal and tumor liver biopsies at the time of surgery. These will be sent to and stored at Dr. David Solit's lab at Memorial Sloan Kettering, Genitourinary Oncology Service.

4.3.2 Planned Experiments

We will evaluate the genomic profiles of the tumors in an effort to identify markers of sensitivity or resistance to therapy. Primary or liver biopsy tissue will be evaluated for all RAS testing in order to determine eligibility for study. We will test the tumor tissue for all patients for mutations in the RAS/BRAF pathway, among others using a next-generation sequencing platform. Additionally, genomic DNA will be extracted by standard techniques and analyzed using MSK-IMPACT (Wagle et al). This assay uses targeted, massively parallel sequencing to analyze all exons of over 400 genes selected for their known roles in cancer initiation or progression (examples include *APC, all RAS, BRAF, TP53, NF1,* etc.).. Genomic DNA will be subjected to solution-phase hybrid capture using the RNA baits, followed by massively parallel sequencing. To exclude germline single nucleotide polymorphisms, concurrent analysis of normal tissue DNA will be performed. Somatic alterations, including mutations, insertions and deletions, and copy number changes, detected by this assay will be correlated with clinical parameters.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 FUDR

5.1.1 Floxuridine (FUDR) is an antimetabolite that blocks the methylation of deoxyuridylic acid interfering with the synthesis of DNA. It is also incorporated into RNA and interferes with its function. The drug is metabolized in the liver.

5.1.2 FUDR is commercially available from Roche and Adria Laboratories in 500 mg/10 cc ampules. It is stable (protected from light) and is a colorless aqueous solution. Store at room temperature.

5.1.3 Toxicities associated with the intrahepatic administration of FUDR include biliary sclerosis, hepatic enzyme elevation, gastric ulcers.

5.2 IRINOTECAN

5.2.1 Irinotecan (CPT-11) is a semi-synthetic derivative of camptothecin that possesses greater aqueous solubility, greater *in vitro* and *in vivo* activity, and is associated with less severe and more predictable toxicity than camptothecin. Both camptothecin and CPT-11 are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription.

5.2.2 CPT-11 will be diluted with 250 ml of 5% Dextrose (D5W) and infused intravenously over 30 min to an hour. Nothing else should be added to the infusate. No other diluent is to be used.

5.2.3 CPT-11 vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. CPT-11 is relatively stable against heat and light but becomes slightly unstable against light in aqueous solution. It is stable for at least three years at room temperature. CPT-11 is stable for at least 24 hours in glass bottles or plastic bags when mixed with D5W.

5.2.4 Phase I and II studies of CPT-11 have reported neutropenia and diarrhea as the dose-limiting toxicities. It is expected that these toxicities will also be encountered in this trial. Other Grade 2-3 toxicities seen in phase I trials include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss.

5.3 FLUOROURACIL

5.3.1 Antimetabolite that will be administered by MSKCC guidelines.

5.3.2 Toxicity: Nausea, vomiting, stomatitis, diarrhea, dermatitis, alopecia, leukopenia, and thrombocytopenia.

5.4 LEUCOVORIN CALCIUM (FOLINIC ACID)

5.4.1 Leucovorin calcium is a stable reduced formyl derivative and the active form of folic acid.

5.4.2 The only adverse reaction reported for Leucovorin has been rare cases of allergic sensitization.

5.5 DEXAMETHASONE

5.5.1 Dexamethasone is an adrenocortical steroid, used for chronic inflammation, neoplastic and autoimmune diseases; used in HAI treatment as an agent to prevent liver damage.

5.5.2 Common potential side effects include anxiety, mood alteration/lability, hyperglycemia, insomnia, peripheral edema, myopathy (with chronic use), acne, and hirsutism.

5.6 PANITUMUMAB

5.6.1 Panitumumab is a recombinant, human IgG2 kappa monoclonal antibody that binds specifically to the human Epidermal Growth Factor Receptor (EGFR). When Panitumumab binds to EGFR it competitively inhibits the binding of ligands for EGFR. This results in inhibition of cell growth, induction of apoptosis, decreased pro-inflammatory cytokine and vascular growth factor production. Panitumumab is specifically indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan- containing chemotherapy regimens. For further details and molecule characterization, see the Panitumumab Investigator Brochure. The panitumumab administered in this study is not a commercially marketed product. Although it is expected to be very similar in safety and activity to the commercially marketed drug, it is possible that some differences may exist. Because this is not a commercially marketed drug, panitumumab can only be administered to patients enrolled in this clinical trial and may only be administered under the direction of physicians who are investigators in this clinical trial.

5.6.2 Panitumumab is supplied as a sterile, colorless, preservative-free solution containing 20 mg/mL designed for intravenous infusion. Each vial of panitumumab will contain 10 mL of a sterile, colorless, preservative-free protein solution containing a 20-mg/mL solution of panitumumab. The vial will contain approximately 200 mg of panitumumab and is for single dose use only. Boxes of panitumumab will contain 12 vials of panitumumab. Each vial of panitumumab will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

5.6.3 Panitumumab must be stored at 2-8 °C (36° to 46°F) in a secured area upon receipt. Vials are to be stored in the original carton under refrigeration at 2-8 °C (36° to 46°F) until time of use. The product should be protected from direct sunlight and should not be frozen or shaken excessively. Exposure of the material to excessive temperature above or below this range should be avoided. Do not allow panitumumab to freeze and do not use if contents freeze in transit or in storage. If vials fall out of specified temperature requirement, please contact Amgen for instructions.

As panitumumab contains no preservative, vials are designed for single use only. Any unused portion of panitumumab remaining in the vial must not be used. The diluted solution should be used ≤ 6 hours after dilution, if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2° to 8°C (36° to 46°F).

Records of the actual storage condition during the period of the study should be maintained.

5.6.4 **Preparation**

NOTE: Panitumumab is a protein and should be handled gently to avoid foaming, which may lead to denaturation of the protein product. This precaution applies not only to panitumumab stored in the vial, but also for diluted panitumumab prepared in the IV bag. It is, therefore, essential to avoid medication delivery methods, particularly pneumatic tube systems that could potentially lead to excessive shaking or vibration that would lead to particulate formation in the protein product.

The pharmacist, using aseptic techniques, will prepare panitumumab infusion. The dose of panitumumab will be 6 mg/kg and will be based upon the subject's baseline weight. The dose will not be recalculated unless the weight changes at least ± 10% from the baseline weight. It is recommended that the calculated amount of panitumumab (may be rounded to the nearest tenth milligram [e.g., 456 mg rounded to 460 mg or 312 mg rounded to 310 mg]) to be removed from the vials and added to a total volume of 100 mL of pyrogen-free 0.9% sodium chloride solution USP.

The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL.

Doses higher than 1000 mg should be diluted to 150 ml with 0.9% sodium chloride injection USP. The diluted solution should be mixed by gentle inversion, do not shake. Once diluted, panitumumab should be used ≤ 6 hours after dilution if stored at room temperature, or ≤ 24 hours after dilution if stored refrigerated at 2° to 8°C (36° to 46°F). The bag should be labeled per site pharmacy standard operating procedures and promptly forwarded to the clinic center for infusion.

No incompatibilities have been observed between panitumumab and sodium chloride injection in polyvinyl chloride bags, polyolefin bags, or glass bottles (study specific per EU label).

5.6.5 **Administration**

The total dose may be rounded up or down by no greater than 10 mg. The panitumumab dose will be calculated based on the subject's actual body weight at baseline and will not be re-calculated unless the actual body weight changes by at least 10%. It is recommended that panitumumab is diluted in to a total volume of 100 mL in pyrogen-free 0.9% sodium chloride solution USP/PhEur (normal saline solution, supplied by the site). The maximum concentration of the diluted solution to be infused should not exceed 10 mg/mL. The volume of normal saline should be increased as needed to ensure the maximum concentration of the diluted solution does not exceed 10 mg/mL. Panitumumab will be administered IV by an infusion pump through a peripheral line or indwelling catheter using a non-pyrogenic, low protein binding filter with a 0.2 or 0.22-micron in-line filter infusion set-up over 1 hour ±15 minutes by a trained healthcare professional.

If the first infusion is well tolerated (i.e. without any serious infusion-related reactions) all subsequent infusions may be administered over 30 ±10 minutes. In the event a subject's actual weight requires greater than 150 mL volume infusion, panitumumab will be administered over 60 minutes ±15 minutes, as tolerated. Doses higher than 1000mg should be diluted to 150ml in 0.9% sodium chloride solution, USP (saline solution) and infused over 60+/- 15 minutes.

Strict adherence to aseptic technique should be used during panitumumab preparation and administration. The bag should be labeled per site pharmacy Standard Operating Procedures and promptly forwarded to the clinical research center for infusion.

The effects of overdose of panitumumab are not known.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- History of histologically confirmed colorectal adenocarcinoma metastatic to the liver with no clinical or radiographic evidence of extrahepatic disease. Confirmation of diagnosis must be performed at MSKCC.
- Completely resected hepatic metastases without current evidence of other metastatic disease.
- Lab values ≤ 14 days prior to treatment start:
  - WBC ≥ 3.0 K/uL
  - ANC > 1.5 K/uL
  - Platelets ≥ 100,000/uL
  - Creatinine <1.5 mg/dL
  - HGB ≥ 9 gm/dL
- Renal function (≤ 14 days prior to treatment start).
  - Creatinine ≤1.5 mg/dL or creatinine clearance ≥ 50 mL/min calculated by the Cockcroft-Gault method as follows:
  - Male creatinine clearance = (140 –age in years) x (weight in Kg) / (serum Cr in mg/dl x 72)
  - Female creatinine clearance = (140 – age in years) x (weight in Kg) x 0.85 / (serum Cr in mg/dl x 72) (use of creatinine clearance per protocol based on chemotherapy regimen)
- Hepatic function, as follows: (≤ 14 days prior to treatment start)
  - Aspartate aminotransferase (AST) (≤ 5 x ULN)
  - Alanine aminotransferase (ALT) (≤ 5 x ULN)
  - Total Bilirubin ≤ 1.5 mg/dl
- Magnesium ≥ lower limit of normal (≤ 48 hours prior to treatment start)
- Calcium ≥ lower limit of normal (≤ 48 hours prior to treatment start)
- Prior chemotherapy is acceptable if last dose given ≥ 3 weeks prior to registration to this study. [Note: no chemotherapy to be given after resection of liver lesions prior to treatment on this study.]
- Any investigational agent is acceptable if administered ≥ 30 days before registration
- KPS ≥ 60% (ECOG (*or Karnofsky)* performance status *(preferably 0 or 1/≥ 60% for Karnofsky)*
- Histologically confirmed all-RAS wild type . Paraffin-embedded tumor tissue obtained from the primary tumor or metastasis (Prior to

6.2 Subject Exclusion Criteria

- Patients < 18 years of age.
- Prior radiation to the liver (Prior radiation therapy to the pelvis is acceptable if completed at least 4 weeks prior to registration.)
- Active infection, ascites, hepatic encephalopathy.
- Prior treatment with HAI FUDR.
- Patients who have had prior anti-EGFR antibody therapy and who have not responded to this treatment will be excluded. However, patients who have responded to prior anti-EGFR therapy are eligible.
- Female patients who are pregnant or lactating – or planning to become pregnant within 6 months after the end of the treatment (female patients of child-bearing potential must have negative pregnancy test ≤ 72 hours before registration).

- If a patient has any serious medical problems which may preclude receiving this type of treatment.
- Patients with current evidence of hepatitis A, B, C (ie, active hepatitis)
- Patients with history or known presence of primary CNS tumors, seizures not well-controlled with standard medical therapy, or history of stroke will also be excluded.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to Panitumumab.
- Serious or non-healing active wound, ulcer, or bone fracture.
- History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan.
- Patients who have a diagnosis of Gilbert's disease.
- History of other malignancy, except:

1. Malignancy treated with curative intent and with no known active disease present for ≥ 3 years prior to registration and felt to be at low risk for recurrence by the treating physician
2. Adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease
3. Adequately treated cervical carcinoma in situ without evidence of disease

7.0 RECRUITMENT PLAN

We will make every effort to include women and minorities. Patients will be recruited from medical and surgical oncology clinics based on their eligibility criteria. The consenting professional will explain in detail the study to the patient and will review the informed consent with the patient. Patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. Upon signing the requisite three copies of the informed consent, the patient will be registered to Step One of the protocol. This will —pend‖ the patient to the study, allowing for liver tissue procurement at surgery. If the patient remains eligible for study participation after surgery, he/she will be registered to Step Two, and then will be randomized to Arm A or Arm B. There will be no financial compensation for patients enrolling on this protocol.

8.0 PRETREATMENT EVALUATION

Prior to treatment start, patients will undergo the following procedures:

- CT Angiogram or liver triphasic to determine arterial structures: any time prior to surgery
- Perfusion flow scan (TcMAA): any time prior to treatment start
- RAS Testing: any time prior to surgery; if not done previously, adequate tissue will be obtained at surgery
- CT scan of chest, abdomen*, pelvis: within 6 weeks prior to treatment start
- Surgery, pump placement: within 6 weeks prior to treatment start
- Post-surgery CT chest, abdomen*, pelvis: within 3 weeks prior to treatment start
- EKG: within 3 weeks prior to treatment start
- MediPort placement: any time prior to treatment start
- HX, PE, BP; Ht / Wt: within 2 weeks prior to treatment start
- Pregnancy test (females of child-bearing potential): 72 hours prior to treatment start
- Magnesium and Calcium: within 48 hours prior to treatment start
- KPS, CBC with diff/plts, albumin, LDH, BUN, creatinine, alk phos, SGOT, SGPT, bilirubin, CEA, serum electrolytes: within 14 days prior to treatment start.

* *MRI may be obtained instead of CT if patient's disease is not visible on CT*

8.1 Patients will have full resection of liver metastases along with pump placement within 6 weeks prior to treatment. Surgeons will report whether the resection is R0 or R1 and whether patients have positive or negative lymph nodes.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Chemotherapy will be administered on a 5-week cycle basis. Pump therapy with FUDR and Dex will be administered on Day 1 of each cycle. The pump will be emptied and filled with heparin and normal saline on Days 15 and 29. Systemic chemotherapy will be administered on Days 15 and Day 29 of each cycle. Treatment recycles on Day 36.

On Days 15 and 29, patients will receive systemic chemotherapy. Patients on the panitumumab arm will receive the drug over a 60 minute infusion first. CPT-11/LV will be administered subsequently via a Y-line over a 30 to 60 minute infusion, and 5FU will follow by a 48-hour infusion.

9.2 For the first cycle, the dose of FUDR will be calculated based on the predetermined flow rate provided by the pump manufacturer. Thereafter, doses will be adjusted (lowered, if necessary, but never increased) based on actual observed flow rate. The pump will be filled with FUDR, Dexamethasone, heparin and saline.

Dose calculation:

$$\text{FUDR: } \frac{0.12 \text{ mg/kg} \times \text{kg (patient weight)} \times \text{pump volume}}{\text{pump flow rate}}$$

Dexamethasone: flat dose of 25 mg

Overweight patients:
If a patient is 35% above ideal weight, dose of FUDR chemotherapy will be calculated as follows:

To calculate Ideal Body weight (kg):

Males: 50kg + (2.3 x height in inches above 5 ft)
(i.e.: for a patient who is 5‘10‖, use 10)
Females: 45.5 kg + (2.3 x height in inches above 5 ft)

Example: An overweight male is 106 kg and 5‘11‖
50kg + (2.3 x 11) = 50kg + 25.3 = 75.3 is the Ideal Body Weight

To calculate Ideal Average weight (kg):

$$\frac{\text{Actual weight} + \text{Ideal Body Weight}}{2}$$

Using the male example from above:
106 + 75.3 = 181.3 ÷ 2 = 90.65 is the Ideal Average Weight

Use the Ideal Average Weight to calculate the FUDR dose in patients who are overweight*.

* If PI feels the patient is an appropriate weight, the ideal average weight equation should not be used and patients can have the regular dose calculation of FUDR.

Heparin: 30,000 units total dose
Normal saline: quantity sufficient to make total reservoir volume of 30 ml.

If no dose modification due to toxicity is required, the dosages given above (adjusted for changes in weight and pump flow rate) will be repeated on Day 1 of Cycle 2 and all subsequent cycles.

Pump Flow Rate: The first total dose of FUDR should be calculated using the precalculated flow rate provided by the pump manufacturer. The pump will be filled with FUDR, Dexamethasone, heparin and saline. Thereafter, the flow rate should be recalculated each cycle. If a significant (≥ 20%) discrepancy is seen, notify the Principal Investigator.

To recalculate flow rate, the amount of any residual infusate removed from the pump at the end of the 14-day infusion is subtracted from the total pump volume. This result is divided by the number of days in the infusion period (usually 14). See example below:

Example: Pump is filled with 30.0 ml infusate on Day 1. At pump emptying on Day 15, pump yields 12 ml residual.

Total infusion over the 14-day period was 30 – 12 = 18 ml

Flow rate = 18 ml ÷ 14 days = 1.3 ml/day

9.3 On Days 15 and 29 of each cycle, the pump will be emptied and then filled with 30,000 units of heparin in normal saline (q.s. 30cc) for 14 days.

9.4 Patients must meet all hematologic and blood chemistry criteria outlined in Section 6.0 before beginning the first cycle of therapy. For subsequent cycles, patients must meet the following criteria:

WBC	≥ 2.5 K/uL
ANC	≥ 1.0 K/uL
Platelet count	≥ 75 K/uL
Creatinine	≤ 1.8 mg/dL
Bilirubin	< 1.5 mg/dL

If counts are outside these levels on date of schedule treatment, therapy will be delayed one to two weeks or at the discretion of the treating physician.

Parameters for treatment with FUDR via intrahepatic pump are outlined in Section 11.4.2.

9.5 The starting panitumumab dose is 6 mg/kg. The total dose may be rounded up or down by no greater than 10 mg. The panitumumab dose will be calculated based on the subject‘s actual body weight at baseline and will not be re-calculated unless the actual body weight changes by at least 10%.

9.6 All reasonable efforts will be made to adhere to treatment and evaluation schedules, however minor infrequent variations to accommodate holidays, transportation issues, or patient's personal schedule will be permitted if these do not, in the opinion of the investigator, constitute a major safety or compliance issue. Such variations, assuming they do not occur with unreasonable frequency or regularity, will not be considered protocol violations.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Day 1* each cycle	Days of systemic chemotherapy**	Q10 weeks approximately after treatment start
HX, PE, MD or NP visit	**X**		
HX, Nurse visit		**X**	
Tox assessment	**X**		
Weight	**X**		
KPS	**X**		
CBC, Plts	**X**	**X**	
BUN, Creat	**X**	**X**	
Bili, SGOT, SGPT	**X**	**X**	
Alk phos, LDH	**X**	**X**	
Electrolytes	**X**	**X**	
CEA	**X**	**X**	
Magnesium (for patients randomized to Panitumumab arm)	**X**	**X**	
Calcium	**X**	**X**	
CT Chest/abdomen/pelvis***			**X**

***** *Or within 48 hours prior to Day 1*

* Or within 72 hours prior to Day 15 and Day 29

**** MRI may be obtained instead of CT if patient's disease is not visible on CT. Allowances of +/-3 weeks will be acceptable.*

10.1 While being treated with protocol therapy, patients will be seen at or prior to the first day of each cycle by their medical oncologist.

In cases approved by the Principal Investigator, patients randomized to Arm B (no panitumumab) can see local oncologists for systemic treatments.

10.2 Patients will be assessed for adverse events prior to administration of systemic chemotherapy, panitumumab, or HAI.

10.3 Patients will have an end of study assessment for toxicity.

11.0 TOXICITIES/SIDE EFFECTS

All toxicities will be rated as per the NCI Common Toxicity Criteria, with the exception of skin or nail related toxicities, which will be graded using CTC version 3.0 with modifications (see appendix B). Hepatic enzyme toxicities will also be captured according to the schema on page 30 as well (see FUDR Dose Modifications and Table I).

11.1 Toxicity Related to Chemotherapy

11.1.1 FUDR: gastritis, gastroduodenal ulcers, chemical hepatitis, sclerosing cholangitis with jaundice, pruritus, diarrhea.

11.1.2 Dexamethasone: sodium retention, fluid retention, hypertension, development of cushingoid state, secondary adrenocortical and pituitary hypo-responsiveness, decreased carbohydrate tolerance, manifestations of latent diabetes.

11.1.3 Systemic Chemotherapy (CPT-11, 5FU/LV): diarrhea, myelosuppression, nausea, vomiting, stomatitis, neurotoxicity; neutropenia, thrombocytopenia, cumulative asthenia (CPT-11).

11.2 Toxicity Related to Panitumumab

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute‘s Common Toxicity Criteria (CTC) version 4.0.

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Panitumumab monotherapy. The clinical symptoms include, but are not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. In some cases, it may cause infected sores requiring medical and/or surgical treatment, or cause severe skin infections that could be fatal. Subsequent to the development of severe dermatologic toxicities, infectious complications, including sepsis, septic death, and abscesses requiring incisions and drainage were reported.

Infusion Reactions: Severe infusion reactions included anaphylactic reactions, bronchospasm, and hypotension, which occurred in approximately 1% of patients.

Pulmonary fibrosis: In patients enrolled in clinical studies of Panitumumab, pulmonary fibrosis occurred in less than 1% (2/1467). Patients with a history of interstitial pneumonitis, pulmonary fibrosis, evidence of interstitial pneumonitis, or pulmonary fibrosis were excluded from clinical studies. Therefore, the probability of risk in a general population is uncertain.

Electrolyte Depletion/Monitoring: In patients enrolled in a clinical trial, 2% experienced hypomagnesemia (NCI-CTC grade 3 or 4), which required oral or IV electrolyte repletion. Hypomagnesemia occurred 6 weeks or longer after the initiation of Panitumumab. In some patients, both hypomagnesemia and hypocalcemia occurred.

Photosensitivity: Exposure to sunlight can worsen dermatologic toxicity. It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving Panitumumab.

Dermatologic, Mucosal, and Ocular Toxicity: Ocular toxicities occurred in 15% of patients and included, but were not limited to: conjunctivitis (4%), ocular hyperemia (3%), increased lacrimation (2%), and eye/eyelid irritation (1%). Stomatitis (7%) and oral mucositis (6%) were reported. One patient experienced an NCI-CTC grade 3 event of mucosal inflammation. The incidence of paronychia was 25% and was severe in 2% of patients. Nail disorders were observed in 9% of patients.

Other adverse effects include: nausea, vomiting, mouth irritation, fever, headache, cough, shortness of breath, diarrhea (sometimes causing severe dehydration), abdominal pain, constipation, swelling of the hands and feet, and fatigue/weakness, hair loss, a decrease in magnesium, calcium and potassium levels in the blood, nose dryness or bleeding, increased growth of eyelashes and excessive hair growth.

The following adverse are rare but serious: blood clots in legs and lungs, stroke, acute kidney failure, lung complications, heart attack, shortness of breath, and septic death.

Pregnancy: Adequate contraception in both males and females must be used while receiving Panitumumab and for 6 months after the last dose of Panitumumab therapy.

Pre-medication for Panitumumab: Panitumumab specific pre-medication is not required for routine panitumumab infusions. If, during or after any infusion, a reaction occurs, pre-medication may be used for subsequent panitumumab infusions (e.g., acetaminophen/paracetemol and/or an H1 blocker, e.g., diphenhydramine).

Interruption of Panitumumab Infusion: Subjects who experience any serious infusion reaction during panitumumab administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event. Suspected infusion reactions should be reported as an adverse event. All subjects who experience such an event will be followed for safety.

Pre-emptive Management of Panitumumab Associated Skin Toxicities: Clinical trial data indicate that integument and eye toxicities associated with panitumumab therapy are consistent with what has been observed for other EGFr inhibitors. Most integument- and eye-related toxicity events were mild or moderate in intensity.

Pre-emptive treatment for skin toxicity includes (recommended):

- Sunscreen SPF>30 when going outside
- Topical steroid (0.05% alclometasone cream) twice daily on face, chest and upper back
- Prophylactic use of alcohol-free emollient creams or ointments to combat dryness
- Doxycycline 100mg twice daily or Minocycline 100 mg tabs 1 tab daily

The optimal duration of pre-emptive skin treatment is 6 weeks from panitumumab initiation. Subjects who subsequently experience skin toxicities ≥ grade 2 may discontinue the pre-

emptive skin treatment, and their symptoms should be managed appropriately according to the institution‘s standard procedures.

11.3 Toxicity Related to the Pump and Catheters

Infection, hepatic artery thrombosis, pump malfunction, catheter occlusion, intra-abdominal bleed. The rate of pump failure is less than 1 percent. Patients will receive standard systemic therapy if the pump is unusable.

11.4 Dose Modifications

11.4.1 Irinotecan, 5FU, Leucovorin Dose Modifications

- If patients have delays in treatments due to hospitalization or other reasons, they should proceed with treatment as scheduled.
- Patients who experience grade 3 or 4 toxicity may continue treatment at a lower dosage level once toxicities have fully resolved (refer to tables below). Toxicity should resolve within two weeks. If the physician feels the patient cannot tolerate systemic therapy, they can hold therapy for one week. If the patient has elevated liver function tests in the PI‘s discretion, systemic therapy can be held and Decadron can be placed in the pump with heparin saline.
- Guidelines for re-starting medication are listed in table below:

Dose Reduction for Hematologic Toxicities: Irinotecan + 5FU + LV (mg/m^2/day)

Grade	Toxicity	Irinotecan	5FU Infusion	Leucovorin
3	Neutropenia	20% decrease	20% decrease	20% decrease
4	Neutropenia	30% decrease	30% decrease	30% decrease
3	Febrile neutropenia[a]	20% decrease	20% decrease	20% decrease
4	Febrile neutropenia[a]	30% decrease	30% decrease	30% decrease
3	Thrombocytopenia	20% decrease	20% decrease	20% decrease
4	Thrombocytopenia	30% decrease	30% decrease	30% decrease

[a]Febrile Neutropenia = ANC < 1.0 x 10^9/L with fever $\geq$ 38.5° C

Dose Reductions for Non-Hematologic Toxicities: Irinotecan + 5FU + LV (mg/m^2/day)

Grade	Toxicity	Irinotecan	5FU Infusion	Leucovorin
3	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	20% decrease	20% decrease	20% decrease
3	Diarrhea despite premedication with an effective antidiarrheal therapy	20% decrease	20% decrease	20% decrease
4	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	30% decrease	30% decrease	30% decrease
4	Diarrhea despite premedication with an effective antidiarrheal therapy	30% decrease	30% decrease	30% decrease

3	Stomatitis	No dose reduction	20% decrease	20% decrease
4	Stomatitis	No dose reduction	30% decrease	30% decrease
≥ 2	Cardiac toxicity	No dose reduction	Stop treatment	Stop treatment
3 or 4	Hand/Foot Skin reaction	No dose reduction	20% decrease	20% decrease

11.4.2 FUDR Dose Modifications

—Reference value‖ is defined as the value obtained on the first day of the most recent FUDR dose.

To determine if a FUDR dose modification is necessary, compare reference value to the either the value obtained on the day pump was emptied (e.g. day 14) or the value obtained on the day of planned pump filling (e.g. day 28), whichever is higher. Percentages listed under —FUDR Dose‖ refer to percentage of last dose of FUDR administered.

TABLE I: FUDR DOSE MODIFICATION SCHEMA:

	Reference Value*	**% FUDR dose**
SGOT *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 2 x reference value	100%
	2 to < 3 x reference value	80%
	3 to < 4 x reference value	50%
	> 4 x reference value	Hold[A]
ALK PHOS *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 1.2 x reference value	100%
	1.2 to < 1.5 x reference value	50%
	> 1.5 x reference value	Hold[B]
TOT BILI *(at pump emptying or day of planned retreatment, whichever is higher)*	0 to < 1.2 x reference value	100%
	1.2 to < 1.5 x reference value	50%
	> 1.5 x reference value	Hold[C]
If SGOT > 4X reference value, alkaline phosphatase > 1.5X reference value, total bilirubin > 1.5X reference value, then treatment will be held and will not be reinstituted until values come down to more normal levels, as indicated in section —Recommencing FUDR Treatment After Hold‖. [A]SGOT elevation, [B]Alkaline Phosphatase elevation, [C]Total bilirubin elevation		

***** *If patient's Alkaline Phosphatase or T Bili shows a continual rise from Day 1 of treatment, then the Day 1 value will be used as the reference value for that patient when determining whether to hold treatment, and time of re-treatment after hold.*

RECOMMENCING TREATMENT AFTER HOLD

Reason for treatment delay	**Chemotherapy resumed when value has returned to:**	**% FUDR dose**

SGOT elevation	3 X reference value	25% of last dose
Alkaline Phosphatase elevation	1.2 X reference value	25% of last dose
Total bilirubin elevation	1.2 X reference value	25% of last dose

- If patient develops a total bilirubin $\geq$ 3.0 mg/dl, the pump should be emptied and Dex 25 mg plus heparin 30,000 u and saline 30 cc placed in the pump q 14 days. Once there is no longer evidence of toxicity, Dex dose should be tapered in increments of 5 mg every 14 days. Tapering will continue unless enzymes increase. FUDR should be permanently discontinued unless there is evidence of disease progression (increasing CEA, worsening CT scan, worsening clinical status) AND bilirubin has returned to $\leq$ 1.5 mg/dl. In this case, FUDR can be restarted as follows: Use 25% of the last FUDR dose given with Dex, heparin and saline in the pump for 7 days. Pump should be emptied after 7 days, and patients given a 3-week rest period. This treatment and treatment schedule should continue as long as bilirubin remains $\leq$ 1.5 mg/dl and liver enzyme values do not increase.

- If a patient presents with abdominal pain, HAI FUDR should not be given and, if the pump is already filled with FUDR, then the FUDR should be emptied immediately. Epigastric pain unresponsive to oral H_2 blocker use is suggestive of gastroduodenal irritation or ulcer. Severe pain should prompt workup with an upper gastrointestinal endoscopy. Serum amylase should be checked along with the routine blood (screening profile, creatinine, and CBC) in patients with abdominal pain. If an ulcer or gastroduodenitis is documented, therapy should be held for one month to allow healing. If abdominal pain is severe, the pump should be emptied of FUDR until results of workup are available.

If patients have delays in FUDR treatment, the cycle numbering will go as follows:

- 2 systemic treatments = 1 cycle
- If patients return for FUDR and the liver function tests (SGOT, alkaline phosphatase and/or bilirubin) are too elevated (as in table 1) patients will wait one to two weeks. If they are still elevated, patients will start the next cycle with systemic and not with FUDR. During that cycle if the liver function tests come down enough (according to Table Recommencing Treatment After Hold), patients will be able to receive FUDR again at a lower dose. In that case they can receive the FUDR, then two weeks later they will receive systemic once afterwards and then move onto the next cycle.
- If liver function tests are too high for a patient to receive FUDR, they may continue on study treatment with systemic chemotherapy for a total of 12 systemic treatments. In this case, the patient will be treated with systemic treatment on Day 1 and on Day 15, then move onto the next cycle starting with Day 1.

11.4.3 Panitumumab Dose Modifications

- Infusion-Related Adverse Events: If a patient experiences an infusion-associated adverse event, premedication will be given for the next infusion; however, the infusion time may not be decreased. If the next infusion is well-tolerated with premedication, the subsequent infusion time may then be decreased by 30 + 10 minutes as long as the patient continues to be premedicated. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 + 15 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 + 10 minutes.

- For subjects who experience toxicities while on study, one or more doses of panitumumab may need to be withheld, reduced, or delayed. On resolution of toxicity, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed. Dose escalations above **6 mg/kg** starting dose are not allowed. Panitumumab dose reductions are listed in Table 1.

Symptomatic skin- or nail-related toxicity felt to be intolerable by the subject can have a reduction in dose according to Table 1.

Table 1. Panitumumab Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	6	4.8	3.6

11.4.4 Criteria for Withholding a Dose of Panitumumab

Skin- or nail-related toxicities:

- Skin or nail infection requiring IV antibiotic or IV antifungal treatment
- Any skin- or nail-related serious adverse event

Non-skin- or nail-related toxicities:

Any grade 3 or 4 toxicity with the following exceptions:

- Panitumumab will only be withheld for symptomatic hypomagnesemia and/or hypocalcemia that persists despite aggressive magnesium and/or calcium replacement
- Panitumumab will only be withheld for grade 3 or 4 nausea, diarrhea, or vomiting that persists despite maximum supportive care
- Panitumumab will only be withheld for grade ≥ 3 anemia or grade 4 thrombocytopenia that cannot be managed by transfusion(s) or cytokine therapy

11.4.5 Criteria for Re-treatment with Panitumumab

Skin- or nail-related toxicities:

Panitumumab administration may recommence once:

- The adverse event has improved to ≤ Grade 2 or returned to baseline, or;
- The subject has recovered to the point where symptomatic skin- or nail-related toxicity is felt to be tolerable; or,

- Systemic steroids are no longer required, or
- IV antibiotic or IV antifungal treatment is no longer required

Non-skin- or nail-related toxicities:

Panitumumab administration may recommence once the adverse event has improved to ≤ Grade 1 or returned to baseline.

11.4.6 Dose Modification Schedule

- Subjects should be assessed for toxicity before each dose. Dose modification should be performed according to the schedule described below.
- Subjects who develop a toxicity that does not meet the criteria for withholding a dose of panitumumab (Section 11.4.4) should continue to receive panitumumab and their symptoms should be treated.
- Panitumumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with panitumumab (Section 11.4.5).

For subjects who experience a toxicity that meets the criteria for withholding a dose of panitumumab:

- Subjects receiving either 100% or 80% of the starting dose of panitumumab are allowed to have up to 2 subsequent doses withheld for toxicity. However a second dose should only be withheld if the toxicity has not resolved by the time that the subsequent dose is due.
- Subjects treated at the 100% dose level whose toxicity resolves after 1 dose of panitumumab is withheld should be re-started at the 100% dose level (recommended but not required, reduction to the 80% dose is allowed as an alternative to re-challenge with the 100% dose).
- If toxicity recurs, subjects treated at the 100% dose or 80% dose should be re-started at the 80% dose or 60% dose, respectively, when the toxicity resolves after withholding 1 or 2 doses of panitumumab.
- Subjects treated at the 100% dose level whose toxicity resolves only after 2 subsequent doses of panitumumab are withheld should be re-started at the 80% dose level.
- Subjects treated at the 80% dose level whose toxicity resolves after withholding 1 or 2 doses of panitumumab should be re-started at the 60% dose level.
- Subjects who experience toxicity at the 60% dose level will not be re-treated with panitumumab.

It is recommended that panitumumab doses will be escalated in subjects whose toxicity resolves to the degree that meets the criteria for re-starting a dose of panitumumab (Section 11.4.5). Dose escalations are recommended but not required. Dose escalations should occur in the following manner:

- Subjects treated at the 80% dose level whose toxicity does not recur should receive the 100% dose level at the next dose unless a previous attempt to re-escalate to the 100% dose level was not tolerated (re-initiation of the 80% dose is allowed as an alternative to dose escalation).
- Subjects treated at the 60% dose level whose toxicity does not recur should receive the 80% dose at the next dose unless a previous attempt to re-escalate to the 80% dose level was not tolerated (re-initiation of the 60% dose is allowed as an alternative to dose escalation).

- Subjects who miss more than 2 consecutive scheduled doses due to toxicity or are unable to receive a dose of panitumumab within 6 weeks of having received their previous dose of panitumumab due to toxicity will be considered unable to tolerate panitumumab and will not be retreated with panitumumab.
- If a subject demonstrates a clinical benefit with a documented response of stable disease, partial response or complete response and there are reasons that the dose modification rules above cannot be implemented, the investigator should contact and discuss these reasons with Amgen. The investigator must obtain written agreement from Amgen before any changes in the dose modification rules can be implemented.

11.4.7 Panitumumab Delayed- or Missed-Doses

- Delays of panitumumab administration beyond 6 weeks from the previous dose of panitumumab are not allowed.
- Reasons to withhold a dose of panitumumab are described in Section 11.4.4. More than 2 consecutively missed doses (i.e. 4 weeks without panitumumab) are not allowed. Missed panitumumab doses will not be made up.

11.4.8 Discontinuation of Panitumumab

Panitumumab will be administered until subjects develop disease progression or are unable to tolerate panitumumab.

11.4.9 Guidelines for Diarrhea Management

- Symptoms of diarrhea and/or abdominal cramping may occur at any time and should be managed according to standard institutional practice.
- Subjects should also be instructed to notify the investigator or nurse for the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline) within 24 hours. Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.
- Changes in electrolytes, even without BUN/urea and/or creatinine elevation, may reflect early physiologic consequences of treatment-induced gastrointestinal toxicity. Subjects with clinically significant electrolyte changes should be evaluated for dehydration and receive aggressive fluid and electrolyte replacement, if indicated.

11.4.10 Electrolyte Management

- Subjects should be evaluated as outlined in Section 11 and managed as per local medical practice. If hypomagnesemia is present, replacement should be managed with either oral or parental replacement, or both, according to institutional practice and to the degree of hypomagnesemia present. It is recommended that subject‘s serum magnesium level should be maintained within the normal range during study treatment.
- It is important to assess and manage serum potassium and calcium (adjusted for albumin) in subjects who have concomitant hypomagnesemia. Subject‘s serum potassium and calcium parameters are recommended to be maintained, as per local medical practice, within the normal ranges during study treatment.

11.4.11 Proscribed Therapy During Study Period

- Subjects must be withdrawn from the study if they receive any other investigational agents, anti-EGFr targeting agents other than panitumumab, experimental or approved anti-tumor therapies (e.g., bevacizumab), chemotherapy or radiotherapy (with the exception of use for pain control).

- Subjects should not schedule any elective surgeries (excluding central venous catheter placement) during their participation in the study, or until 7 days after their last administration of study treatment. If a subject undergoes any unexpected surgery during the course of the study, that subject must discontinue all study treatment immediately, and the sponsor should be notified as soon as possible. A subject may be allowed to resume study treatment after each surgical case is reviewed by the sponsor study team in conjunction with the investigator to determine the appropriateness of treatment resumption.
- Patients will be prophylactically administered minocycline and a topical steroid. If toxicity cannot be managed, Dr. Mario Lacouture will see the patients for evaluation.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Assessments of tumor response to treatment while on treatment are not appropriate since tumor is resected.

12.2 Patients will receive 3 CT scans of the chest, abdomen and pelvis during treatment (every 2 cycles). Scans will be assessed closely for disease status and possible recurrence. Our definition of recurrence will be any lesion growing in the liver or extrahepatic sites that is felt by the reference radiologist to be new disease.

12.3 CT scan of the chest, abdomen and pelvis and CEA every 12 weeks for the first 2 years after the completion of treatment. A CT scan will coincide with 15 months after treatment start, which will allow us to determine 15 month RFS.

Baseline CT scan	0 weeks
CT # 2	10 weeks after treatment start
CT # 3	20 weeks
CT # 4	30 weeks
End treatment	
CT # 5	42 weeks
CT # 6	54 weeks
CT # 7	66 weeks (+/- 3 weeks)

12.3 Colonoscopy within the first 2 years after completion of treatment; this test will enable us to determine whether the patients are NED.

12.4 CT scan of the chest, abdomen and pelvis and CEA every 4 months between 2 and 4 years after completion of the treatment. CT scan of the chest, abdomen and pelvis and CEA every 6 months for five years, and yearly thereafter until patient expires. The follow-up scans are necessary to determine the RFS of this patient population.

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 Development of clear-cut evidence of recurrent colorectal cancer in the liver compared to the baseline postoperative CT scan, via clinical exam or imaging studies. These patients will still be followed for recurrence and survival.

13.2 Development of clear-cut evidence of extrahepatic recurrence via clinical exam or imaging studies. These patients will still be followed for recurrence and survival.

13.3 Patient is unable to resume hepatic arterial FUDR due to hepatic toxicity. These patients will still be followed for recurrence and survival.

13.4 Unacceptable toxicity that does not respond to the dosage modification. Even if patients cannot tolerate treatment they will be continued to be followed for survival and recurrence.

13.5 Patient elects to discontinue treatment.

13.6 Changes in a patient‘s condition which render the patient unacceptable for further treatment in the judgment of the investigator. These patients will still be followed for recurrence and survival.

14.0 BIOSTATISTICS

This study will 1:1 randomize 78 patients to two treatment arms: HAI FUDR and dexamethasone with systemic chemotherapy, +/- systemic Panitumumab. Randomization procedures will be discussed in section 15.2.

The primary endpoint is 15 month recurrence free survival (RFS). Based on an exact binomial single stage design, with 39 patients in each arm we are able to differentiate between unacceptable 15 month RFS of 50% and acceptable 15 month RFS of 70% with type I error (falsely accepting a non-promising therapy) and II error (falsely rejecting a promising therapy) rates of 10 % each. For a particular arm, if 24 or more patients are alive and disease free at 15 months the regimen in that arm will be considered worthy of further investigation. We will use the —pick the winner‖ format based on the randomized phase II clinical trials approach proposed by Simon et al. (1985) to differentiate between 15 month RFS of 50% and 70%. The pick the winner role only occurs if both regimens are efficacious. If the number of patients who are disease free and alive at 15 months in one arm is at least 24 and it exceeds by at least 3 patients the number of alive and disease free patients at 15 months in the other arm, then the arm with the higher 15 months RFS would be declared the winner. If neither arm had at least 24 patients alive and disease free at 15 months, the regimens in both arms would be considered unworthy of further evaluation. The probability of selecting the better regimen is 85%; the probability that no regimen is selected is approximately 9%, while the probability of a tie is 6 % (Simon R, Wittes RE, Ellenberg SS. (1985). Randomized phase II clinical trials. *Cancer Treat Rep* 69, 1375-1381.)

RFS will also be estimated using the Kaplan Meier method. As secondary endpoint, overall survival will be estimated by the Kaplan Meier method. Associations between biomarkers and RFS and overall survival will be assessed using the log-rank test. In each arm, safety and tolerability will be summarized using descriptive statistics.

The prevalence of RAS mutations is about 40%; therefore we would have to approach about 120 patients in order to accrue 78 patients. On average, we see about 40 eligible patients per year; therefore we would need three years to reach 120.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Patients from the GI medical oncology clinic at MSKCC who meet the inclusion criteria are eligible for enrollment and randomization. We plan to consecutively recruit 78 patients. Patients will be randomized with a 1:1 ratio to the HAI FUDR + systemic chemotherapy, + Panitumumab arm or the HAI FUDR + systemic chemotherapy, - Panitumumab arm. After eligibility is established and immediately after consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system and randomized using the Clinical Research Database (CRDB), by calling the MSKCC PPR Office at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday – Friday. Two stratification variables will be used: prior chemotherapy status and clinical risk score (0-2 vs. 3 or more) [See Appendix A, Fong Score]. Patients will be randomized after surgery and immediately prior to study enrollment.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be

monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/indexx.htm. There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e. g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center‘s Research Council and Institution Review Board.
During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSKCC‘s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.1.1 Study Costs

The cost of the study drug, Panitumumab, will be supplied by Amgen. All other costs will be billed to the patient.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following

- A explanation of how the AE was handled
- A description of the subject‘s condition
- Indication if the subject remains on the study

- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI‘s signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Reporting of Serious Treatment Emergent Adverse Events to Amgen

Investigators are required to report to Amgen Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Panitumumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Panitumumab treatment and is not a chronic condition that is part of the patient‘s medical history OR (2) was present at the start of Panitumumab treatment or as part of the patient‘s medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Is fatal
- Is life threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other significant medical hazard

A hospitalization meeting the regulatory definition for —seriousǁ is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (e.g., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the —other significant medical hazardǁ criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Hospitalization for the performing of protocol-required procedures or administration of study treatment is not classified as an SAE.

Serious adverse events will be collected and recorded at least throughout the study period, beginning with the signing of the informed consent through 30 days after the end of the treatment phase or through the safety follow-up visit, whichever is longer.

The investigator should notify the Sponsor of all serious adverse events occurring at the site(s) in accordance with FDA Regulations. The Sponsor will medically review all SAEs. The Sponsor will ensure the notification of the appropriate Ethics Committees/Institutional Review Boards, of all serious adverse events occurring at the site(s) in accordance with FDA regulations.

The study sponsor is responsible for providing all suspected serious adverse drug reactions (SADRs) related or possibly related to panitumumab to Amgen within 1 month of the event. It is possible that Amgen may request follow-up information from the sponsor.

All suspected unexpected serious adverse reactions (SUSARs) related or possibly related to panitumumab and their follow-up reports must be reported to Amgen within 1 working day of

submission to the FDA, IRB or IEC. A copy of any safety report submitted to the FDA, IRB or IEC should be faxed to Amgen, within 24 hours of such submission. All reporting to the FDA must go through MSKCC's IND Office. The sponsor is responsible to ensure that the latest investigator's brochure is used as the source document for determining the expectedness of an SAE.

A copy of any safety report submitted to the FDA, or any other regulatory agency, IRB or IEC, should be faxed with the Amgen Adverse Event fax coversheet to Amgen, within 24 hours of such submission, at:

Amgen Global Safety
Fax: 888-814-8653

REPORTING	FREQUENCY
SADRs	Within 1 month of the event
SUSARs	Within 1 business day of FDA submission

Investigators should not wait to receive additional information to fully document the event before notifying the sponsor of the SAE. Any SAE, if brought to the attention of the investigator at any time after cessation of study drug, and considered by the investigator to be possibly related to study drug, should be reported.

17.2.2 Reporting Procedures for All Adverse Events to Amgen

All AEs occurring after informed consent signing observed by the investigator or reported by the subject (whether or not attributed to investigational product) will be reported. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by subjects are properly captured in the subjects' medical records.

An adverse event is defined in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice as —any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.‖ (ICH E6:1.2). The ongoing review of safety data will include review of clinical AEs and SAEs including skin-related toxicity assessment and laboratory studies. The CTCAE version 4.0 will be used to grade all AEs, except Panitumumab related toxicity which will be graded by modified CTCAE version 3.0 Dermatology Skin Assessment (Appendix B). The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory or clinical findings without clinical significance (Grades 1 and 2 or based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events. All Grade 3 and Grade 4 or clinically significant toxicities will be recorded.

The following adverse event attributes must be assigned by the investigator:

- Adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known)
- Event description (with detail appropriate to the event)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to study treatment
- Action taken.

Amgen may request follow-up information.

Medically significant adverse events considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable.

It will be left to the investigator‘s clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject‘s removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

20.1 APPENDIX A: Clinical Risk Score for Tumor Recurrence

20.2 APPENDIX B: Dermatology/Skin/Nail Assessment (from CTCAE version 3.0 with modifications)