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**Estudo de fase II avaliando eficácia e toxicidade de
UFT (uracil e tegafur) e leucovorin, administrados
duas vezes ao dia, no tratamento de pacientes com
câncer metastático de cólon e reto**

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DEDICATÓRIA

Agradeço à minha esposa Ana Amélia, que sempre me apoiou e incentivou, às minhas filhas, Camilla, Julianna e Isabella, que dão razão à minha vida."

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LISTA DE ABREVIATURAS

DPD	Desidrogenase de dihidropirimidina
FAP	Adenomatose Polipóide Familiar
HNPCC	Síndrome do Câncer de Cólon Hereditário Não Polipóide
DNA	Ácido Desoxirribonucléico
CEA	Antígeno cárcino-embrionário
FOLFOX	Infusão de 5-fluorouracil, leucovorin e oxaliplatina
FLOX	Bolus de 5-fluorouracil, leucovorin e oxaliplatina
FOLFIRI	Infusão de 5-fluorouracil, leucovorin e irinotecano
IFL	Bolus de 5-fluorouracil, leucovorin e irinotecano
NSABP	National Surgical Adjuvant Bowel and Breast
ECOG	Eastern Cooperative Oncology Group
RC	Resposta completa
RP	Resposta parcial
DE	Doença estável
DP	Doença progressiva
UFT	Uracil e tegafur

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RESUMO

Hoff PM. *Estudo de fase II avaliando eficácia e toxicidade de UFT (uracil e tegafur) e leucovorin, administrados duas vezes ao dia, no tratamento de pacientes com câncer metastático de cólon e reto* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2007.

Infusões prolongadas de 5-fluorouracil são mais seguras e potencialmente mais efetivas no tratamento do câncer de cólon metastático do que infusões rápidas da mesma medicação. No entanto, infusões prolongadas requerem a disponibilidade de um acesso venoso central, bem como de bombas de infusão dispendiosas. O desenvolvimento de fluoropirimidinas orais permitiu que pacientes fossem expostos ao 5-fluorouracil por longo tempo, com maior conveniência. UFT e leucovorin administrados três vezes ao dia demonstraram previamente uma eficácia equivalente, com menor toxicidade, quando comparados a um regime convencional de infusão rápida de 5-fluorouracil e leucovorin. Este estudo com 98 pacientes foi desenhado e conduzido com objetivo de demonstrar equivalência no tempo de progressão com o uso de UFT e leucovorin administrados duas vezes ao dia, com o uso da mesma combinação administrada três vezes ao dia. Objetivos secundários incluíram análise de toxicidade, resposta objetiva e sobrevida global. O tempo mediano de progressão foi de 3,8 meses, comparado com 3,5 meses observados com o uso da medicação três vezes ao dia e a taxa de resposta foi de 11%, com uma sobrevida mediana de 12,8 meses, sendo comparável aos resultados de 12% e 12,4 meses obtidas com o uso da combinação três vezes ao dia. A incidência de diarreia com graus 3 e 4 foi de 30% no regime de administração duas vezes ao dia, e 21% no de três vezes ao dia. Esses resultados sugerem que o uso de UFT e leucovorin duas vezes ao dia tem eficácia e toxicidade similares às aquelas obtidas com o uso da mesma medicação três vezes ao dia.

DESCRITORES: Neoplasias colorretais/quimioterapia 2.Tegafur/administração & dosagem 3.Uracila/administração & dosagem 4.administração oral 5.Ensaio clínico fase II

SUMMARY

Hoff PM. *Phase II trial evaluating the efficacy and toxicity of UFT and toxicity of UFT and leucovorin twice-daily as a treatment for metastatic colorectal cancer* [thesis]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2007.

Prolonged infusions have been shown to be safer and potentially more effective than bolus regimens of 5-fluorouracil as treatment for advanced colorectal cancer. However, infusional 5-fluorouracil requires central venous access and costly infusion pumps. Development of oral fluoropyrimidines has allowed longer exposures to 5-fluorouracil with increased convenience. UFT and leucovorin given thrice daily showed improved safety and no significant difference in survival or response rate compared with bolus 5-fluorouracil and leucovorin. This study with 98 patients was conducted to evaluate whether UFT and leucovorin given twice daily provided comparable time to progression (TTP) to the same combination administered three times a day. Secondary objectives included evaluation of toxicity, overall tumor response rate, and survival. Median time to progression was 3.8 months, compared with 3.5 months observed with the thrice-daily regimen. The twice-daily regimen had a response rate of 11% and median survival of 12.8 months, comparable to the 12% and 12.4 months seen with the thrice-daily regimen. The incidence of grade 3-4 drug-related diarrhea was 30% on the twice-daily and 21% on the thrice-daily schedule. Results suggest that the twice-daily schedule has similar safety and efficacy to the thrice-daily schedule.

DESCRIPTORS: 1.Colorectal neoplasms/drug therapy 2.Tegafur/administration & dosage 3.Uracil/administration & dosage 4.Administration, oral 5.Clinical trials, phase II

1 INTRODUÇÃO

O tegafur é uma fluoropirimidina originalmente sintetizada na extinta União Soviética por Hiller et al.¹. Essa droga foi originalmente investigada para administração endovenosa, e seu uso foi abandonado devido às altas taxas de neurotoxicidade². No entanto, as características farmacodinâmicas do tegafur permitem seu uso como uma formulação oral, o que gerou grande interesse entre investigadores e médicos japoneses.

Na década de 80, o desenvolvimento dessa medicação como opção oral ao 5-fluorouracil ganhou força no Japão. O 5-fluorouracil não deve ser administrado de forma oral devido à alta concentração da enzima desidrogenase de dihidropirimidina (DPD) no intestino humano. No entanto, o tegafur é absorvido de forma intacta e não é metabolizado por essa enzima na luz intestinal, podendo ser administrado por via oral³.

Uma vez absorvido, o tegafur é metabolizado para 5-fluorouracil, primariamente no fígado, e entra nas mesmas vias metabólicas do 5-fluorouracil administrado por via endovenosa, com o mesmo perfil de atividade⁴.

O UFT é um desenvolvimento mais recente do mesmo conceito de uma fluoropirimidina oral³. No UFT, o tegafur é combinado com uracil numa razão molar de 1:4. O uracil é o substrato natural da enzima DPD, e compete favoravelmente com o 5-fluorouracil pela enzima quando ambos são administrados juntos e estão presentes na circulação, resultando em uma meia-vida mais prolongada do 5-fluorouracil, imitando infusão contínua^{5,6}. O UFT tornou-se rapidamente uma das

drogas mais utilizadas no tratamento de tumores originados no trato gastrointestinal no Japão, e gerou interesse considerável no mundo ocidental.

Praticamente todo o desenvolvimento inicial do UFT foi feito no Japão, onde essa medicação foi utilizada com sucesso em uma grande variedade de tumores, quase sempre utilizado como agente único^{3,7}. Esse sucesso do UFT no Japão levou ao seu desenvolvimento nos EUA e na Europa, começando no início da década de 90⁸⁻¹⁰.

Apesar das dúvidas quanto ao real benefício clínico do leucovorin, essa medicação foi combinada ao UFT desde o princípio de seu desenvolvimento nos EUA e na Europa, com o intuito de maximizar o efeito do 5-fluorouracil, gerado pelo tegafur, sobre as células tumorais^{6,11}. Estudos de fase I indicaram que a dose recomendada para estudos de fase II seria UFT 300 a 350 mg/m²/dia, combinado com leucovorin em doses de até 150 mg/dia. Determinou-se ainda que a dose diária deveria ser dividida em 3 doses iguais, que seriam administradas uma a cada 8 horas por um total de 28 dias, a cada 35 dias^{9,10}. A toxicidade foi modesta, e a toxicidade limitante foi a ocorrência de diarreia.

Devido à similaridade do UFT com o 5-fluorouracil, os primeiros estudos de fase II utilizando UFT e leucovorin foram dirigidos para pacientes com adenocarcinomas de cólon e reto metastáticos. Um estudo do *M. D. Anderson Cancer Center*, incluindo 45 pacientes, descreveu uma taxa de resposta de 42%, com toxicidade bastante aceitável¹². O efeito colateral mais comum foi novamente diarreia, com quatro pacientes apresentando grau 3 dessa toxicidade. Esse resultado foi extremamente animador, sendo complementado por bons resultados obtidos em outros estudos de fase II nos EUA e na Europa^{13,14}.

Os resultados promissores obtidos nas pesquisas de fase II levaram ao desenvolvimento de dois grandes estudos randomizados de fase III, comparando UFT e leucovorin com o regime da Clínica Mayo de 5-fluorouracil e leucovorin^{15,16}. Ambos os estudos incluíram pacientes sem tratamento prévio, com câncer de cólon e reto metastático.

O principal estudo incluiu 816 pacientes e avaliou um regime de 300 mg/m²/dia de UFT combinado com 25-30 mg de leucovorin três vezes ao dia por 28 dias, repetidos a cada 35 dias, contra o regime clássico da Clínica Mayo, incluindo 425 mg/m²/dia de 5-fluorouracil endovenoso, combinado com 20 mg/m²/dia de leucovorin por 5 dias, repetido a cada 28 dias¹⁵. Não houve diferença significativa quanto à taxa de resposta (12% *versus* 15%), tempo para progressão (3,5 *versus* 3,8 meses) ou quanto à sobrevida mediana (12,4 *versus* 13,4 meses) entre o grupo que recebeu UFT e leucovorin e o grupo que recebeu 5-fluorouracil e leucovorin, respectivamente. Pacientes expostos a UFT e leucovorin tiveram menores índices de neutropenia grave (56% *versus* < 1%), diarreia (67% *versus* 76%) e estomatite (24% *versus* 75%) do que aqueles expostos ao 5-fluorouracil e leucovorin endovenosos¹⁵.

O segundo estudo foi consideravelmente menor, incluindo 380 pacientes, e avaliando os mesmos regimes de quimioterapia. A única diferença foi o intervalo entre os ciclos de 5-fluorouracil e leucovorin, que foi estendido para 5 semanas, com o intuito de equiparar esse regime ao mesmo intervalo dos ciclos de UFT e leucovorin. Apesar dessa pequena diferença, os resultados foram praticamente iguais àqueles apresentados pelo estudo anteriormente descrito¹⁶.

Embora os estudos iniciais tenham dividido a dose diária de UFT e leucovorin em três doses ao dia^{15,16}, um regime com doses menos frequentes teria

impacto potencialmente positivo na qualidade de vida dos pacientes. O grupo cooperativo espanhol Oncopaz conduziu um estudo de fase II em que os pacientes receberam 500 mg/m² de leucovorin endovenoso no dia 1, seguido de 195 mg/m² de UFT com 15 mg de leucovorin oral a cada 12 horas nos dias 2-14, a cada 28 dias¹⁷. Em um grupo de 75 pacientes com câncer de cólon e reto avançado, a taxa de resposta foi de 39%. A sobrevida mediana foi de 13,5 meses, e os efeitos colaterais mais comuns foram diarreia, náusea e vômitos¹⁷. Esse estudo indicou que uma dosagem mais cômoda de UFT e leucovorin poderia ser efetiva, e que essa modificação poderia ser explorada em outros estudos.

2 REVISÃO DA LITERATURA

O câncer de cólon e reto é doença bastante comum, afetando preferencialmente pessoas com mais de 50 anos, embora possa ser ocasionalmente encontrado em pessoas bem mais jovens, quando está freqüentemente associado a síndromes genéticas hereditárias. Esse tipo de câncer é incomum em países subdesenvolvidos da África, mas apresenta uma incidência bastante alta nos países mais desenvolvidos e em desenvolvimento do ocidente, levando a uma suspeita de que fatores como nutrição e atividade física possam estar correlacionadas com seu aparecimento.

A despeito dos grandes progressos feitos no entendimento das bases moleculares de predisposição e progressão do câncer de cólon e reto, e de intensos esforços na prevenção e diagnóstico precoces, essa patologia permanece como a segunda causa de morte por câncer nos EUA¹⁸, onde mais de 150.000 novos casos são diagnosticados, e mais de 50.000 pacientes morrem anualmente por causa da doença. Apesar de menos prevalente do que nos países mais desenvolvidos, o câncer de cólon e reto continua sendo problema também no Brasil e no mundo¹⁹. As estimativas publicadas na página da internet do Instituto Nacional do Câncer (INCA) para o Brasil apontam uma incidência de 16.165 novos casos anuais, com 7.230 óbitos.

Embora outros tumores, como de mama e estômago, entre outros, sejam encontrados com maior freqüência em nosso país, a tendência é que o câncer de cólon se torne mais prevalente à medida que as condições socioeconômicas da população melhorem e comecem a se equiparar com aquelas das populações do primeiro mundo.

Essa mudança na incidência relativa do câncer de cólon parece estar associada principalmente com alterações na dieta e nos hábitos alimentares²⁰. Outro fator importante a ser considerado é a genética. Acredita-se hoje que entre 10% e 30% dos casos de câncer de cólon estejam relacionados à predisposição genética, ou seja, aparecem em pessoas cujas famílias apresentam características que facilitam o aparecimento da doença. Entre as síndromes mais importantes podemos destacar a Adenomatose Polipóide Familiar (FAP) e a Síndrome de Lynch, ou do Câncer de Cólon Hereditário Não Polipóide (HNPCC), descritas abaixo de forma mais detalhada. O câncer de cólon e reto tem sido alvo de estudos profundos nesta área e o conhecimento acumulado está abrindo oportunidades importantes de prevenção e de tratamento mais efetivo²¹⁻²⁴.

Embora continuemos a aprender sobre sua gênese, a história natural do câncer de cólon está bem estabelecida. Como o resto do trato gastrointestinal, o cólon e o reto são revestidos internamente por uma mucosa composta por uma fina camada de células. Devido à predisposição genética, ou por uma série de estímulos externos, uma pequena área da mucosa desenvolve células com características anormais. Em certas ocasiões, por falhas nos mecanismos naturais de supressão de tumores, em vez de essas células anormais entrarem em apoptose, como seria esperado, elas podem evoluir para um fenótipo de características indesejáveis²¹⁻²⁴ e, com o passar do tempo, tornarem-se displásicas, e eventualmente formarem pólipos²⁵⁻²⁹. Essa lesão, ainda benigna, pode ser facilmente removida sem necessidade de cirurgia de grande porte. Se isso não ocorrer, ela poderá eventualmente evoluir para câncer de cólon ou reto. Quanto maior o tamanho do pólio, maior o risco de que essa evolução para câncer tenha ocorrido^{25,27,29}.

De maneira geral, podemos separar os cânceres de cólon e reto entre aqueles relacionados à predisposição genética e àqueles considerados “esporádicos”, ou seja, sem relação aparente. Os tumores relacionados à predisposição genética ou familiar geralmente são encontrados entre pacientes mais jovens e com outros casos de câncer na família. As síndromes mais comuns são a Adenomatose Polipóide Familiar e a Síndrome de Lynch, ou do Câncer de Cólon Hereditário Não Polipóide^{21,23,30-32}.

A Adenomatose Polipóide Familiar é causada por alteração no gene *APC*, localizado no cromossomo 5. Esse é um importante gene supressor de tumores, e sua ausência quase sempre causa o aparecimento de centenas a milhares de pólipos, começando na puberdade^{31,32}. Se o cólon e o reto de pacientes portadores dessa doença não forem removidos, a evolução para câncer é praticamente certa, embora exista hoje medicação disponível para reduzir o número de pólipos em pacientes portadores dessa síndrome³³. O uso do celecoxib, um inibidor específico da enzima ciclooxigenase-2, diminui a incidência de pólipos nesses pacientes, mas a ressecção cirúrgica permanece como tratamento padrão³³. Felizmente essa síndrome é incomum e dá origem a um número pequeno de casos de câncer anualmente.

A síndrome do Câncer de Cólon Hereditário Não Polipóide é bem mais prevalente, sendo responsável por até 10% dos casos de câncer de cólon e reto³⁴. Como o nome indica, não está relacionada a um grande número de pólipos. Tende a se apresentar após os 20 anos, e pode estar relacionada com o aparecimento de outros tumores, tais como de endométrio e ovário³⁴. É causada por alteração em um dos genes responsáveis pelo aparato celular que repara o DNA. A localização do defeito varia entre famílias afetadas e pode estar nos cromossomos 2, 3, ou 7³⁵. É

interessante notar que pacientes com câncer de cólon associado a essa síndrome tendem a ter melhor prognóstico do que pacientes com câncer esporádico³⁶⁻³⁸.

Outras síndromes menos comuns, e mesmo algumas ainda não identificadas, resultam em aumento do risco de câncer de cólon. É importante ressaltar que o fato de uma pessoa ter parentes com câncer não indica necessariamente que ela tenha predisposição genética, nem que tenha risco aumentado de desenvolver a doença. Entretanto, pessoas com múltiplos parentes diretos com câncer de cólon devem procurar auxílio de especialista para determinar a magnitude do seu risco individual de desenvolverem câncer, e estudar qual seria o modo mais indicado de se fazer acompanhamento preventivo.

A maioria dos casos de câncer de cólon e reto é esporádico, sendo bastante incomum seu aparecimento em pacientes com menos de 50 anos. A história natural é semelhante à dos tumores relacionados a predisposição genética, com as mesmas alterações progressivas da mucosa, e usualmente com o aparecimento de pólipos antes do desenvolvimento do câncer. As maiores diferenças estão nas causas da alteração inicial que acomete as células da mucosa, no maior tempo necessário para o aparecimento das alterações e do câncer, e no pequeno número de pólipos usualmente presentes.

O câncer esporádico parece estar relacionado a múltiplos fatores, com destaque para os hábitos alimentares³⁹⁻⁴⁸. Pessoas oriundas de lugares onde a dieta é rica em frutas e verduras, com muita fibra vegetal, parecem ter incidência menor da doença. Acredita-se que a fibra acelere o trânsito intestinal e faça com que toxinas fiquem menos tempo em contato com a mucosa. Além disso, frutas e verduras são ricas em folato. Áreas com grande consumo de produtos lácteos, como os países

escandinavos, apresentam número relativamente pequeno de tumores de cólon, sugerindo possível papel protetor do cálcio. Pessoas oriundas de regiões onde a dieta é pobre em fibra e rica em gordura animal parecem ter risco aumentado de desenvolver a doença³⁹⁻⁴⁸.

Pacientes com colite ulcerativa e com doença de Crohn também apresentam risco aumentado de apresentar câncer de cólon, particularmente quando desenvolvem displasia grave na mucosa⁴⁹.

2.1 Estadiamento

Quando a presença de câncer é confirmada, o paciente é encaminhado para uma série de exames complementares para se fazer o estadiamento apropriado, que guiará as decisões terapêuticas subseqüentes. O estadiamento mínimo exigido inclui exame físico completo, com exame digital do reto, além de raios X de tórax, tomografias ou ultra-som de abdome e pélvis, além de exames básicos de sangue, incluindo o CEA.

O estadiamento do câncer de cólon e reto é fundamental, pois determina o prognóstico bem como o tipo de tratamento recomendado. O regime de Dukes foi utilizado por muitas décadas, mas recentemente caiu em desuso. O sistema mais usado atualmente é o TNM (Tumor, Node, Metastasis). O **T** (Tumor) é classificado como: **TX** (tumor não avaliável); **Tis** (carcinoma *in situ*); **T1** (tumor infiltra a submucosa); **T2** (tumor infiltra a muscular própria); **T3** (tumor infiltra até a subserosa ou gordura perirretal) ou **T4** (tumor invade outros órgãos ou estruturas e/ou perfura o peritônio visceral). O **N** (Node) é classificado como: **N0** (sem

metástases linfonodais); **N1** (metástases em um a três linfonodos regionais) ou **N2** (metástases em quatro ou mais linfonodos regionais). Já o **M** (Metástases) é classificado apenas como **M0** (sem metástases à distância) ou **M1** (metástases à distância). O estadiamento final da neoplasia é cirúrgico, e está listado na Tabela 1.

Tabela 1 - Estadiamento TNM para tumores de cólon e reto e expectativa de sobrevida

Estádio	TNM	Sobrevida em 5 anos
0	TispN0M0	100%
I	T1-2pN0M0	93,2%
IIa	T3pN0M0	84,7%
IIb	pT4pN0M0	72,2%
IIIa	T1-2pN1M0	83,4%
IIIb	T3-4pN1M0	64,1%
IIIc	qqTpN2M0	44,3%
IV	qqTqqNM1	8,1%

- Sobrevida em 5 anos baseada no TNM ao diagnóstico

O número de linfonodos analisados pelo patologista é fator prognóstico importante, e em pacientes com linfonodos negativos, um mínimo de 12 linfonodos deve ser reportado⁵⁰. Nos pacientes operados em caráter de urgência ou com lesões suboclusivas, é importante a realização de colonoscopia completa, mesmo no pós-operatório, para que se afaste a presença de tumores sincrônicos ou de pólipos.

2.2 Tratamento

A maior parte dos cânceres de cólon e reto é constituída por adenocarcinomas, e o principal método de tratamento permanece sendo a cirurgia,

que pode ser curativa, dependendo do estágio do tumor no momento do diagnóstico. A presença de gânglios metastáticos e o estadiamento TNM, baseado no grau de invasão do tumor, número de linfonodos comprometidos e presença ou não de metástases, são os mais importantes indicadores de sobrevida em 5 anos. A sobrevida global mediana varia desde menos de 10% para pacientes com estágio IV, até mais de 90% para pacientes com estágio I⁵⁰⁻⁵². Muitos esforços estão sendo concentrados na elaboração de melhores estratégias para rastreamento e detecção precoce da doença⁵³⁻⁵⁶. No presente, aproximadamente 80% dos pacientes são diagnosticados em estágios iniciais, sendo, portanto, passíveis de tratamento cirúrgico, potencialmente curativo. Apesar disso, cerca de metade desses pacientes evoluirá com morte por recidiva devido à doença residual não aparente no momento da cirurgia^{51,57}. Infelizmente, o número de pacientes potencialmente curáveis após recorrência continua muito pequeno^{58,59}.

A disponibilidade de regimes quimioterápicos mais modernos e eficientes está lentamente aumentando o número de pacientes que podem ser tratados cirurgicamente após recorrência, particularmente quando essa recorrência restringe-se a apenas um órgão, e, principalmente, quando esse órgão é o fígado⁶⁰⁻⁶².

2.2.1 Estádio I

A curabilidade desses pacientes é da ordem de 90%, e a recomendação é de tratamento cirúrgico apenas. Devido ao excelente prognóstico, não há indicação de tratamento adjuvante.

2.2.2 Estádio II

O tratamento inclui ressecção cirúrgica, com retirada em bloco de linfonodos até a origem do vaso que nutre o tumor. Dependendo do grau de risco, pode-se aplicar quimioterapia adjuvante para os pacientes com doença de alto risco. Pacientes com instabilidade de microssatélite de alta frequência e sem fatores de alto risco têm baixo risco de recorrência. Como o benefício da quimioterapia nesse grupo é pequeno, usualmente recomenda-se quimioterapia adjuvante.

Pacientes com tumores primários perfurados ou obstruídos, tumores com invasão linfovascular ou perineural, CEA pré-operatório > 10 ng/ml, menos de 12 linfonodos regionais analisados no espécime cirúrgico, tumores aneuplóides, indiferenciados ou com células em anel de sinete ou que apresentam deleção parcial do cromossomo 18 têm alto risco de recorrência e devem receber tratamento quimioterápico adjuvante. Na ausência de fatores prognósticos negativos, deve-se discutir cada caso individualmente. O benefício do tratamento adjuvante nos pacientes em estágio II permanece relativamente pequeno, e altamente controverso.

2.2.3 Estádio III

O prognóstico de pacientes com estágio III é mais reservado, e o tratamento usualmente inclui a ressecção cirúrgica, com retirada em bloco de linfonodos até a origem do vaso que nutre o tumor, seguida de quimioterapia adjuvante.

Os primeiros estudos positivos compararam observação com o uso de 5-

fluorouracil combinado à levamisole, ou leucovorin, e demonstraram que haveria benefício em relação ao número de recorrências, bem como na sobrevida dos pacientes que receberam o tratamento adicional.⁶³⁻⁶⁵ O advento de drogas quimioterápicas mais potentes levou ao desenvolvimento de novas opções de tratamento na adjuvância. Entre as drogas recentemente estudadas, não há dúvida de que a que trouxe maior benefício foi a oxaliplatina, quando combinada ao 5-fluorouracil e leucovorin.

O estudo MOSAIC com 2.200 pacientes comparou FOLFOX (5-fluorouracil, leucovorin e oxaliplatina) com 5-fluorouracil e leucovorin na adjuvância, tanto em pacientes em estágio II, como III⁶⁶. Com seguimento mediano de 4 anos, observou-se uma redução relativa do risco de recorrência de 20% em pacientes em estágio II, e de 25% em pacientes em estágio III. Em termos absolutos, houve aumento no intervalo livre de doença de 3,8% em pacientes em estágio II, e de 8,7% em pacientes em estágio III.

Um segundo estudo, NSABP C-07 com 2.407 pacientes, em estágio II (28,8%) e III (71,2%), confirmou os resultados do estudo MOSAIC, mas ainda não foi publicado. Nesse estudo, além da dose de oxaliplatina corresponder a 75% da dose total acumulada no estudo MOSAIC, usou-se um regime com bolus de 5-fluorouracil (FLOX). Com seguimento mediano de 34 meses, a sobrevida livre de progressão em 3 anos foi de 76,5% para o FLOX, e de 71,6% para o 5-fluorouracil e leucovorin ($p < 0,004$) [Apresentação oral, ASCO 2005].

No estudo MOSAIC, a incidência de neutropenia grau 3 e 4 foi de 41%, levando os grupos cooperativos americanos a adotarem o esquema modificado de FOLFOX, evitando o bolus de 5-fluorouracil e leucovorin no segundo dia. Essa

pequena modificação é suficiente para reduzir significativamente a incidência de neutropenia.

Os pacientes idosos parecem ter o mesmo benefício relativo da quimioterapia adjuvante, e a idade apenas não deve servir como fator importante na decisão de se oferecer ou não quimioterapia adjuvante⁶⁷.

2.2.4 Estádio IV

Apesar dos avanços cirúrgicos e quimioterápicos recentes, uma vez que o tumor tenha formado metástases à distância, o tratamento usualmente não é mais considerado curativo, e embora pacientes com doença avançada ocasionalmente se beneficiem de tratamento cirúrgico, na vasta maioria das vezes o tratamento inicial deve se basear em quimioterapia sistêmica⁶⁸. Esse tratamento evoluiu muito nas últimas décadas, com a integração de novas classes terapêuticas, mas a espinha dorsal de todos os regimes utilizados continua sendo o 5-fluorouracil, ou uma de suas variantes orais, tais como a capecitabina ou o UFT.

2.2.5 Quimioterapia sistêmica

O primeiro tratamento efetivo desenvolvido foi o 5-fluorouracil, descrito em grande detalhe abaixo, e embora hoje existam muitas outras opções disponíveis, as fluoropirimidinas, incluindo 5-fluorouracil, UFT, ou capecitabina, continuam sendo a

espinha dorsal dos regimes de tratamento para câncer de cólon e reto. Os novos tratamentos baseiam-se em seis classes e pelo menos 10 drogas diferentes, listadas na Tabela 2, o que possibilita um número de combinações extremamente alto.

Tabela 2 – Drogas quimioterápicas com atividade em câncer de cólon e reto

Drogas	Via de administração	Alvo
Fluoropirimidinas 5-fluorouracil UFT Capecitabina S-1	Endovenosa Oral Oral Oral	Timidilato sintetase
Raltitrexed	Endovenosa	Timidilato sintetase
Platinas Oxaliplatina	Endovenosa	DNA
Inibidor de Topoisomerase Irinotecano	Endovenosa	Topoisomerase I
Anti-VEGF Bevacizumabe	Endovenosa	Fator de crescimento vâsculo-endotelial
Anti-EGFR Cetuximabe Panitumomabe	Endovenosa Endovenosa	Receptor do fator de crescimento endotelial

Tanto a adição da oxaliplatina como a adição do irinotecano a regimes baseados em 5-fluorouracil aumentaram as taxas de resposta para 40% a 50%, bem como a sobrevida dos pacientes com câncer de cólon e reto, atingindo até 21 meses de sobrevida mediana^{69,70}.

O estudo N9741 avaliou três diferentes combinações quimioterápicas comumente utilizadas na prática clínica: FOLFOX, IFL, e IROX (irinotecano e oxaliplatina). Esse estudo demonstrou aumento de resposta (45% *versus* 31% *versus* 35%, respectivamente) e aumento do tempo livre de progressão para pacientes

tratados com FOLFOX (8,7 *versus* 6,9 *versus* 6,5 meses, $p = 0,0014$ e $p = 0,001$, respectivamente). Quanto à sobrevida, o regime de FOLFOX foi significativamente superior ao IFL (19,5 *versus* 15 meses, $p = 0,0001$)⁷¹. Entretanto, esses dados devem ser analisados com cautela, pois houve desequilíbrio quanto ao tratamento de resgate. Apenas 24% dos pacientes que progrediram com irinotecano receberam oxaliplatina, ao passo que 60% dos pacientes que progrediram com oxaliplatina receberam irinotecano.

Explorando as deficiências do estudo N9741, um estudo francês com dois braços tratou pacientes com o mesmo regime de 5-fluorouracil com leucovorin, combinado com oxaliplatina ou com irinotecano em primeira linha, seguido de "crossover" para o outro regime após progressão⁷². Os regimes mostraram eficácia semelhante em termos de resposta (57% *versus* 56%), sobrevida livre de progressão (8,5 *versus* 8 meses) e sobrevida global (21,5 *versus* 20,6 meses)⁷².

O consenso hoje é de que qualquer das combinações contendo uma fluoropirimidina, associada à oxaliplatina ou ao irinotecano, pode ser considerada como opção aceitável de tratamento para câncer de cólon e reto metastático.

A mais nova adição ao armamentário disponível para o tratamento do câncer de cólon e reto metastático é o bevacizumabe, um anticorpo monoclonal que bloqueia a ação do fator de crescimento vâsculo-endotelial.

A combinação de bevacizumabe com o regime de IFL em pacientes sem tratamento anterior demonstrou, em estudo randomizado com 813 pacientes, aumento significativo em resposta objetiva (45% *versus* 35%, $p = 0,004$), tempo livre de progressão (10,6 *versus* 6,24 meses, $p < 0,001$) e sobrevida global (20,3 *versus* 15,6 meses, $p < 0,001$), quando comparada a IFL associado a placebo⁷³. Embora a

incidência de sangramento grave e de eventos trombóticos venosos não tenha sido significativamente diferente entre os braços desse estudo, houve maior incidência de hipertensão de grau 3 no braço com bevacizumabe. Ademais, embora rara, a perfuração gastrointestinal foi bem documentada.

Um segundo estudo randomizado de fase II com 209 pacientes, avaliando o papel do bevacizumabe em combinação com 5-fluorouracil e leucovorin como tratamento de primeira linha, também demonstrou aumento significativo do tempo livre de progressão (9,2 *versus* 5,5 meses) e tendência a aumento da sobrevida global (16,6 *versus* 12,9 meses) e resposta objetiva (26% *versus* 15%) em favor do tratamento combinado^{74,75}.

O cetuximabe, anticorpo direcionado contra o receptor para o fator de crescimento epitelial, presente em grande parte das células tumorais, é comumente utilizado em tratamento de resgate, para pacientes que tenham mostrado progressão da doença apesar de tratamentos iniciais. O estudo BOND avaliou o uso de cetuximabe como agente único ou combinado com irinotecano. Esse estudo demonstrou taxa de resposta de 10,8% e 23%, respectivamente, com aumento significativo do tempo livre de progressão ($p < 0,001$), mas não houve impacto na sobrevida global⁷⁶. A toxicidade dermatológica ocorre em cerca de 80% dos pacientes tratados. A presença de reação intensa na pele eleva significativamente os índices de resposta objetiva (6,3 para 33,6%), tempo livre de progressão (3,0 para 10,8 meses) e sobrevida global (4,1 para 14,9 meses), quando comparada à ausência de reação ($p = 0,0001$)⁷⁶. O panitumomabe, anticorpo monoclonal contra EGFR totalmente humanizado, parece ter atividade semelhante ao cetuximabe, e seu uso comercial foi recentemente aprovado nos EUA.

2.2.6 5-Fluorouracil

A droga quimioterápica mais utilizada, e ainda mais importante, no tratamento de tumores de cólon e reto é o 5-fluorouracil, ou um de seus derivados^{77,78}. Essa medicação foi inicialmente desenvolvida em 1957, e não é somente ativa, mas extremamente versátil. Ela pode ser utilizada como agente único ou combinada com agentes moduladores ou outras medicações antitumorais, tais como irinotecano, oxaliplatina, bevacizumabe ou cetuximabe⁷⁹⁻⁸¹. Praticamente todos os regimes quimioterápicos utilizados em primeira linha no tratamento de câncer de cólon e reto continuam baseados no 5-fluorouracil.

O 5-fluorouracil pode ser administrado de forma rápida, na forma de infusão de poucos minutos, ou de forma contínua, por períodos variando entre 24 horas e 21 dias. Metanálise incluindo estudos que haviam comparado infusões rápidas e contínuas de 5-fluorouracil como tratamento para adenocarcinomas de cólon e reto demonstrou que as infusões contínuas são superiores em termos de resposta objetiva (22% *versus* 14%) e sobrevida mediana (12,1 meses *versus* 11,3 meses)⁸². Essa diferença baseia-se nas características farmacocinéticas do 5-fluorouracil.

Após sua entrada na circulação, a maior parte do 5-fluorouracil infundido é rapidamente convertida pela enzima desidrogenase de dihidropirimidina (DPD) em metabólitos inativos^{83,84}. O restante do 5-fluorouracil entra em uma via anabólica, sendo convertido em monofosfato de fluorouridina, que é por sua vez convertido para difosfato de fluorouridina e, posteriormente, em trifosfato de fluorouridina (FUTP) ou monofosfato de fluorodeoxiuridina (FdUMP)⁸⁵.

O mecanismo de citotoxicidade do 5-fluorouracil inclui inibição de síntese de DNA a partir da inibição da enzima timidilato sintase (TS) pelo FdUMP e da inibição da síntese de RNA quando o FUTP é incorporado no RNA⁸⁵.

Os efeitos colaterais da infusão rápida do 5-fluorouracil e a inconveniência das infusões prolongadas levaram diversos investigadores a procurarem maneiras alternativas de administração do 5-fluorouracil, incluindo drogas orais precursoras como o tegafur, uracil com tegafur (UFT), e capecitabina^{77,86,87}.

Os resultados desapontadores obtidos com o uso do 5-fluorouracil isolado levaram diversos investigadores a estudarem agentes moduladores do 5-fluorouracil. Muitos agentes foram testados, como o leucovorin, metotrexato, PALA, alfa-interferon, e levamizol, entre outros⁸⁸. Destes, com certeza o leucovorin é o que apresentou os melhores resultados.

Leucovorin, também conhecido como ácido folínico, é um derivado do ácido tetraidrofólico, e aumenta os efeitos terapêuticos e tóxicos de fluoropirimidinas, tais como o 5-fluorouracil. Esse efeito deve-se à propriedade do tetraidrofolato intracelular de estabilizar o complexo FdUMP/TS, aumentando a inibição da síntese e reparo do DNA^{88,89}. Diversos estudos randomizados de tratamento paliativo em câncer de cólon e reto demonstraram aumento da taxa de resposta no grupo de pacientes que recebeu a combinação de 5-fluorouracil e leucovorin, quando comparada com o grupo que recebeu somente 5-fluorouracil, porém essa vantagem resultou apenas em um aumento mínimo na sobrevida mediana^{90,91}.

3 OBJETIVOS

O objetivo primário deste estudo de fase II foi:

- avaliar se um regime de quimioterapia oral, utilizando UFT e leucovorin como tratamento de pacientes com câncer de cólon e reto metastático, administrado duas vezes ao dia, seria comparável em eficácia a regime utilizando as mesmas medicações, com a mesma dose total diária, administrado três vezes ao dia e a proporção de pacientes que permaneceriam sem progressão após 6 meses de tratamento.

Objetivos secundários:

- incluíram a determinação da incidência de toxicidade, taxa de resposta objetiva e o tempo de sobrevida global.

4 MÉTODOS

Devido às limitações no número de pacientes interessados e disponíveis para estudo deste tipo, e para agilizar o tempo necessário para a determinação dos resultados, optamos por estudo de fase II multicêntrico, aberto, não randomizado, com braço único de tratamento. A principal instituição participante foi o *M. D. Anderson Cancer Center*, da Universidade do Texas em Houston, EUA, que fez o papel de instituição coordenadora e ficou encarragada dos dados coletados. Outros centros que participaram deste estudo foram o *Royal Victoria Hospital* de Montreal, no Canadá, o *Louisiana Oncology Associates de Lafayette*, na Louisiana, EUA, e a Universidade Estadual da Louisiana em Nova Orleans, EUA. O estudo foi patrocinado pela empresa *Bristol-Myers Squibb* de Nova Jersey, EUA, que forneceu suporte financeiro, monitoria, além de toda a medicação utilizada no estudo, distribuída gratuitamente para os participantes, seguindo o protocolo descrito abaixo.

4.1 Critérios de elegibilidade

Os critérios de elegibilidade incluíam idade acima de 18 anos, confirmação histológica do diagnóstico de adenocarcinoma metastático de cólon ou reto, presença de doença mensurável pelo critério da Organização Mundial de Saúde (medido como a somatória dos produtos dos diâmetros dos tumores mensuráveis, por método de imagem)⁹², e ausência de tratamento prévio para doença metastática. Tratamento adjuvante era aceitável, desde que tivesse sido completado pelo menos seis meses antes da entrada neste estudo. Os pacientes precisavam ter nível de desempenho medido pela escala ECOG (Eastern Cooperative Oncology Group) de dois ou menos,

e uma expectativa de vida de pelo menos 12 semanas. As funções hematopoiética, renal e hepática deveriam estar adequadas. As mulheres não podiam estar amamentando, e deveriam ter teste para gravidez negativo por exame de sangue ou urina, a menos que estivessem na menopausa ou que tivessem sido esterilizadas cirurgicamente. Todos os pacientes participando do estudo deveriam praticar métodos aceitos de contracepção durante o estudo. Todas as manifestações de toxicidade relacionadas a tratamentos anteriores deveriam ter retornado ao seu nível basal, antes do início do tratamento experimental.

Critérios de inelegibilidade incluíam qualquer uma das seguintes situações: tratamento anterior para doença metastática, com exceção de radioterapia com intuito paliativo para lesões sintomáticas; uso concomitante de outros agentes experimentais; histórico de metástases intracranianas ou carcinomatose meníngea; exposição pregressa a fluoropirimidinas orais; histórico de outros cânceres, com exceção de câncer basocelular, carcinoma de cérvix *in situ* ou cânceres tratados com intuito curativo e que não tenham recorrido em cinco anos ou mais. Pacientes com infecção séria ativa ou condição médica que os impedisse de receber o tratamento, ou que manifestassem demência ou estado mental alterado em um nível que afetasse sua capacidade de entender e assinar o consentimento informado também foram excluídos.

O protocolo de estudo foi aprovado pelos comitês de ética de todos os centros participantes, e todos os pacientes foram instruídos quanto à natureza experimental do tratamento, tendo assinado o documento de consentimento informado aprovado pelo comitê de ética local.

4.2 Medicação e ajuste de doses

UFT foi administrado no formato de cápsulas contendo 100 mg da medicação, e o leucovorin foi administrado como tabletes contendo 15 mg. Ambas as medicações foram entregues pelo laboratório *Bristol-Myers Squibb*. Os pacientes receberam uma dose de $300 \text{ mg/m}^2/\text{dia}$ de UFT dividida em 2 doses administradas por via oral a cada 12 horas, por 28 dias. Uma dose de 30 mg de leucovorin foi administrada com cada dose do UFT. A dose diária total do UFT foi arredondada para cima ou para baixo, até a dose mais próxima divisível por 100 mg. Os pacientes foram instruídos a manterem jejum por uma hora antes e uma hora após a ingestão da medicação do estudo.

A dose de UFT de cada ciclo foi reduzida em $50 \text{ mg/m}^2/\text{dia}$ no caso de toxicidades grau 2 ou maior, de acordo com a escala de toxicidade do Instituto Nacional do Câncer (*National Cancer Institute Common Toxicity Criteria Scale*, Versão 2.0) (Tabela 3). As reduções de dose foram baseadas na toxicidade do ciclo anterior e do ciclo atual. Uma vez reduzida, a dose não poderia ser novamente aumentada. Para eventos que atingiram grau 3 de toxicidade, a administração do UFT era interrompida até que a toxicidade retornasse ao nível basal. A dose de leucovorin permaneceu constante, sem alterações por toxicidade, mas se a administração do UFT fosse interrompida o leucovorin não era administrado também. O tratamento poderia ser interrompido por até duas semanas para permitir recuperação da toxicidade, mas os dias de terapia omitidos ainda eram contados como dias de tratamento. Quando o tratamento era interrompido por toxicidade,

mas os efeitos colaterais se resolviam ainda durante os dias de tratamento planejado, os pacientes voltavam a tomar a medicação, com a dose ajustada.

Tabela 3 - Doses de UFT e leucovorin utilizadas no estudo

Nível	Leucovorin (mg/dose)	UFT (mg/m ² /dia)
0	30	300
-1	30	250
-2	30	200

4.3 Avaliação de resposta

Todos os pacientes foram avaliados com anamnese e exame físico completos, avaliação do nível de *performance status*, exames radiográficos apropriados, e testes laboratoriais. Os pacientes foram contatados semanalmente, por telefone, para coleta de informações relacionadas à toxicidade e à aderência ao tratamento. A toxicidade também foi avaliada diretamente em cada visita médica, marcada para o início de cada ciclo de tratamento. Os pacientes preencheram diários em que o horário de ingestão de cada dose da medicação do estudo deveria ser marcado, bem como todos os efeitos colaterais percebidos pelo paciente.

A resposta objetiva dos tumores foi avaliada a cada dois ciclos, até a determinação de progressão da doença. Resposta Completa (RC) foi definida como desaparecimento completo de todos os tumores e normalização dos marcadores tumorais. Resposta Parcial (RP) foi definida como um decréscimo de mais de 50% na somatória dos produtos dos dois maiores diâmetros perpendiculares de todas as

lesões mensuráveis, na ausência de progressão de qualquer lesão ou do aparecimento de novas lesões. Doença Estável (DE) foi definida como ausência de resposta objetiva, como definido acima, e ausência de Doença Progressiva (DP), definida como um aumento de mais de 25% no tamanho de qualquer lesão mensurável ou avaliável, aparecimento de nova lesão, ou aparecimento de efusão pleural maligna ou ascite. Mortes causadas pelo câncer também foram classificadas como DP⁹². As respostas objetivas foram confirmadas com novo exame de imagem realizado o mais próximo possível de quatro semanas após a documentação inicial de resposta.

O tratamento continuava até a determinação de progressão ou desenvolvimento de toxicidade intolerável. Para os pacientes que permaneciam sem progressão por um ano, a decisão quanto à continuidade do tratamento foi deixada a critério dos investigadores locais. O tempo de progressão foi calculado para todos os pacientes a partir da data de início do estudo até a data em que DP ou morte foram primeiramente reportadas. Os dados dos pacientes em que a doença não havia documentação de progressão ou morte foram censurados na última data em que havia documentação de que estes pacientes estavam vivos sem progressão. Para os pacientes que faleceram sem que tenha havido documentação de progressão antes do evento, utilizou-se a data da morte como data de progressão. A sobrevida de todos os pacientes foi calculada utilizando-se a data de início do estudo e a data do falecimento. Para os pacientes que não morreram, os dados foram censurados na última data em que se documentou que eles estavam vivos. Os eventos adversos (toxicidade) foram graduados e avaliados usando-se a tabela de toxicidades comuns (CTC) do *National Cancer Institute* (NCI), versão 2.0 (<http://ctep.cancer.gov/reporting/ctc.html>).

4.4 Desenho estatístico

O objetivo primário do estudo foi a avaliação do tempo até progressão (TP) e a proporção de pacientes que permaneciam sem progressão após 6 meses de tratamento. Baseada nos resultados dos estudos de fase III em primeira linha, a hipótese nula era de que 30% dos pacientes estariam livres de progressão após 6 meses. Isso equivaleria a um tempo mediano até a progressão de 3,45 meses e a um *hazard rate* mensal de 0,201, considerando-se que o tempo até a progressão teria distribuição exponencial.

O tamanho da amostra foi determinado em 90 pacientes elegíveis, o que permitiria estimar o *hazard rate* real com diferença de 0,082 entre o limite superior (0,244) e o limite inferior (0,162) do intervalo de confiança de 95%. Se a estimativa máxima de tempo até a progressão fosse maior que 2,8 meses, o que corresponderia ao limite superior de confiança para o *hazard rate* (0,244), então o regime seria considerado tão efetivo quanto o regime de dosagem de três vezes ao dia, com base em um teste de não-inferioridade unicaudal com nível de significância de 5%.

As estimativas de Kaplan-Meier foram usadas para demonstrar as distribuições empíricas de tempo até a progressão e sobrevida global. Todos os pacientes elegíveis foram incluídos nessas análises.

5 RESULTADOS

Noventa e oito pacientes foram incluídos no estudo entre setembro de 1999 e dezembro de 2001. Todos os pacientes receberam pelo menos uma dose de UFT e leucovorin, e eram elegíveis para participarem na avaliação de segurança do tratamento. Sete pacientes apresentaram desvios nos critérios de elegibilidade: um paciente havia recebido UFT na adjuvância; em um a doença havia progredido dentro de seis meses após tratamento adjuvante; dois tinham lesões menores do que a medida requerida de 1,5 cm para mensuração e três pacientes tinham elevações basais das enzimas hepáticas ou nas bilirrubinas. Foram incluídos 97 pacientes no denominador da análise de eficácia. A característica demográfica dos pacientes incluídos está listada na Tabela 4.

Tabela 4 - Características dos pacientes

Características	N	%
Pacientes	98	-
- Homem	58	59
- Mulher	40	41
Local do primário		
- Cólon	81	83
- Reto	17	17
Raça		
- Branca	73	75
- Negra	12	12
- Hispânica	7	7
- Outros	6	6
Idade mediana (variação)	64 (38-93)	
Performance (ECOG)		
- 0	34	35
- 1	49	50
- 2	15	15
Terapia anterior		
- Quimioterapia	24	25
- Imunoterapia	1	1
- Radioterapia	13	13
Locais de metástases		
- Fígado	81	83
- Pulmão	29	30
- Linfonodos	21	21
- Outros	35	36

Durante todo o período do estudo, um total de 394 ciclos foram administrados, com média de 4 ciclos por paciente (1 a 17). Dos 98 pacientes que iniciaram o estudo, 71 (72%) foram removidos do estudo por progressão de doença, 6 pacientes (6%) recusaram-se a continuar o tratamento, 5 pacientes (5%) pelo investigador local, 6 pacientes (6%) por toxicidade, 6 pacientes (6%) faleceram durante o estudo, 3 pacientes (3%) devido doenças concomitantes, e 1 paciente (1%) para tentar-se ressecção potencialmente curativa da metástase hepática.

Todos os pacientes experimentaram pelo menos um evento adverso durante o tratamento. Os eventos mais comuns foram astenia em 75%, diarreia em 66%, e náusea em 57% dos pacientes. Quarenta e três pacientes (43,8%) tiveram pelo menos um evento adverso severo, de grau 3 ou maior de acordo com a tabela CTC-NCI (<http://ctep.cancer.gov/reporting/ctc.html>), durante o tratamento. Os eventos adversos severos relacionados ao tratamento mais comuns foram diarreia em 30%, astenia em 12%, desidratação em 9%, náusea em 5%, e vômitos em 4% dos pacientes. Quatro pacientes (4%) tiveram anemia grau 3, e sete (7%) tiveram hiperbilirrubinemia graus 3-4 (seis com grau 3 e um com grau 4). Sete pacientes (7%) foram removidos do estudo devido a eventos adversos severos (dois com diarreia, dois com desidratação, um com fadiga e dor abdominal, um com hiperbilirrubinemia, e um com náusea e vômitos). Um total de 13 pacientes morreram durante o estudo, ou até 30 dias após terem recebido a medicação do estudo. Duas mortes foram consideradas associadas à terapia administrada no estudo. A primeira envolveu paciente com 79 anos, com diarreia grave complicada por insuficiência renal, e a segunda envolveu paciente com 82 anos, com diarreia severa complicada por septicemia. As causas presumidas de todas as 13 mortes estão listadas na Tabela 5.

Tabela 5 - Causa atribuída às mortes ocorridas durante, ou até 30 dias após a última dose de UFT e leucovorin no estudo

Causa da morte	Número de pacientes
Progressão da doença	7
Diarréia *	2
Doença pulmonar obstrutiva crônica	1
Infarto do miocárdio	1
Pneumonia (paciente não neutropênico)	1
Acidente vascular-cerebral	1

* Um caso levando à insuficiência renal e 1 levando à septicemia. Essas duas mortes foram consideradas como tendo sido causadas pelo tratamento.

As respostas observadas em todos os pacientes incluídos no estudo estão resumidas na Tabela 6. Dois pacientes (2%) tiveram resposta completa, e nove pacientes (9%) tiveram resposta parcial (95% CI, 4,7-16,8). A taxa de resposta observada, usando-se critério de “intenção de tratamento”, incluindo-se todos os pacientes foi de 11% (95% CI, 6,1-19,2).

Trinta e nove pacientes (40%) tiveram doença estável como melhor resposta (95% CI, 30,3-50,1) e 31 pacientes (32%) tiveram progressão da doença na primeira reavaliação (95% CI, 22,9-41,7). Não foi possível determinar o tipo de resposta em 17 pacientes (17%) porque eles nem receberam 2 ciclos de tratamento, nem tiveram evidência clara de progressão de doença. No entanto, todos esses pacientes foram incluídos no denominador para cálculo de taxas de resposta.

O tempo de progressão foi calculado em dias a partir da primeira administração da medicação experimental, até a determinação de progressão. Os dados dos pacientes sem progressão documentada foram censurados na data da última avaliação médica. O tempo mediano de progressão foi de 3,8 meses (95% CI, 3,11-4,65), e a percentagem de pacientes livres de progressão em 6 meses foi de

33%, baseada numa distribuição exponencial. A metodologia de Kaplan-Meier foi utilizada para demonstrar a distribuição empírica do tempo de progressão para os 97 pacientes elegíveis, mas essa análise foi considerada secundária. O tempo mediano de progressão foi de 137 dias (aproximadamente 4,5 meses), e a proporção de pacientes livres de progressão em seis meses foi de 29%. O modelo de Cox (*Cox proportional hazards regression model*) foi usado para avaliar a interação do tempo de progressão com a idade, performance, local do tumor primário, uso anterior de terapia adjuvante, e tempo entre a terapia adjuvante e o diagnóstico de doença metastática. Nenhuma dessas variáveis foi um fator preditivo significativo para o tempo de progressão durante o tratamento.

A sobrevida global para todos os 98 pacientes incluídos no estudo foi calculada a partir da data da primeira administração do medicamento experimental, até a data do falecimento. No momento em que os dados do estudo foram fechados, 15 pacientes ainda estavam vivos. Para esses pacientes, a sobrevida global foi calculada a partir da data da primeira administração do medicamento experimental até a última data em que se sabia estarem vivos. A sobrevida global baseada na análise de Kaplan-Meier foi de 12,8 meses (95% CI, 9,6-15,8).

Tabela 6 - Melhor resposta obtida durante o período de tratamento

Resposta	Pacientes (%)
Resposta objetiva	11 (11)
Resposta completa	2 (2)
Resposta parcial	9 (9)
Doença estável	39 (40)
Doença progressiva	31 (32)
Não avaliável	17 (17)

6 DISCUSSÃO

Embora tenhamos testemunhado avanços importantes no tratamento do câncer de cólon e reto, a espinha dorsal dos regimes de quimioterapia utilizados tanto na adjuvância como no tratamento de pacientes com doença avançada continua sendo o 5-fluorouracil ou um de seus derivados orais, incluindo o UFT.

O uso do UFT, embora muito popular no Japão, tem sido restrito no mundo ocidental. As causas são múltiplas, mas a mais importante parece ser a disponibilidade de outras medicações similares, como a capecitabina, que pode ser administrada em um regime mais conveniente, duas vezes ao dia. Entretanto, apesar de ter uma atividade similar à da capecitabina, o UFT apresenta algumas vantagens comparativas, particularmente em relação à síndrome de mão e pé, que é bastante comum com a capecitabina e é virtualmente ausente nos pacientes que recebem o UFT. Por essa razão, alguns pacientes não toleram a capecitabina e se beneficiariam do uso do UFT. Portanto, há espaço para mais de uma fluoropirimidina oral no tratamento do câncer de cólon e reto, e a disponibilidade do UFT adiciona uma opção ao tratamento utilizado no dia-a-dia desses pacientes.

Naturalmente, um regime que deve ser administrado três vezes ao dia, por longos períodos, representa problema quanto à conveniência e à aderência ao tratamento. O desenvolvimento de regime em que a droga possa ser administrada de forma menos freqüente representaria avanço importante, e nossos resultados indicam que isso é possível.

O racional para o estudo clínico aqui descrito foi a necessidade de avaliação de regime de UFT e leucovorin administrados duas vezes ao dia, avaliando se sua eficácia e toxicidade são comparáveis àquelas observadas em estudos anteriores, utilizando regime de administração três vezes ao dia. A hipótese nula era de que a

proporção de pacientes livres de progressão em 6 meses seria de 30%, o que equivaleria a uma mediana de 3,45 meses no tempo de progressão.

Dos 97 pacientes elegíveis, 33,4% estavam livres de progressão após 6 meses, e o tempo de progressão mediano foi de 3,8 meses. A metodologia de Kaplan-Meier também foi utilizada para demonstrar a distribuição empírica do tempo de progressão como uma análise secundária, demonstrando que 29% dos pacientes estavam livres de progressão aos 6 meses e que o tempo de progressão mediano era de aproximadamente 4,5 meses.

Enquanto o maior estudo de fase III, com 816 pacientes, demonstrou que o UFT e leucovorin administrados três vezes ao dia atingiam uma taxa de resposta de 12% e uma sobrevida mediana de 12,4 meses, o regime de administração duas vezes ao dia apresentou resultados comparáveis, com uma taxa de resposta de 11% e uma sobrevida mediana de 12,8 meses. Como esperado, toxicidades hematológicas severas foram eventos incomuns neste estudo, e limitaram-se a quatro pacientes (4%) com grau 3 de anemia. As toxicidades severas mais comuns no estudo foram diarreia (30%) e astenia (12%), mais uma vez refletindo os números observados no estudo de fase III anterior.

A maior toxicidade encontrada em ambos os regimes de administração é gastrointestinal. A incidência de diarreia e náusea e vômitos graus 3-4 no estudo de fase III com o regime administrado três vezes ao dia foi, respectivamente, de 21% e 13%. A incidência dessas toxicidades com o regime administrado duas vezes ao dia foi de 30% e 9%, respectivamente. Dois pacientes (2%) faleceram devido a complicações relacionadas à diarreia, mas a mortalidade relacionada ao tratamento

foi consistente com outros regimes comumente utilizados no tratamento do câncer colorretal metastático.

Nossa conclusão foi de que o regime de UFT e leucovorin administrados duas vezes ao dia para tratamento de pacientes com câncer colorretal metastático resulta em benefícios e toxicidade muito similares àqueles obtidos com a administração das mesmas medicações três vezes ao dia. Isso foi confirmado na análise da mediana de tempo de progressão e na porcentagem de pacientes livres de progressão em 6 meses. A taxa de resposta e a sobrevida global foram também muito parecidas, justificando o uso desse regime como uma alternativa ao regime convencional.

Abre-se, assim, nova opção bastante razoável para a maior parte dos pacientes candidatos a tratamento com UFT e leucovorin. Como o UFT representa maneira mais conveniente de administração da fluoropirimidina, nada mais natural de que se explore o uso de combinações de novas drogas com UFT, usando o esquema de administração da medicação duas vezes ao dia, que se revelou comparável ao regime convencional, administrado três vezes ao dia. Esses resultados também se comparam favoravelmente aos resultados históricos obtidos com o 5-fluorouracil e com a capecitabina.

7 CONCLUSÕES

- A administração de UFT e leucovorin duas vezes ao dia resulta em eficácia e toxicidade comparáveis àquelas obtidas com o uso da mesma combinação administrada três vezes ao dia como tratamento para pacientes com câncer de cólon e reto metastático.

- A disponibilidade de UFT e leucovorin representam adição importante ao armamentário disponível para o tratamento de pacientes com adenocarcinoma metastático de cólon e reto

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9 ANEXOS

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

MEMORANDUM

DATE: July 21, 1999

TO: Gail Bland/Paolo Hoff, M.D.
Box 78

FROM: Cathy Scherer, IRB Coordinator
Office of Protocol Research (Box 38)

SUBJECT: Approval of Protocol DM99-179 Entitled, "A Phase II Study of Orzel (UFT + Leucovorin) Given as a Twice-Daily Regimen in the Treatment of Patients With Metastatic Colorectal Cancer (UFT/Men.04 Theradex # B99-1320)"

Official Approval Date: July 21, 1999

On July 21, 1999, the Surveillance Committee reviewed and approved the above named and numbered protocol.

The committee noted that the protocol and informed consent document are satisfactory and in compliance with federal and institutional guidelines. No patients may be entered on this protocol until it has been officially activated by the Office of Protocol Research.

In keeping with the requirements of the Department of Health and Human Services and the Food and Drug Administration, this clinical study must be reviewed twelve months from the date of approval. If the study is terminated or completed during the next twelve months, the Surveillance Committee should be so advised. You are responsible for promptly reporting to the Surveillance Committee:

- a) any severe adverse effects;
- b) any death while patient is on study;
- c) any anticipated problems involving risks to subjects or others;
- d) any proposed changes in the research activity (changes may not be initiated without Surveillance Committee review and approval, except where necessary to eliminate apparent immediate hazards to the subjects).

c: Leonard A. Zwelling, M.D., M.B.A.

PLEASE RETURN THE ATTACHED SHEET TO OPR AT BOX 38 FOR ACTIVATION OF THIS STUDY.

A PAGINATED COPY OF THE PROTOCOL IS REQUIRED FOR ACTIVATION.

TEXAS MEDICAL CENTER
1515 HOLCOMBE BOULEVARD • HOUSTON, TEXAS 77030 • (713) 792-2121
A Comprehensive Cancer Center Designated by the National Cancer Institute

THE UNIVERSITY OF TEXAS
M. D. ANDERSON CANCER CENTER

A Phase II Study of ORZEL™ (UFT® + Leucovorin) Given as a Twice-Daily Regimen in the Treatment of Patients with Metastatic Colorectal Cancer (UFT/MEN.04 Theradex #B99-1320)

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Study Chairman:
James L. Abbruzzese, M.D.

The Division of Cancer Medicine, Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 426, Houston, Texas 77030. Telephone (713)792-2828, FAX (713)745-1163.

Protocol Abstract Page

Study Chairman: James L. Abbruzzese, M.D.
Department: Gastrointestinal Medical Oncology
Phone: (713)792-2828
Box: Box 426

Study Co-Chair: None

Full Title: A Phase II Study of ORZEL™ (UFT® + Leucovorin) Given as a Twice-Daily Regimen in the Treatment of Patients with Metastatic Colorectal Cancer (UFT/MEN.04 Theradex # B99-1320)

Objectives:

- To determine the time to disease progression for patients receiving a twice-daily treatment regimen of ORZEL™ (UFT® + leucovorin).
- To evaluate the tumor response rate, toxicity profile, and overall survival of this patient population.
- To explore through pharmacogenetic analyses the relationship between genetic variants and clinical outcomes.

Rationale: The most commonly prescribed systemic treatment for advanced colorectal cancer is 5-fluorouracil (5-FU). UFT, a combination of uracil and tegafur in a 4:1 molar ratio, was developed to combine the cytotoxic effects of 5-FU with the convenience of oral dosing. Tegafur is hydroxylated and converted to 5-FU by hepatic microsomal enzymes which may lead to a slow but sustained level of 5-FU in tumors. Uracil is a modulator of 5-FU which inhibits dihydropyrimidine dehydrogenase (DPD) leading to increased and sustained levels of 5-FU. The extensive use of leucovorin (LV) to modulate 5-FU led to studies combining UFT with oral LV (ORZEL™). Response rates ranging from 25-42% were reported in phase II studies of UFT and LV in patients with advanced colorectal cancer. The regimen is well tolerated with the most common side effects including diarrhea, nausea, vomiting, abdominal cramping, anorexia, fatigue, and rash. **Addendum 11/11/99:** Based on a recent report that suggests ORZEL (UFT + LV) may potentiate warfarin activity, patients on anticoagulant therapy will have frequent PT assays performed.

There is a marked reduction of grade III or IV neutropenia, oral mucositis, and hand-foot syndrome compared to intravenous 5-FU. A randomized phase III trial of UFT plus LV versus 5-FU plus LV reported at ASCO in May 1999 demonstrated that there was no significant difference in survival or response rate between the two arms. However, UFT plus LV demonstrated an improved safety profile compared to 5-FU plus LV.

Most trials with UFT plus LV have used a three times a day (every 8 hours) dosing schedule. A BID schedule would be more convenient for patients and preferable if efficacy and toxicity are equal to those observed with a TID schedule.

In addition to the traditional efficacy and safety parameters, pharmacogenetic assessments will be

included in this trial. Participation in the pharmacogenetic studies is optional. The relationship between genetic variants and the clinical outcomes will be explored. Genetic variants will be determined by analyzing DNA and RNA extracted from lymphocytes contained in a sample of the patient's peripheral blood.

Eligibility Criteria

Inclusion (major):

- Patients with histologically-confirmed colorectal cancer that is metastatic.
- Disease must be bidimensionally measurable located outside of previously radiated fields.
- Patients must be ≥ 18 years of age, with ECOG PS of ≤ 2 .
- Patients who have received prior adjuvant treatment must have completed adjuvant treatment at least 6 months prior to study enrollment.
- Patients must have a pretreatment AGC of $\geq 1,500/\text{mm}^3$, platelet count of $\geq 100,000/\text{mm}^3$, creatinine $\leq 1.5 \times \text{ULN}$, total bilirubin $\leq 1.5 \text{ mg/dL}$, and AST or ALT $\leq 4 \times \text{ULN}$.
- Life expectancy ≥ 3 months.
- Patients must sign an informed consent form.
- Patients must be nonpregnant and nonlactating. Patients of childbearing potential must implement an effective method of contraception during the study.

Exclusion (major)

- Patients who progress while receiving or within 6 months of receiving an adjuvant regimen are not eligible.
- Patients who have received prior therapy with UFT +/- leucovorin, capecitabine, S-1, or ethynyl uracil.
- Patients with an active serious infection.
- Patients with a history of brain metastases or carcinomatous meningitis.
- Pregnant or breast-feeding females or patients not using adequate methods of birth control.

Please refer to section 5.0 of the protocol for complete list of inclusion and exclusion criteria.

Treatment Plan: Patients will receive UFT $300 \text{ mg/m}^2/\text{d}$ divided into two doses administered orally every 12 hours. A 30-mg dose of leucovorin will be given with each dose of UFT. Treatment will be given for 28 days followed by one-week of rest. Courses will be repeated every 35 days. Patients will be assessed for response after every 2 courses. Treatment will continue until occurrence of documented disease progression or unacceptable toxicity, not ameliorated by a dose reduction. Please refer to section 7 of the protocol for dose modification guidelines.

In patients who agree to participate in the optional pharmacogenetic assessment, one pretreatment blood sample collection will be performed. Samples will be shipped to Bristol-Myers Squibb for analysis.

Does your research involve the use of Recombinant DNA technology? No
If yes, appropriate forms are obtainable through the Office of Research.

Statistical Considerations: The primary endpoint is time to disease progression (TTP). Of particular interest are the median TTP and the proportion of patients progression-free 6 months after receiving initial protocol therapy.

The null hypothesis is that the proportion of patients who are progression-free at 6months is 30%. Assuming an exponential distribution of TTP, this equates to a median TTP of 3.45 months and a per month hazard rate of 0.201. The total sample size will be 90 eligible patients. Assuming an exponential distribution of TTP, this allows for estimating the true hazard rate to within 0.082 in the sense that the 95% confidence interval is (0.162, 0.244) if the observed hazard rate is 0.201.

Please refer to section 11.0 of the protocol for complete description of statistical considerations

Patient Evaluation: (Pretreatment and Interim Testing)

Pretreatment: Imaging scans necessary to assess tumor, medical history and physical exam, hematology, (CBC with differential and platelet count), serum chemistries (creatinine, total bilirubin, AST and/or ALT), and serum pregnancy test (if applicable). PTs for patients on anticoagulant therapy. One blood draw for genomic studies (optional).

Evaluation During Treatment: Weekly: Toxicity assessment. Patients on anticoagulant therapy will have weekly PTs performed (or more frequently if clinically indicated). **Before each course:** physical exam, hematology and serum chemistries. **Every 2 courses:** Imaging studies necessary to assess response.

Estimated Accrual:

It is estimated that accrual will be 4 participants per month.

Site of Study:

This protocol is performed on an **outpatient** basis.

Length of Stay: What is the length and frequency of hospitalization?

Patients will not be hospitalized for this treatment.

Return Visits: How often must participants come to MDACC?

Every 5 weeks for testing, evaluation, and treatment.

Home Care: (Specify what [if any] treatment may be given at home)

Patients may take UFT plus LV at home and have weekly laboratory work drawn in local community.

Where will Study be Conducted:

a) Multicenter

Competing Protocols: (List the Protocol Number[s])

None

Name of Research Nurse/Data Manager

Jennifer Adams, R.N.

If your protocol has a diagnostic step requiring informed consent and registration on the protocol (e.g., a blood test or biopsy) that will determine whether or not the patient will subsequently receive or not receive experimental therapy; please check the appropriate box(es) so that the appropriate registration process may be established.

Applicable?   N/A

Blood Test No   Biopsy No   Other No

Public Display of Protocol on the Office of Protocol Research Web Site:

The Office of Protocol Research maintains a website (www.clinicaltrials.org) listing protocols actively accruing patients. No information is given about drug dose or schedule. Would you like this protocol listed on this website?

No

If this protocol has a corporate sponsor, we also need to get the sponsor's written approval to post this trial on the website. Would you like OPR to send a letter requesting this permission to the sponsor?

No

Name of Sponsor Funding Source:

Sponsor:	Bristol-Myers Squibb Oncology
Sponsor Contact:	Judy Wagner
Company Address:	777 Scudders Mill Road
City:	Plainsboro
State:	New Jersey 08536
Country:	USA
Zip Code:	08536
Telephone:	(609)897-2032
Fax Number:	(609)897-6055

Bristol-Myers Squibb Oncology	
Clinical Trial Protocol	
Final version date: July 12, 1999A Amendment 1: December 13, 1999	Clinical phase: II
Trial number: UFT/MEN.04 (Theradex #B99-1320)	
Title: A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer	
Summary:	Patients with metastatic colorectal cancer will receive 300 mg/m²/day of UFT divided into two doses for 28 days followed by a 1-week break; this cycle will be repeated every 35 days. All patients will receive a 30-mg dose of leucovorin with each UFT dose. The primary objective of the trial is to determine the time to disease progression. Secondary objectives include the evaluation of the tumor response rate, toxicity profile, and overall survival.
Study chair:	Paulo Hoff, MD The University of Texas M.D. Anderson Cancer Center Division of Medicine 1515 Holcombe Boulevard Houston, TX 77030 Phone: (713)792-0601
Funder:	Bristol-Myers Squibb Oncology 777 Scudders Mill Road Plainsboro, New Jersey 08536
Clinical monitor:	Theradex® CN 5257 Princeton, NJ 08543 (609)799-7580
This protocol contains information that is confidential and proprietary to Bristol-Myers Squibb Company (BMS) and Theradex. This information is being provided to you for the purpose of conducting a clinical trial for BMS and Theradex. You may disclose the contents of this protocol to study personnel under your supervision who need to know the contents for this purpose, as well as to your IRB(s) or Ethics Committee(s). The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of BMS and Theradex. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, you will give prompt notice to BMS and Theradex of any such disclosure. Any supplemental information that may be added to this protocol is also confidential and proprietary to BMS and Theradex and must be kept in confidence in the same manner as the contents of this protocol.	

Final protocol: July 12, 1999A
Amendment 1: December 13, 1999

BMS protocol UFT/MEN.04
Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer

Protocol agreement

1. I have read the protocol "A study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of recurrent metastatic colorectal cancer" and I agree that it contains all the necessary information required to conduct the study. I agree to conduct the trial as outlined in this protocol.
2. I understand that this trial will not be initiated without approval of the appropriate Institutional Review Committee, and that all administrative requirements of the governing body of the institution will be complied with fully.
3. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration requirements as specified in Title 21, Code of Federal Regulations, Part 50.
4. I will provide copies of the protocol and access to all information furnished by BMS and Theradex to all study personnel under my supervision. I will discuss the material with them to ensure that they are fully informed about the trial medication and procedures.
5. I understand that the trial may be terminated or enrollment suspended at any time by BMS, with or without cause, or by myself if it becomes necessary to do so to protect the best interests of the patients in the trial.
6. The total study population will consist of an anticipated sample size of 90 patients and I will enroll only patients who meet the protocol criteria for entry.
7. I understand that my signature on each Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
8. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Funder unless this requirement is superceded by the Food and Drug Administration.

Investigator:

Name: _____

Signature: _____

Address: _____

Date: _____

Telephone: _____

( )

Theradex:

Signature: _____

Date: _____

BMS protocol UFT/MEN.04
Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily
regimen in the treatment of patients with metastatic colorectal cancer

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BMS protocol UFT/MEN.04
Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer

Abbreviations

ALT	alanine transaminase (SGPT)	FUTP	fluorouridine triphosphate
AGC	absolute granulocyte count	IRB	Institutional Review Board
AST	aspartate transaminase (SGOT)	LDH	lactic dehydrogenase
BMS	Bristol-Myers Squibb	Me-THP	5-10 methylene tetrahydrofolate
BSA	body surface area	ORZEL	UFT+leucovorin
CBC	complete blood count	PD	progressive disease
CR	complete response	PR	partial response
CRF	case report form	RNA	ribonucleic acid
CTC	Common Toxicity Criteria	SD	stable disease
DNA	deoxyribonucleic acid	SGOT	serum glutamic oxaloacetic transaminase (AST)
DPD	dihydropyrimidine dehydrogenase	SGPT	serum glutamic pyruvic transaminase (ALT)
ECOG	Eastern Cooperative Oncology Group	TS	thymidylate synthase
FdUMP	fluorodeoxyuridine monophosphate	TTP	time to disease progression
FT	ftorafur	UFT	uracil + ftorafur
FUMP	Fluorouridine monophosphate	5-FU	5-fluorouracil

BMS protocol UFT/MEN.04
 Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer

SYNOPSIS

Trial design/objectives: Multicenter, open label/The primary objective is to determine the time to disease progression for patients receiving a BID treatment regimen of ORZEL™ (UFT®+leucovorin) every 28 of 35 days. Secondary objectives include the evaluation of the tumor response rate, toxicity profile, and overall survival. For pharmacogenetic assessments, variations in the genes encoding proteins involved in the metabolism and efficacy of UFT and leucovorin will be correlated with toxicity, response rate, time to disease progression, overall survival, and age.

Number of patients: 90

Inclusion criteria:

Patients meeting all of the following criteria are eligible for the trial:

- Males and females 18 years of age or older.
- Patients with histologically-confirmed colorectal adenocarcinoma that is metastatic.
- Patients who have received prior colorectal adjuvant treatment must have completed their adjuvant treatment at least 6 months prior to study enrollment. This includes any modality, e.g., chemotherapy, radiation, immunotherapy, etc. Patients who progressed while receiving or within 6 months of receiving an adjuvant regimen are not eligible.
- Disease must be bidimensionally measurable (defined in Section 9) located outside of previously radiated fields.
- Performance status ≤ 2 by the ECOG scale (see Appendix 1 for scale).
- Laboratory values must be as follows:

Absolute granulocyte count:	$\geq 1,500/\text{mm}^3$
Platelets:	$\geq 100,000/\text{mm}^3$
Total bilirubin:	$\leq 1.5 \text{ mg/dL}$
Serum creatinine:	$\leq 1.5 \times$ institutional upper normal limit
AST or ALT:	$\leq 4 \times$ institutional upper normal limit
- Patients must have recovered from toxicities from previous therapy.
- Patients must be nonpregnant and nonlactating. Patients of childbearing potential (see Part II, Section 2 for definition) must implement an effective method of contraception during the study. All female patients must have a negative pre-study serum or urine pregnancy test except those who are postmenopausal or surgically sterilized.
- Life expectancy must be ≥ 3 months.
- Patients must be informed of the investigational nature of the study and sign an informed consent form.

Exclusion criteria:

Patients meeting any of the following criteria will not be eligible for the trial.

- Patients who have received any type of prior treatment for metastatic disease with the exception of radiotherapy to treat locally symptomatic disease.
- Patient with a history of brain metastases or carcinomatous meningitis, regardless of prior treatment, are excluded.
- Patients who have received prior therapy with UFT+/-leucovorin, capecitabine, S-1, or ethynyl uracil.
- Patients with a history of other cancers except basal cell skin cancers, carcinoma in situ of the cervix, or curatively-treated cancers with >5 years non-recurrence prior to entry into the trial.
- Patients with an active serious infection or other serious underlying medical condition that would otherwise impair their ability to receive protocol treatment.
- Dementia or significantly altered mental status that would prohibit the understanding and/or giving of informed consent.
- Pregnant or breast-feeding females or patients not using adequate methods of birth control.
- Patients receiving other investigational therapy.
- Patients with known hypersensitivity to UFT or leucovorin.

BMS protocol UFT/MEN.04
Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer

Synopsis, cont.

Medication:	UFT	Leucovorin
Dose:	300 mg/m ² /day divided into two doses	30 mg BID (30 mg given with each UFT dose)
Duration:	28 days (repeat every 35 days)	
Efficacy assessments: • Time to disease progression • Tumor response • Survival		
Safety assessments: • Toxicity • Laboratory tests		
Pharmacogenetic assessments: Pharmacogenetics can be defined as the study of how variation in genes predicts response to drug therapy. The responses affected by genetic variation include drug metabolism, efficacy, and toxicity. Several genes involved in the metabolism and mechanism of action of UFT and leucovorin have been cloned and genetic variants in these genes have been determined. Genetic variants in a patient will be determined by analyzing DNA and RNA extracted from lymphocytes contained in a sample of the patient's peripheral blood. Variations in genes, which encode enzymes such as thymidylate synthase and DPD, will be studied for association with toxicity, tumor response, time to disease progression, overall survival, and age. **Consenting to the pharmacogenetic assessments is not mandatory for the patient to participate in the clinical portion of the trial.		

PART I--CLINICAL TRIAL PROTOCOL

1. INTRODUCTION

1.A. Colorectal cancer

1.A.1. BACKGROUND INFORMATION

Colorectal cancer, which encompasses cancer of the colon or large bowel and the rectum, is second to lung cancer as a cause of death due to cancer in the United States.¹ Approximately 10% of all cancers in the U.S. involve either the colon or the rectum. The majority of colorectal cancers are adenocarcinomas that develop in the inner lining of the colon or rectum. Colorectal cancer is a disease that responds well to therapy and is often curable, but only when it is diagnosed at an early stage. The odds that a cure can be achieved are greatest when the cancer is localized. The chances decrease as invasion into the bowel wall occurs, followed by spread into nearby lymph nodes. The most common site of metastasis for colorectal cancer is the liver.

Environmental factors contributing to colorectal cancer include high fat diets and a sedentary lifestyle (lack of exercise). As one might expect, it is more common in industrialized areas. In fact, people from areas where colorectal cancer is less prevalent are at higher risk of developing the disease if they move to a more industrialized area and their lifestyle and diet change. In addition to environmental factors, several genetic factors have been identified that are linked to colorectal cancer. Some of the genes contributing to colorectal cancer include the ras oncogene and tumor suppressor genes p53 and DCC (Deleted in Colon Cancer). The various genetic defects (mutations, deletions, and inactivation) may be passed on in families and, when environmental effects trigger further genetic alterations, can lead to the development of cancer.

1.A.2. TREATMENT OF COLORECTAL CANCER

The primary method of treatment of colorectal cancer is surgery.¹ Surgery can result in a cure, but this is again related to the stage of the disease at the time of diagnosis. The goal of surgery is to remove the tumor along with the nearby lymph nodes. Often, because a portion of the colon that is disease free is also removed to allow for a safety margin, one-third to one-half of the colon is removed during surgery.

In terms of chemotherapy, the standard has been 5-fluorouracil (5-FU) in various regimens, including in combination with leucovorin or levamisole. The side effects of 5-FU (including neutropenia, diarrhea, and hand/foot syndrome) have led investigators to search for alternatives. Among the candidates are the 5-FU prodrugs UFT and capecitabine, the topoisomerase

inhibitor irinotecan, the dihydropyrimidine dehydrogenase inactivator eniluracil, and oxaliplatin, a platinum compound.

In the present trial, ORZEL™ (UFT®+leucovorin) will be administered to patients with metastatic colorectal cancer.

1.B. UFT and ORZEL™ (UFT®+leucovorin) therapy

1.B.1. BACKGROUND INFORMATION

To fully understand the rationale for the development of UFT, a brief review of another therapeutic agent, 5-fluorouracil (5-FU) is necessary. Since 5-FU was first developed in 1957, it has been used primarily in patients with colorectal, breast, and gastric and pancreatic cancers.² In vivo, the majority of the drug is converted to inactive metabolites by dihydropyrimidine dehydrogenase (DPD). The remainder is converted to fluorouridine monophosphate (FUMP) through one of two pathways: (1) the direct transfer of a ribose phosphate (from phosphoribosylpyrophosphate) to 5-FU catalyzed by orotic acid phosphoribosyltransferase or (2) a sequence involving the addition of a ribose by uridine phosphorylase followed by phosphorylation by uridine kinase. The FUMP is subsequently converted to fluorouridine diphosphate (FUDP) and then to either fluorouridine triphosphate (FUTP) or fluorodeoxyuridine monophosphate (FdUMP). The mechanisms of 5-FU cytotoxicity include the inhibition of DNA synthesis via the inhibition of thymidylate synthase by FdUMP and the inhibition of RNA synthesis when FUTP is incorporated into RNA.²

The majority of an administered dose of 5-FU is rapidly metabolized by the liver.³ In fact, the mean plasma half-life of the drug when given as an intravenous bolus is only 16 minutes in humans. Data indicate that continuous infusion may be a more efficacious method of administration of 5-FU for patients with colorectal carcinoma.⁴ Results of a meta-analysis of randomized advanced colorectal cancer trials comparing 5-FU bolus to 5-FU continuous infusion showed that continuous infusion was superior to administration as a bolus in terms of tumor response (14% bolus vs. 22% continuous infusion) and median survival time (11.3 months bolus vs. 12.1 months continuous infusion).⁴

The primary toxicities observed with 5-FU therapy are either gastrointestinal in nature or myelotoxicity.² When 5-FU is administered intravenously, the most common adverse events are stomatitis and diarrhea. Attempts to maintain the anti-tumor effects of 5-FU while reducing the side effects lead to the development of fltorafur and, ultimately, to UFT.

1.B.2. DEVELOPMENT OF UFT

Fltorafur (FT), also known as tegafur, is a fluorinated pyrimidine first synthesized by Hiller et al.⁵ The chemical name of FT is 1-(2-tetrahydrofuryl)-5-fluorouracil. The development of an injectable formulation of FT in the United States was discontinued in the 1980's due to its neurotoxicity (when given at higher doses of 1-3 gm), although its

efficacy was found to be similar to that of 5-FU.⁶ It was subsequently developed in Japan as an oral formulation where it is used as adjuvant therapy for gastrointestinal, head and neck, breast, and lung cancers. In vivo, FT is metabolized to 5-FU via two pathways: (1) enzymatic cleavage at the N-1—C-2' bond to yield 5-FU and 4-hydroxybutanal^{7,8} which is further metabolized to γ -butyrolactone and (2) hepatic microsomal oxidation at the C5' position to yield 5-FU and succinaldehyde.⁹ The 5-FU released when FT is metabolized is itself metabolized by the same pathway as intravenous 5-FU and has the same cytotoxic mechanism.

UFT, a combination of uracil and FT in a 4:1 molar ratio, was developed in Japan to combine the cytotoxic effects of 5-FU with the convenience of oral dosing. Uracil is also metabolized by DPD and competes with 5-FU for the enzyme when the two are co-administered¹⁰, resulting in a significantly prolonged half-life for 5-FU. The pharmacokinetics of UFT have been extensively studied in comparison to those of 5-FU and FT alone.¹¹⁻¹⁴ Peak plasma concentrations of 5-FU were achieved within 30 to 120 minutes following administration of UFT. In comparison to equivalent doses of FT or intravenously-administered 5-FU, the administration of UFT resulted in higher peak plasma concentrations of 5-FU, which were still at therapeutic levels after 3 hours.

Further benefit to the combination of FT and uracil is evident from preclinical data which suggest that co-administration of the compounds enhances the uptake of 5-FU by tumor tissue.¹⁵ These data showed that the ratios of 5-FU concentration in tumor versus normal tissues were higher in animals that were treated with UFT than in those receiving FT alone. A clinical trial in 36 patients with a variety of solid tumors provided further evidence that 5-FU accumulates in higher concentrations in tumor tissue in patients treated with UFT.¹⁶ In that trial, the tumor:normal tissue 5-FU concentration ratio was 4.1:1 in patients receiving UFT compared to a 1.6:1 ratio in patients receiving FT alone. It is postulated that this differential concentration in tumor tissue may provide chemotherapeutic effect while minimizing the toxicity to normal tissue.

In summary, UFT provides higher peak plasma concentrations of 5-FU and prolonged therapeutic 5-FU concentrations compared to continuous infusion of 5-FU and may reduce the toxic effects on normal tissue seen with the administration of 5-FU or FT alone.

1.B.3. COMBINATION OF UFT AND LEUCOVORIN

Leucovorin, also known as folinic acid or Citrovorum factor, is a tetrahydrofolic acid derivative that can enhance the therapeutic and toxic effects of fluoropyrimidines such as 5-FU.³ It is combined with UFT to further potentiate the effect of 5-FU on tumor cells. The reduction in DNA synthesis by 5-FU involves the formation of a complex of FdUMP, thymidylate synthase (TS), and a cofactor designated 5-10 methylene tetrahydrofolate (Me-THP). The enzyme thymidylate synthase is integral to DNA synthesis because it is the only source of thymidylate in the cell,

converting dUMP to dTMP.² If the enzyme becomes trapped in a complex with FdUMP and Me-THP, it is no longer available to convert dUMP to dTMP and DNA synthesis is reduced. DNA synthesis is not completely inhibited because there is turnover of the FdUMP/TS/Me-THP complex, freeing up the TS to convert dUMP to dTMP, although in reduced quantities. Leucovorin enhances the inhibition of DNA synthesis by stabilizing the FdUMP/TS/Me-THP complex, preventing the conversion of dUMP to dTMP by TS.

1.B.4. UFT IN CLINICAL TRIALS

1.B.4.a. Phase I trials

Phase I trials of UFT, both alone and in combination with leucovorin, set the stage for the further development of UFT in the United States. As the phase I trials proceeded, UFT alone was studied as both a 5-day regimen and a 28-day regimen. With the addition of leucovorin, the 28-day regimen was used and repeated every 35 days.¹⁷ Diarrhea was the dose-limiting toxicity observed using the 28-day regimen. Pharmacokinetic analyses from the phase I trials showed that while 5-FU levels were detectable during the 28-day treatment period, there was no evidence of significant accumulation of uracil, FT, or 5-FU.¹⁷ A 14-day regimen has been explored in another phase I trial.¹⁸ In that trial, 7 patients received a 350 mg/m²/day dose of UFT with 150 mg/day of leucovorin for 14 days. Grade 3 diarrhea was experienced at that dose level by 2 of the 7 patients.

1.B.4.b. Colorectal and gastric cancer

Because the treatment of metastatic colorectal cancer remains generally palliative, the therapy chosen for a patient should take into consideration the quality of life. The ideal therapeutic agent would be an easily administered active anti-tumor agent causing minimal toxicities. ORZEL has initially been developed in the United States for the treatment of metastatic colorectal cancer. The efficacy and safety profiles of ORZEL have been or will be examined in a variety of completed and planned phase II and III trials examining ORZEL alone or ORZEL versus 5-FU and leucovorin.¹⁹⁻²⁸

Response rates and evaluations of toxicities were the primary focus of the phase II trials of ORZEL in patients with metastatic colorectal cancer.¹⁹⁻²³ Overall response rates in these trials ranged from 16.9% to 42%. Details of three of the phase II trials in colorectal cancer are presented in the following table.

BMS protocol UFT/MEN.04
Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer

	Pazdur et al ¹⁹	Saltz et al ²⁰	Gonzalez-Baron et al ²¹
# of patients treated	45	21	75
Regimen	UFT 300-350 mg/m ² /day; leucovorin 150 mg/day; x 28 days	UFT 350 mg/m ² /day; leucovorin 15 mg/day; x 28 days	UFT 390 mg/m ² /day x 14 days; leucovorin 500 mg/m ² IV x 1, then 30 mg/day Days 2-14
Median age (range)	45 (21-77)	69 (47-84)	57.5 (32-75)
Gender (n)			
female	21	9	34
male	24	12	41
ECOG performance status (n)			
0	21	not reported	10
1	24		36
2	0		29
Prior therapy (n)			
adjuvant chemo	3	3	not reported
prior radiation	4	2	
chemoradiation	0	2	
Site of metastatic disease (n)			
liver	42	15	51
lung	13	3	14
bone	1	not reported	12
other	0	3	3
Overall response	42%	25%	39%
Complete response	1 (2%)	1 (5%)	7 (9%)
Partial response	18 (40%)	4 (20%)	22 (30%)
Minor response/ stable disease	7 (16%)	7 (35%)	20 (27%)
Median overall survival	15.9 months	12+ months	13.5 months

The toxicity profiles observed in the phase II trials were generally considered to be less severe than those seen when 5-FU was used alone or in combination with leucovorin; most notable was the absence of the "hand-foot" syndrome associated with 5-FU. The most frequent toxicities were gastrointestinal in nature.

Phase III trials have been completed which compare ORZEL to 5-FU+leucovorin in the treatment of metastatic colorectal cancer.^{25,26} A dose of 300 mg/m²/day of UFT with 25-30 mg TID of leucovorin for 28 days and repeated every 35 days is the most common regimen for these trials. Preliminary results from one of the trials indicate that the patients receiving ORZEL experienced less diarrhea and mucositis than those on 5-FU+leucovorin and were able to be treated on schedule with minimal need for dose interruption or reduction.²⁵ Two additional phase III trials in metastatic colorectal cancer have been completed testing the regimen of 300 mg/m²/day UFT plus 25-30 mg leucovorin TID for 28 days and repeated every 35 days. The results of these trials have been submitted to the FDA as part of the registrational package for ORZEL. In another phase III trial²⁷, which has a planned enrollment of 1452 patients and is being conducted by the National Surgical Adjuvant Breast and Bowel Project, the population

consists of post-surgical patients with colon carcinoma treated by potentially curative resection.²⁷

An ongoing phase I trial is designed to determine the maximum tolerated dose of ORZEL when given with radiation to patients with resectable rectal cancer.²⁹ UFT is administered (with 30-mg leucovorin at each UFT dose) in three divided doses for 5 days followed by a 2-day rest period (same as radiation) for 5 consecutive weeks. Patients have been entered at UFT dose levels ranging from 250 to 400 mg/m²/day. Dose-limiting toxicity of grade 3 diarrhea has been observed in one patient. The 2-day rest periods are thought to minimize gastrointestinal toxicity.

ORZEL, in combination with the topoisomerase inhibitor irinotecan, will be examined in a planned phase I trial of patients with colorectal cancer.³⁰ Irinotecan will be administered as an IV infusion on Day 1 and ORZEL will be given on Days 1-14; cycles will be repeated every 3 weeks. Goals of this trial include the determination of the maximum tolerated doses of each drug, the toxicity profile of the two drugs in combination, and the response rate.

In addition to the above trials in colorectal cancer, ORZEL has been used as therapy for gastric cancer. In a phase II trial of patients with metastatic gastric cancer³¹, 300 mg/m²/day of UFT was administered with 30 mg of leucovorin at each UFT dose. Treatment was for 28 days followed by a one-week rest period. Preliminary results indicate an approximately 17% response rate and a favorable toxicity profile (main grade 3/4 toxicities were diarrhea, nausea, and vomiting, as expected with ORZEL therapy).

1.B.4.c. BID dosing

Although the daily dose of UFT+leucovorin has been divided into three doses per day for more frequent augmentation of blood levels of drug throughout a 24-hour period, BID dosing has also been studied. The Spanish Oncology Cooperative group, Oncopaz, conducted a phase II trial of UFT 195 mg/m² every 12 hours with leucovorin 15 mg every 12 hours on Days 2-14 every 28 days.³² The therapy was preceded by a dose of 500 mg/m² of leucovorin IV on Day 1. In a group of 75 patients with advanced colorectal cancer (69% with liver metastases), the overall response rate was 39% (51% for PS 0-1 and 22% for PS 2). Median survival was 13.5 months overall. The most common toxicities were diarrhea (grade 1-2 in 8.5% of courses and grade 3-4 in 3.5% of courses) and nausea/vomiting (grade 1-2 in 7% of courses and grade 3-4 in 1% of courses).

1.C. Pharmacogenetic aspects of the trial

In addition to the traditional efficacy and safety parameters, pharmacogenetic assessments will be included on this trial. Pharmacogenetics can be defined as the study of how variation in genes predicts response to drug therapy. Genetic factors are considered to play an important role in the observed inter-individual differences in the metabolism, toxicity, and pharmacologic response of drugs.³³⁻³⁵ For example, 10% of the Caucasian population carry variants of the cytochrome P450 CYP2D6 gene which results in low

metabolism of a wide variety of drugs.³⁴ Also, very rare genetic variants of the DPD gene that codes for an enzyme involved in the metabolism of 5-FU have been identified.³⁶ Individuals that carry this genetic variant of the DPD gene have lower levels of the DPD enzyme, which can result in severe toxicity when these individuals undergo 5-FU therapy.³⁶ Many documented examples of genetic variants explain decreased efficacy or increased toxicity; however, it might also be expected that some genetic variants lead to more favorable therapeutic responses. Therefore being able to determine which genes and their variants are associated with toxicity and efficacy will improve drug therapy and subsequently be beneficial to patient therapy.

In this trial, the relationship between genetic variants and the clinical outcomes will be explored. In order to study the relationship between genetic variation and clinical outcome, the genetic variants existing in each patient who voluntarily enrolls in the pharmacogenetic aspect of this clinical trial will be determined. Genetic variants in a patient will be determined by analyzing DNA and RNA extracted from lymphocytes contained in a sample of their peripheral blood. Current genomic techniques allow for the analysis of many genes simultaneously. Therefore multiple candidate genes involved in the metabolism of UFT and leucovorin will be selected for study.

Statistical analyses will be performed to delineate if genetic variants are associated with clinical outcomes such as tumor response, toxicity, time to disease progression, and overall survival. An exploratory correlation of toxicity, pharmacogenetic profile, and age will also be considered. The information gained from the proposed pharmacogenetic analyses will:

1. facilitate the identification of molecular targets and genetic markers that can be used in developing better drug therapies,
2. help predict patient populations that are more or less likely to respond favorably to UFT therapy, and
3. help predict patient populations that may be at risk for treatment-related toxicity.

2. TRIAL OBJECTIVES

The primary objective is to determine the time to disease progression for patients receiving a twice-daily treatment regimen of ORZEL™ (UFT®+leucovorin).

Secondary objectives include the evaluation of the tumor response rate, toxicity profile, and overall survival.

In addition to the more traditional assessments, pharmacogenetic assessments will be performed. Pharmacogenetics can be defined as the study of how variation predicts response to drug therapy. The responses affected by genetic variation include drug metabolism, efficacy, and toxicity. Several genes involved in the metabolism and mechanism of action of UFT and leucovorin have been cloned and genetic variants in these genes have been determined. Genetic variants in a patient will be determined by analyzing DNA and RNA extracted from lymphocytes contained in a sample

of the patient's peripheral blood. Variants in genes, which encode enzymes such as thymidylate synthase and DPD, will be studied for association with toxicity, tumor response, time to disease progression, and overall survival. An exploratory correlation of toxicity, pharmacogenetic profile, and age will also be considered.

3. RATIONALE

ORZEL offers a type of prolonged exposure to 5-FU due to the double modulation by uracil and leucovorin. Previously, prolonged exposure to 5-FU was achieved by administering 5-FU by infusion pump, but this method required catheter insertion and the accompanying risks of leakage, clotting, and infection. ORZEL is administered orally, thereby eliminating these risks. ORZEL also offers a more acceptable toxicity profile than other 5-FU regimens, as demonstrated in clinical trials exploring a variety of ORZEL treatment schedules. There has been a consistent lack of hand/foot syndrome, as well as a lower incidence of serious adverse events such as stomatitis, mucositis, and neutropenia with ORZEL therapy.

ORZEL is convenient, both in terms of dosage form and frequency of administration. Patients are receptive to oral therapy that may decrease trips to the doctor's office for treatment. Clinical trials utilizing a schedule of ORZEL given TID for 28 days of treatment and repeated every 35 days have been submitted to the FDA for drug approval. A BID schedule may be more convenient for patients and preferable if efficacy and toxicity are equal to those observed with a TID schedule. There is also the potential of reduced costs for patient care based on a better toxicity profile and less office visits due to oral dosing.

Pharmacogenetic analyses will be included in this trial for those patients who consent to these assessments. This will involve the analysis of several cloned genes involved in the metabolism of UFT and leucovorin, or in the biological pathways upon which these drugs act. The purpose of these pharmacogenetic analyses is the identification of genetic variants in the genes that may serve as molecular targets and genetic markers. Variations in these genes may result in altered pharmacokinetic or pharmacodynamic responses to treatment with ORZEL. By correlating the variations observed in the target genes with tumor response, toxicity, time to disease progression, overall survival, and age, these analyses may prove critical in advancing scientific knowledge about how genetic variation alters toxicity and efficacy of ORZEL.

4. OVERVIEW OF TRIAL DESIGN

This is a phase II, open label trial of ORZEL (UFT+leucovorin) in patients with metastatic colorectal cancer. Patients will receive 300 mg/m²/day of UFT divided into two doses given for 28 days followed by a 1-week break; this cycle will be repeated every 35 days. A 30-mg dose of leucovorin is given with each UFT dose.

Patients will be assessed for the time to disease progression, tumor response, toxicity, and overall survival.

Pharmacogenetic assessments will be performed to analyze the genetic variation in genes involved in the metabolism and efficacy of UFT and leucovorin. The relationship of the genetic variants to clinical outcome will be evaluated. An exploratory correlation of toxicity, pharmacogenetic profile, and age will also be considered. The pharmacogenetic assessments included in the trial will require a blood sample to be drawn from consenting patients prior to therapy and sent to BMS.

5. SELECTION OF PATIENTS

Patients determined to be eligible for enrollment, and who have signed informed consent, will be registered by automated telephone service available on a 24-hours per day basis. Only authorized personnel from approved sites can register patients to the trial. Information on all eligibility and stratification questions must be known in order to register a patient.

Patients should begin treatment within 5 working days of registration.

5.A. Sample size

A total of 90 patients will be enrolled in this trial.

5.B. Inclusion/exclusion criteria

5.B.1. INCLUSION CRITERIA

Patients meeting all of the following criteria are eligible for the trial.

1. Males and females 18 years of age or older.
2. Patients with histologically-confirmed colorectal adenocarcinoma that is metastatic.
3. Patients who have received prior colorectal adjuvant treatment must have completed their adjuvant treatment at least 6 months prior to study enrollment. This includes any modality, e.g., chemotherapy, radiation, immunotherapy, etc. Patients who progressed while receiving or within 6 months of receiving an adjuvant regimen are not eligible.
4. Disease must be bidimensionally measurable (defined in Section 9) located outside of previously radiated fields.
5. Performance status ≤ 2 by the ECOG scale (see Appendix 1 for scale).

6. Laboratory values must be as follows:

Absolute granulocyte count:	$\geq 1,500/\text{mm}^3$
Platelets:	$\geq 100,000/\text{mm}^3$
Total bilirubin:	$\leq 1.5 \text{ mg/dL}$
Serum creatinine:	$\leq 1.5 \times$ institutional upper normal limit
AST or ALT:	$\leq 4 \times$ institutional upper normal limit

7. Patients must have recovered from toxicities from previous therapy.
8. Patients must be nonpregnant and nonlactating. Patients of childbearing potential (see Part II, Section 2 for definition) must implement an effective method of contraception during the study. All female patients must have a negative pre-study serum or urine pregnancy test except those who are postmenopausal or surgically sterilized.
9. Life expectancy must be ≥ 3 months.
10. Patients must be informed of the investigational nature of the study and sign an informed consent form.

5.B.2. EXCLUSION CRITERIA

Patients meeting any of the following criteria will not be eligible for the trial.

1. Patients who have received any type of prior treatment for metastatic disease with the exception of radiotherapy to treat locally symptomatic disease.
2. Patient with a history of brain metastases or carcinomatous meningitis, regardless of prior treatment, are excluded.
3. Patients who have received prior therapy with UFT+/-leucovorin, capecitabine, S-1, or ethynyl uracil.
4. Patients with a history of other cancers except basal cell skin cancers, carcinoma in situ of the cervix, or curatively-treated cancers with >5 years non-recurrence prior to entry into the trial.
5. Patients with an active serious infection or other serious underlying medical condition that would otherwise impair their ability to receive protocol treatment.
6. Dementia or significantly altered mental status that would prohibit the understanding and/or giving of informed consent.
7. Pregnant or breast-feeding females or patients not using adequate methods of birth control.
8. Patients receiving other investigational therapy.
9. Patients with known hypersensitivity to UFT or leucovorin.

5.C. Withdrawal criteria

A patient may be withdrawn from the trial if:

1. a toxicity develops which, in the opinion of the investigator, precludes further therapy
2. the investigator considers it, for safety reasons, to be in the best interest of the patient that they be withdrawn.

A patient must be withdrawn from the trial if:

1. disease progression occurs
2. they withdraw their consent
3. they become pregnant.

The date and reason for discontinuation must be noted on the Case Report Form (CRF). Every effort should be made to complete the appropriate assessments.

6. CONCOMITANT THERAPY

Palliative and supportive care for disease-related symptoms will be offered to all patients in this study. Patients who require radiotherapy on-study will be considered to have progression of disease and will be taken off-study.

Patients may not receive any other anticancer drugs while receiving trial medication, including hormonal agents and immunotherapy. Patients may not receive any other clinical investigational drugs.

In addition, colony-stimulating factors (G-CSF, GM-CSF, etc.) may be used therapeutically. ASCO guidelines for the use of colony-stimulating factors should be consulted. They should not be administered within 24 hours prior to or after a dose of UFT is administered.

It is very important that any use of colony-stimulating factors be documented in the case report form.

Under no circumstances should a halogenated anti-viral agent such as FDDA, FIAU, FMAU, FTC, or sorivudine be used in patients receiving 5-FU or UFT. Severe myelosuppression and CNS toxicity may result.

7. TRIAL MEDICATION

7.A. Identification of trial medication

7.A.1. UFT

UFT, a combination of uracil and fluorouracil (FU, also known as tegafur) in a molar ratio of 4:1, will be supplied as 100-mg capsules by Bristol-Myers Squibb (BMS). UFT contains not less than 95% of the labeled amounts of FU and uracil.

FU, or 1-(2-tetrahydrofuryl)-5-fluorouracil, is an odorless white crystalline powder with a bitter taste. It is soluble in acetone, chloroform, or methanol, sparingly soluble in ethanol or water, and slightly soluble in ether or benzene. It has a melting point of 165°C to 169°C.

BMS protocol UFT/MEN.04
Theradex protocol B99-1320

A phase II study of ORZEL™ (UFT®+leucovorin) given as a twice-daily regimen in the treatment of patients with metastatic colorectal cancer

Uracil, or 2,4(¹H, ³H)-pyrimidinedione, occurs as white crystals or crystalline powder and is odorless and tasteless. It is very soluble in methanol, ethanol, or acetone and slightly soluble in water, but nearly insoluble in chloroform, benzene, or ethyl acetate. The melting point of uracil is 335°C.

7.A.2. LEUCOVORIN

Leucovorin, also known as Citrovorum factor, is folinic acid. BMS will supply an oral dosage form available as 15-mg tablets.

7.A.3. STORAGE OF DRUG

Drug supplies should be stored in a secure area, at room temperature (preferably between 59-77°F or 15-25°C).

7.A.4. ADVERSE EVENTS ASSOCIATED WITH UFT AND LEUCOVORIN

The most frequent toxicities observed in clinical trials with UFT are gastrointestinal in nature (nausea, vomiting, stomatitis, mucositis, abdominal cramping, anorexia, and diarrhea). Other possible side effects could include: hair loss, fatigue, rash, dizziness, fever, paresthesia, elevated PT in patients taking Coumadin®, and elevated liver enzymes. Myelosuppression is uncommon at UFT doses used in this study. Gastrointestinal erosion, ulceration and perforation, sometimes associated with bleeding, may occur. Rare instances of neurological effects, including seizures and dyskinesia, have been reported. Myocardial ischemia, myocardial infarction, renal failure, and pulmonary edema have been reported.

Adverse events noted in the fluoropyrimidine class of drugs include watery eyes and photosensitivity.

Allergic sensitization, including anaphylactoid reactions, has been reported following the administration of leucovorin. No other adverse events have been associated with leucovorin.

7.B. Dose administration

The total daily UFT dose will be rounded up or down to the nearest 100 mg. If the total number of capsules a patient is to receive in one day cannot be divided equally, the highest dose will be given in the morning.

Leucovorin will be administered concurrently with each dose of UFT. It should be taken with 4-8 oz. of water.

The patients should not consume any food for 1 hour prior to and 1 hour following the ingestion of trial medication.

The patients should be instructed to return any unused medication at the Day 35 visits of each cycle.

7.B.1. DOSING INSTRUCTIONS

Patients should begin trial medication within 5 working days of registration.

30-mg dose of leucovorin will be given with each dose of UFT. Each cycle will be 35 days and patients will receive trial medication for the first 28 days of each cycle.

The following example shows the calculation of total daily dose based on 300 mg/m²/day and BID dosing for a patient whose BSA is 1.8m²:
 $1.8\text{m}^2 \times 300\text{ mg/m}^2/\text{day} = 540\text{ mg/day}$; rounded to the nearest 100 mg = 500 mg/day. UFT is then taken as 300 mg in the morning and 200 mg in the evening. If the dose for a patient were 550 mg/day, the dose would be rounded up to 600 mg/day.

The following table summarizes the dosing schedule for a total daily dose ranging from 200 mg to 800 mg.

Total daily dose —BID dosing*

UFT total Daily dose	UFT AM dose (+30 mg leucovorin)	UFT PM dose (+30 mg leucovorin)
200 mg	1	1
300 mg	2	1
400 mg	2	2
500 mg	3	2
600 mg	3	3
700 mg	4	3
800 mg	4	4

*Two tablets of leucovorin (for a total of 30 mg) will be taken with each UFT dose.

7.C. Dose modification

Dose reductions for UFT will be based on toxicity during both the current cycle and the previous cycle. Toxicities will be graded according to the Common Toxicity Criteria (CTC) version 2.0 (Appendix 2).

No changes will be made in the leucovorin dose. However, if UFT is held, leucovorin will also be held. If doses are held for toxicity, these days are still counted as part of the 28 days of a treatment cycle (e.g., the 28th day of treatment, if started on the first of the month, will still be the 28th of the month, even if drug was held for several days).

If UFT is held for toxicity during a treatment period and the toxicity resolves, as outlined below, the patient should resume treatment at the indicated dose level. Treatment should not be extended beyond the number of treatment days designated. Once decreased due to toxicity, the UFT dose level will not be increased.

The following table summarizes dose levels when modifications are required. Each decreasing level corresponds to a reduction of 50 mg/m²/day in the dose of UFT.

Dose level	UFT mg/m ² /day
0	300
-1	250
-2	200

If any patient requires dose reduction greater than the -2 level, that patient should be removed from the trial.

7.C.1.a. Dose modification during a treatment cycle

Administration of trial medication will be interrupted if the following toxicities occur:

- Hematologic toxicity

If the absolute granulocyte count (AGC) is ≥ 500 to $<1,000/\text{mm}^3$ or platelets are $\geq 10,000$ to $<50,000/\text{mm}^3$ (grade 3 hematologic toxicity), trial medication will be withheld until the AGC is $\geq 1,500/\text{mm}^3$ and platelets are $\geq 100,000/\text{mm}^3$. Following recovery, UFT therapy should be resumed at the same dose level.

Note that this is the only grade 3 toxicity that does not result in an automatic dose reduction.

If a hematologic toxicity of grade 4 develops (AGC $< 500/\text{mm}^3$ or platelets $< 10,000/\text{mm}^3$), the investigator should withhold UFT.

Following recovery, UFT therapy should be resumed at a dose reduced by 50 mg/m²/day (decrease one dose level).

- Gastrointestinal toxicity

Diarrhea—UFT therapy must be withheld for a $\geq$ grade 2 diarrhea (increase of 4-6 stools/day over patient's normal pattern, nocturnal stools, or moderate cramping) that develops even with reasonable support using common antidiarrheals. UFT may be resumed when associated symptoms, including diarrhea, weakness, and dehydration, have subsided to baseline or $\leq$ grade 1. Following the resolution of grade 2 diarrhea, UFT should be resumed at full dose. Following resolution of grade 3 or 4 diarrhea, UFT should be restarted at a dose reduced by 50 mg/m²/day (decrease one dose level).

Mucositis—UFT must be withheld for ulcerative mucositis (gingivitis and glossitis) or stomatitis $\geq$ grade 2 (painful erythema, edema, or ulcers; can eat or swallow). Following resolution of grade 2 toxicity, UFT should be resumed at full dose. Following resolution of grade 3 (painful erythema, edema, or ulcers; requires hydration) or 4 (severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation) mucositis, therapy should be restarted at a dose reduced by

50 mg/m²/day (decrease one dose level). Angular stomatitis (cheilitis) as an isolated event is not a reason for treatment modification.

- Other non-hematologic toxicities

Upon the development of any non-hematologic toxicity $\geq$ grade 2, UFT therapy must be withheld until the toxic event subsides to baseline or $\leq$ grade 1. Therapy should be restarted at the same dose level if the toxicity is grade 2 or at dose reduced by 50 mg/m²/day (decrease one dose level) if the toxicity is grade 3 or 4. Nausea controlled with antiemetic therapy and/or alopecia do not warrant dose reductions or interruptions.

Chronic fatigue—for patients in whom general decline is felt to be due entirely to therapy and not related to progressive disease, therapy may be withheld for a decrease in performance status by more than one level from pretreatment baseline.

Neurologic toxicity—UFT must be withheld for a neurologic toxicity $\geq$ grade 2 unless the condition(s) are related to the patient's disease or some other pre-existing condition, which, in the opinion of the investigator, was not brought on or exacerbated by treatment with UFT. Such conditions might include headache, anxiety, or tinnitus.

Cardiac toxicity—any symptoms suggestive of cardiac ischemia require cessation of UFT and patients must undergo a cardiac assessment prior to resuming UFT therapy.

Integument—UFT must be withheld for hand-foot syndrome severe enough to interfere with daily activities. Treatment is not modified for generalized pigmentation.

Ocular toxicity—epiphor (tearing due to overproduction or to lacrimal duct stenosis), conjunctivitis, or loss of eyelashes are not causes for treatment modification.

In those patients for whom the calculated dose reduction would result in the patient taking the same dose (due to rounding), the total daily UFT dose should be reduced by 100 mg/day.

The time during which trial medication is discontinued due to toxicity will be counted as days of treatment. Therefore, administration of trial medication should not extend longer than Day 28.

7.C.1.b. Dose modification for subsequent courses

Subsequent courses of treatment will be modified according to the following rules, regardless of relation of study medication to toxicity:

1. Patients may not be retreated unless the AGC is $\geq 1,500/\text{mm}^3$ and the platelet count is $\geq 100,000/\text{mm}^3$.
2. For a non-hematologic toxicity during the previous cycle, treatment may resume if the toxicity has subsided to baseline (except for alopecia) or $\leq$ grade 1, whichever is less restrictive. A cardiac or neurologic toxicity should be discussed with Theradex prior to resuming treatment.
3. Adjust the dose level based on the highest grade of toxicity observed during the previous cycle:

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Grade 0-2—same dose level (including grade 3 hematologic toxicity)

Grade 3-4—decrease dose by one dose level, i.e., decrease dose by 50 mg/m²/day (except grade 3 hematologic toxicity)

In those patients for whom the calculated dose reduction would result in the patient taking the same dose (due to rounding), the total daily UFT dose should be reduced by 100 mg/day.

Treatment may be delayed for up to 2 weeks beyond planned resumption of the next cycle. If a patient does not fulfill retreatment criteria by that time, they will be removed from the trial.

7.D. Treatment continuation

Treatment should be continued until disease progression occurs or intolerable toxicities develop. For patients who remain progression-free for one year, continuation of therapy beyond one year should be at the investigator's discretion.

8. TRIAL PROCEDURES

8.A. Schedule of assessments

The following table summarizes the schedule of assessments for the trial.

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Assessment	Screening	Day					Follow-up (q 3 mos.)
		7	14	21	28	35 ^a	
Inclusion/exclusion criteria	X						
Informed consent for clinical portion +/- informed consent for genomic testing ^b	X						
Medical history	X						
Physical examination and weight	X					X	
Performance status	X					X	
Tumor staging ^c	X						
Blood drawn for genomic testing ^d	X						
CBC with differential and platelet count ^e	X					X	
Serum creatinine, total bilirubin, SGOT(AST) and/or SGPT(ALT) ^f	X					X	
PT testing ^g	X	X	X	X	X	X	
Pregnancy test ^h (serum or urine)	X						
Distribute trial medication	X						
Toxicity		X	X	X	X	X ⁱ	
Tumor response						X ^j	
Diary and unused medication collection						X	
Survival							X ^k

^aWithin 3 days prior to beginning the next cycle.

^bPatients may participate in the clinical portion of the trial regardless of whether or not they consent to genomic testing.

^cRadiographic assessments (chest x-ray or CT scan, abdominal CT scan, bone x-rays) will be used to document tumor extent and size, where appropriate. These measurements are baseline measurements and must be within 6 weeks of registration.

^dOnly for those patients who consent to genomic testing.

^eLaboratory tests must be performed within 2 weeks prior to registration.

^fPregnancy test must be performed within 72 hours prior to registration in all women of childbearing potential.

^gToxicity will be assessed weekly via phone call for the first 10 weeks (two cycles), then at the end only (Day 35) of each subsequent cycle. Face-to-face contact with a patient (i.e., office visit) may substitute for a phone call.

^hEvaluations of tumor response will be performed every 10 weeks (every two cycles). All suspected CRs and PRs should be documented with a repeat measurement as close to 4 weeks as possible.

ⁱData concerning the administration of the first therapy off-study and response to the first therapy off-study will also be collected.

^jPT testing weekly, or more frequently if clinically indicated, for patients taking concurrent Coumadin®.

8.B. Trial plan

8.B.1. SCREENING VISIT

A total of 90 patients will be enrolled in the trial through Theradex.

At the screening visit, written informed consent (see Appendix 3 for sample consent forms) will be obtained and, if the patient passes all inclusion and exclusion criteria, they will be enrolled in the trial. A separate consent form will be available for patients who agree to the genomic assessments.

Registration will be completed via an automated phone system maintained by Theradex.

Registration phone number: 1-800-404-7580
If problems occur with automated line, call: (609)799-7580

Patients should begin treatment within 5 working days of registration.

The following assessments will be performed at the screening visit: medical history, physical examination, performance status, tumor staging, laboratory tests, and blood sampling. Blood samples drawn for purposes of genomic testing **must** be drawn pre-therapy from consenting patients.

8.B.1.a. Blood sampling for pharmacogenetic assessments

Prior to blood collection, the patient's identification number and the date the sample was drawn should be written on each Vacutainer® tube. Whole blood will be collected in two different tubes: a 6-7 mL lavender top tube containing EDTA and an 8 mL yellow top tube containing ACD A solution. After filling both tubes with blood, they should be inverted eight to ten times in order to mix the patient's blood with the anticoagulant. Following the collection of both aliquots of blood, the tubes will be placed in a styrofoam insert that contains an absorbent pad. The styrofoam insert, after being sealed, will then be placed in the plastic bag provided. The plastic specimen bag containing the styrofoam insert will be placed in a small cardboard box, also provided. The cardboard box will be inserted into a Fed-Ex Diagnostic Specimen Envelope for shipment.

The Vacutainer® tubes should immediately be shipped to Applied Genomics, Pennington, NJ. Genomics samples should not be shipped the day before a holiday, on a holiday, or Friday through Sunday.

Detailed instructions for shipment of genomics samples are provided in Appendix 4 and the Study Operations Manual.

8.B.2. PATIENT EVALUATION

The following assessments will be made each cycle until the patient withdraws or disease progression occurs.

Each investigator's office will call their patients weekly to elicit information concerning toxicities and compliance. Patients should be called every week

for 10 weeks (first two cycles). Subsequent toxicity assessments will be made in person at the Day 35 office visits. Questions to be asked of each patient during the weekly phone calls are provided in Appendix 5. Face-to-face contact (i.e., office visit) with a patient may substitute for a phone call.

In addition to the phone calls and assessments at office visits, patients will be instructed to complete patient diaries (Appendix 6). The patient diary consists of an instruction sheet for administration of medication (to be completed by the investigator or his/her designee), a chart to record the time each dose of medication is taken, and a chart to record all side effects. The patients should be instructed to complete their diaries daily and to bring them along to each office visit.

Following Day 28, the patients will be off trial medication for 1 week. They will return on Day 35 for a physical examination, laboratory tests, and toxicity assessment. Performance status should be noted on Day 35. If a patient's toxicity profile meets the requirements (see Section 7, Dose Modifications), they will begin the next 35-day cycle of therapy on the following day.

Evaluations of tumor response will be performed every 10 weeks (every two cycles) and will continue until disease progression.

8.B.3. FOLLOW-UP

Following therapy, patients will be followed for resolution of all drug-related toxicities. If possible, all patients will be assessed every 3 months until death for the following: date of disease progression, survival, administration of the first therapy off-study, and response to the first therapy administered. Every attempt should be made to obtain this information.

9. EFFICACY AND PHARMACOGENETIC ASSESSMENTS

9.A. Primary efficacy parameter

The primary efficacy parameter for this trial is the time to disease progression. Time to disease progression will be calculated for all patients from the day on study until the date progressive disease or death is first reported. Patients who did not progress will be censored at the last date they were known to be alive. Patients who die of disease and for whom a date of progression is not available will be considered to have progressed on the day of their death.

9.B. Secondary efficacy parameters

The secondary efficacy parameters include tumor response, survival, and toxicity.

9.B.1. TUMOR RESPONSE**9.B.1.a. Tumor measurement**

In terms of tumor measurement, disease is categorized as measurable, evaluable, or non-evaluable disease.

- **Measurable disease:** tumor is bidimensionally measurable (measurable in two dimensions) and is at least 1.5 cm x 1.5 cm. Lesions that can only be reported in one dimension will be considered evaluable and will not have recorded values for measurements.
- **Evaluable disease:** disease that is assessable, but not measurable. It can be documented on radiographs (e.g., unidimensional mediastinal masses, pleural-based masses, lytic bone metastasis) or photographs (e.g., soft tissue and skin metastases).
- **Non-evaluable disease:** third-space fluid accumulation proven by biopsy or confirmed clinically as evidence of malignant disease (pleural effusions, ascites), blastic osseous metastasis, and previously irradiated lesions.

New lesions occurring inside a previously irradiated field can be measurable or evaluable.

If there are numerous measurable lesions within a single organ, choose a maximum of three lesions at the beginning of the trial for measurement. The other lesions in that organ should be grouped together as an evaluable lesion.

All disease locations (measurable, evaluable, or non-evaluable) will be followed for tumor evaluation.

9.B.1.b. Tumor evaluation

The following should be considered in the evaluation of tumors:

1. Lesions followed by physical examination or chest x-ray must be discrete and measurable with calipers/rulers.
2. Tumor measurements will be obtained every other cycle.
3. Lesions that are only reported as one dimension should be reread and have two dimensional measurements provided. If a second dimension cannot be provided, this lesion will be considered evaluable. No measurement needs to be reported for evaluable lesions.
4. Lesions reported with three dimensions will have the two largest measurements reported and will be followed to determine response.

9.B.1.c. Response criteria

Patients are evaluable for response if they have received at least two cycles of therapy. Patients removed from the study prior to the first tumor response assessment will not be considered evaluable for response unless there is clear evidence of clinical progression.

All suspected responses should be documented with a repeat measurement as close to 4 weeks as feasible.

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Measurable disease response criteria

- Complete response (CR)—complete disappearance of all tumor lesions for at least 4 weeks from the date of documentation of complete response. Normalization of tumor markers, if previously abnormal.
- Partial response (PR)—decrease by >50% in the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by two consecutive observations at least 4 weeks apart. No lesions, measurable or not, should have progressed and no new lesions should appear.
- Stable disease (SD)—failure to observe remissions as defined above, in the absence of any progressive or new lesions, as determined by two consecutive observations at least 4 weeks apart.
- Progressive disease (PD)—≥25% increase in the size of any measurable or evaluable lesion and/or the appearance of any new lesions or the occurrence of malignant pleural effusion or ascites. Death secondary to malignant disease should be documented as progressive disease.

Evaluable disease response criteria

- Complete response (CR)—complete disappearance of all known disease for at least 4 weeks.
- Stable disease (SD)—no significant change in disease status for at least 4 weeks.
- Progressive disease (PD)—appearance of any new lesion not previously identified or estimated increase of ≥25% in existent lesions.

9.B.2. SURVIVAL

For all patients, survival will be calculated from the day of on-study to death. Patients who did not die will be censored at the date they were last known to be alive.

9.B.3. TOXICITY

Any patient who receives treatment on this protocol will be evaluable for toxicity.

Each patient will be assessed for the development of any toxicity as described earlier.

Dose modifications will be made based on toxicities described earlier (Section 7).

This study will utilize the Common Toxicity Criteria (CTC) scale version 2.0 for toxicity and adverse event reporting. A copy of the CTC version 2.0 is provided in Appendix 2 and can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

9.C. Pharmacogenetics

Results of pharmacogenetic testing for patients who consent to these assessments will be correlated to toxicity, response, time to disease progression, and overall survival. An exploratory correlation of toxicity, pharmacogenetic profile, and age will also be considered.

10. SAFETY ASSESSMENTS**10.A. Adverse events**

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to ORZEL will be followed until resolution, even if this occurs post-trial.

Additional adverse event reporting instructions are provided in Section 1 of Part II of this document.

10.A.1. DEFINITIONS OF ADVERSE EVENTS**10.A.1.a. Adverse event (AE)**

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

10.A.1.b. Serious adverse event (SAE)

An adverse event occurring

- while on study
- within 30 days of the last dose, or
- after 30 days after the last dose and considered related to study drug

that results in any of the following outcomes:

-death

-a life-threatening adverse drug experience (including grade 4 hematologic toxicity treated with colony-stimulating factors)

-inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis/paracentesis, or placement of an indwelling catheter, unless associated with other serious events.

-persistent or significant disability/incapacity,

or

-congenital anomaly/birth defect.

Death, regardless of cause, which occurs within 30 days of the last dose of study drug or after 30 days and is considered to be related to study drug, should be reported as a serious adverse event.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.A.1.c. Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

10.A.1.d. Life-threatening

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

10.B. Laboratory tests

The following laboratory tests will be performed within 2 weeks prior to registration, and prior to beginning each new cycle:

Hematology:	CBC, differential, platelet count
Biochemistry:	serum creatinine, total bilirubin, SGOT (AST), and/or SGPT (ALT)

If toxicity develops, laboratory tests may be performed more frequently to monitor the toxicity.

All women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to beginning treatment.

The investigator will review all laboratory test results and report any clinically significant abnormalities in the source documentation.

11. STATISTICAL CONSIDERATIONS

11.A. Endpoints and comparisons

The primary end point is time to disease progression (TTP). Of particular interest are the median TTP and the proportion of patients progression-free 6 months after receiving initial protocol therapy.

Secondary end points are overall tumor response rate (OR=CR+PR), overall survival (OS), toxicity, and the correlation of genomic variation with clinical endpoints and age.

11.B. Sample size

The null hypothesis is that the proportion of patients who are progression-free at 6 months is 30%. Assuming an exponential distribution of TTP, this equates to a median TTP of 3.45 months and a per-month hazard rate of 0.201. The total sample size will be 90 eligible patients. Assuming an exponential distribution of TTP, this allows for estimating the true hazard rate to within 0.082 in the sense that the 95% confidence interval is (0.162, 0.244) if the observed hazard rate is 0.201.

11.C. Statistical analysis

Patients eligible for this study are those who have not been previously treated for metastatic disease and are at least 6 months past the completion of any adjuvant therapy. In addition, they cannot have experienced disease progression while receiving adjuvant therapy or within 6 months after the completion of adjuvant therapy. These patients will be included in the analyses of time to disease progression.

For the primary analysis, TTP will be assumed to have an exponential distribution. Ninety-five percent confidence intervals will be calculated for the hazard rate, median TTP, and rate of 6-month progression-free survival. If the maximum likelihood estimate of median TTP assuming the exponential distribution is greater than 2.8 months, which corresponds to the upper confidence limit of 0.244 for the hazard rate, the protocol regimen will be considered to be effective based on a one-sided test for non-inferiority at the 5% level of significance.

The Kaplan-Meier estimator will be used to show the empirical distributions of TTP and OS. All eligible patients will be included in these analyses. However, the effect of the patient's disease status at study entry on TTP will be examined as well. Cox proportional hazards regression models will be used to relate TTP with patient age, performance score, colon versus rectal disease, +/- prior adjuvant therapy, and interval between adjuvant therapy and diagnosis of metastatic disease.

In addition, 95% confidence intervals will be calculated for the rates of overall response and grade 3 or greater toxicity.

Analysis of the pharmacogenetic studies will be performed by the Applied Genomics Department in conjunction with Nonclinical Biostatistics at BMS. The effect of allelic variation of selected candidate genes will be correlated with the clinical endpoints described above. In particular, various combinations of allelic variants will be used as covariates in Cox regressions. In addition, possible relationships among toxicity, age, and allelic variation will be explored.

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PART II—PROCEDURES

1. REPORTING ADVERSE EVENTS

1.A. Adverse events

Adverse events will be recorded for the duration of a patient's participation in the trial. All adverse events (except grade 1 and 2 laboratory abnormalities unless a dose treatment modification, delay or therapeutic intervention is required), regardless of causal relationship, are to be recorded in the case report form and source documentation. Pre-existing conditions at baseline will be recorded. If a pre-existing condition does not change, it does not have to be reported on subsequent cycles.

The investigator must determine the toxicity of adverse events according to the CTC version 2.0 (Appendix 2) and their causal relationship.

1.B. Serious adverse events

Adverse events classified as serious require expeditious handling and reporting to Theradex to comply with regulatory requirements.

For any serious adverse event (SAE) that occurs while a patient is on-study or within 30 days of the last drug administration, regardless of any opinion as to the relationship of the SAE to trial medication, Theradex must be notified by telephone within 24 hours of becoming aware of the event. If any serious adverse event that the investigator feels is related to study drug occurs later than 30 days after drug administration, the investigator must report the event to Theradex within 24 hours of becoming aware of the event. During both business and non-business hours, the telephone number listed below should be used to notify Theradex. A recorded message will provide the caller with the pager number of the on-call monitor.

All SAEs that are unexpected, whether considered to be drug-related or not, require that a Serious Adverse Event Report Form be completed and faxed to Theradex within 24 hours of the investigator becoming aware of the event. The investigator must immediately report all unexpected SAEs to the Institutional Review Board in writing.

If a serious adverse event occurs that is expected, a Serious Adverse Event Report Form must be completed and submitted to Theradex within 5 days of becoming aware of the event.

Serious adverse events will be reported to:

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Blaire Cooke, PharmD Nora L. Schenk, PharmD Catherine Perez, PhD Ellen Huang, PharmD Tim O'Connor, PharmD Henry J. Durivage, PharmD Cara Angelini, PharmD Slawomir Wojtowicz-Praga, MD Robert B. Royds, MB,BS,MRCP	
<u>Mailing address:</u> CN 5257 Princeton, NJ 08543	<u>Courier address:</u> Theradex 14 Washington Road, Building 3 Princeton Junction, NJ 08550
Phone number: (609)799-7580 Fax number: (609)799-1567	

1.C. Pregnancy

During the course of the trial, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

If pregnancy is suspected while the patient is receiving study drug, the study drug must be immediately withheld until the result of a pregnancy test is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the patient withdrawn from the trial. The investigator must immediately notify Theradex and record the pregnancy on the CRF. In addition, the investigator must report to Theradex follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks.

2. WOMEN OF CHILDBEARING POTENTIAL

Women of childbearing potential are defined to include the following:

- Any females who have experienced menarche and have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not post-menopausal (defined as amenorrhea >12 consecutive months).
- Since no contraceptive method except continuous abstinence is 100% reliable in preventing pregnancy, even women who are using oral, implanted, or injectable contraceptive hormones; mechanical devices such as an intrauterine device; or barrier methods (diaphragm, condoms,

or spermicides) to prevent pregnancy should be considered to be of childbearing potential.

3. CLINICAL SUPPLIES

3.A. Drug supply records at investigational site

It is the responsibility of the investigator to ensure that a current record of trial medication disposition is maintained. Records or logs must comply with applicable regulations and guidelines and should include:

- The amount of drug received and placed in inventory and the amount transferred to a medical professional for storage or to another investigational inventory.
- Label ID number or batch number.
- Dates of drug inventory movement.
- Unique patient identifier.
- The amount of drug dispensed to and returned by each patient.

The initials of the person responsible for each drug inventory entry.

Theradex will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets the above requirements.

Trial medication may only be dispensed by authorized personnel at official trial sites. The trial medication may only be dispensed from institutions specified on FDA Form 1572.

3.B. Return and destruction of trial medication

Upon completion or termination of the trial, all unused and/or partially used trial medication must be destroyed. The investigator is responsible for ensuring the following: all arrangements have been made for the disposal of the medication, procedures for the proper disposal of the medication incorporate the applicable guidelines and regulations of the investigator's institution, and appropriate records of the disposal have been documented.

4. PROTOCOL ISSUES

4.A. Protocol compliance

No deviations from the protocol will be permitted without prior written approval of the principal investigator if the trial is to be conducted at a single site or the study chair if the trial is to be multicenter.

4.B. Amendments to the protocol

All revisions to the protocol must be discussed with BMS and Theradex. If the revision is an administrative letter, the investigator should submit it to the IRB for their information. If the revision is an amendment, it must be signed by the investigator. The investigator must submit the amendment to the IRB for review and approval prior to implementation. Documentation of approval signed by the chairperson or designee of the IRB must be sent to Theradex.

If an amendment substantially alters the study design or increases the potential risk to a patient, the following must be done: (1) the consent form must be revised and submitted to the IRB for review and approval; (2) the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new patients prior to enrollment.

5. CASE REPORT FORM PROCEDURES

Case report forms (CRFs) will be provided for each patient. All forms must be filled in legibly in black ink only. Patients are to be identified by initials, birth date, and patient number, if applicable.

In case corrections to a CRF are required, the incorrect entry must be crossed out with a single line so that the entry remains legible. Correction fluid must NOT be used. The correct data will be inserted, dated, and initialed by the investigator or his/her designee. If an item is not available or not applicable, it should be documented as such; do not leave a blank space.

The investigator or his/her designee is responsible for recording all data relating to the trial in the CRFs. The investigator must verify that all data entries in the CRFs are accurate and correct by signing and dating each CRF on the designated signature page.

The pink copies of the CRFs will be sent to Theradex two weeks after the patient completes a cycle. Copies of all tumor evaluations and the pathology report will also be submitted to Theradex.

6. ETHICS

6.A. Institutional Review Board

Before study initiation, this protocol, the informed consent form, and any advertisement for patient recruitment will be submitted for review and approval to the IRB charged with this responsibility. Written notification of that approval will be submitted by the investigator to Theradex with a description of the board's members (including profession and affiliation). If neither of the former is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet the

FDA regulatory requirements. In addition, the Investigator's Brochure should be submitted to the IRB for informational purposes.

The investigator must provide reports of the progress, or completion, termination, or discontinuation of the trial to the IRB at appropriate intervals: at least yearly for all IND studies or more frequently if required by applicable regulations and guidelines, or institution procedures.

6.B. Patient informed consent

The consent form approved by the IRB must include all elements required by FDA, state, and local regulations, as well as any additional elements relevant to specific study situations (including a statement that BMS, Theradex, and authorities have access to patient records) required by applicable regulations and guidelines.

The study will be completely explained to each prospective candidate and the patient must give consent by signing and dating the approved informed consent form. A legally authorized representative must sign for patients who are: below the legal age, mentally incompetent, or physically incapacitated (e.g., comatose patients). Patients below the legal age should be asked for their assent if capable of understanding the implications of participating in the study. If required by applicable regulations and guidelines, physically incapacitated patients must provide consent when legally capable of doing so.

Theradex will review the proposed informed consent form from each site. Theradex will ensure the informed consent form conforms with FDA guidelines. A sample consent form is provided in Appendix 3. Copies of the signed document should be given to the patient and filed in the investigator's study file as well as the patient's medical record if in conformance with the institutions' Standard Operating Procedures.

6.C. Confidentiality of records

The investigator must ensure that the patient records are accessed only by authorized personnel from the Regulatory Agency, Theradex, and BMS. To maintain that confidentiality, the following procedures should be used:

1. The investigator must assure that the patients' anonymity will be maintained. On all documents submitted to Theradex, patients will be identified by code; patients should not be identified by name.
2. A separate log of patients' names and codes should be maintained at the investigator's site. The written consent forms should be maintained by the investigator in strict confidence.
3. All research/data will be identified only by a coded number in order to maintain confidentiality. All records will be kept in a controlled area.
4. Clinical information will not be released without the written permission of the patient as indicated in the Informed Consent Form.

7. STUDY RECORDS

The investigator shall retain study drug disposition records, copies of CRFs (or electronic files), and source documents for the maximum period required by the FDA and the institution in which the study will be conducted, or for the period specified by the sponsor, whichever is longer. All study records must be kept until official notification from the Funder that they may be destroyed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS and Theradex.

8. PUBLICATION OF TRIAL RESULTS

All data and reports derived from this protocol are considered confidential and may not be used for the commercial benefit of a third party. There will be no objection to publication of such data by the investigator (whether or not such data is favorable to the trial medication).

The investigator must submit a manuscript to the study chair (or the chair's institutional manuscript review committee) to allow the opportunity to determine that such publication will not compromise either ongoing clinical trials under this protocol or patient rights. The study chair will review the manuscript and return comments within 60 days. The study chair must approve the final manuscript for publication, prior to publication. Authorship will be limited to the top accruers of a specific trial.