

Novel Regimens of Capecitabine Alone and Combined with Irinotecan and Bevacizumab in Colorectal Cancer Xenografts

KENNETH KOLINSKY¹, YU-E ZHANG³, UTE DUGAN²,
DAVID HEIMBROOK¹, KATHRYN PACKMAN¹ and BRIAN HIGGINS¹

¹Discovery Oncology, ²Roche Laboratories Inc., ³Pharmaceutical and Analytical R&D,
Hoffmann-La Roche, 340 Kingsland Street, Nutley, New Jersey 07110, U.S.A.

Abstract. *Background: Xenograft and mathematical models have shown that the antitumor activity of capecitabine can be increased by modifying the schedule from 14 days on, 7 off (14/7) to 7/7. Materials and Methods: Capecitabine at two-thirds maximum tolerated dose (MTD) administered using 14/7 (267 mg/kg) and 7/7 (467 mg/kg) schedules, alone and in doublet and triplet combinations with irinotecan (40 mg/kg intraperitoneally) and bevacizumab (5 mg/kg intraperitoneally) were studied in mice bearing HT29 colorectal xenografts. Results: Tumor growth inhibition was >100% in doublet and triplet regimens with capecitabine 7/7 compared with 70% and 98%, respectively, with 14/7. Increase in lifespan was significantly greater with the 7/7 triplet than the corresponding doublet without bevacizumab (288% versus 225%, respectively). Conclusion: Addition of bevacizumab to capecitabine and irinotecan significantly improved tumor growth inhibition and lifespan in the HT29 xenograft model. Modifying the capecitabine schedule from 14/7 to 7/7 improved the efficacy of doublet and triplet combinations without toxicity.*

Combination chemotherapy regimens comprising a fluoropyrimidine with either oxaliplatin or irinotecan are now recommended as first-line treatment for patients with advanced colorectal cancer (CRC) (1), although the optimum treatment strategy remains to be defined (2). Irinotecan, a DNA topoisomerase I inhibitor with significant *in vitro* and clinical activity against metastatic CRC (3-7), was the first chemotherapeutic agent to show a survival benefit when added to traditional fluoropyrimidine-based therapy (8). Treatment with irinotecan, fluorouracil and leucovorin (IFL) reduced the risk of progression by 36% and the risk of death by 22%

compared with fluorouracil and leucovorin (5-FU/LV) (8). The addition of bevacizumab, a recombinant, humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF) (9-11), to fluoropyrimidine-irinotecan combination chemotherapy (IFL) resulted in a further improvement in survival in patients with metastatic CRC (44% reduction in risk of death) (12). Recently, infused 5-FU/LV was shown to be more effective than bolus 5-FU in regimens including irinotecan and bevacizumab (13, 14). In this phase III trial, FOLFIRI (infusional 5-FU/LV and irinotecan) plus bevacizumab conferred a statistically significant overall survival benefit when compared with modified IFL (bolus irinotecan and 5-FU/LV) plus bevacizumab (14).

Clinical studies have shown that 5-FU/LV regimens can be substituted by the orally administered fluoropyrimidine capecitabine (15-17). Capecitabine is converted to 5-FU preferentially in tumors (18-20) and antitumor activity has been shown in CRC xenograft models (21-23). Furthermore, addition of irinotecan to capecitabine was shown to be more active than either drug alone against all colorectal tumor models (24), prompting clinical investigation of this combination. Preliminary phase I/II trials showed that capecitabine and irinotecan can be safely and effectively combined in the XELIRI regimen (25). XELIRI was shown to be active as first-line therapy (26-29) and second-line therapy (30) in patients with advanced CRC. The adverse events associated with XELIRI were manageable with dose reduction (26, 29, 31) and no pharmacokinetic interactions have been reported (32, 33). Data also showed that a 3-weekly schedule of irinotecan provides superior tolerability and efficacy to a weekly schedule (34). Although phase I/II studies were encouraging, two phase III trials investigating fluoropyrimidine-irinotecan regimens, with and without bevacizumab, raised some important questions about the ongoing development of XELIRI as a first-line treatment (13, 14, 35). Firstly, why did toxicity risk, particularly gastrointestinal, appear to be increased with XELIRI compared with FOLFIRI? Secondly, would modification of

Correspondence to: Brian Higgins, 340 Kingsland Street 123/2319, Nutley, New Jersey 07110, U.S.A. e-mail: brian_x.higgins@roche.com

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the XELIRI dose and schedule improve its therapeutic ratio? Finally, what is the optimal dosing regimen for XELIRI plus bevacizumab in this setting?

The registered dosing schedule for capecitabine in patients with advanced CRC is 1,250 mg/m² twice daily (*bid*) using a 14/7 schedule (14 days on followed by 7 days off) (15-17, 36). However, dose modification is commonly required in clinical practice to manage adverse events, principally hand-foot syndrome (37). Furthermore, data from breast cancer xenograft studies (38) and mathematical modeling (39, 40) suggest that the greatest antitumor effect of capecitabine occurs after approximately 7 days of treatment and that continued administration beyond 7 days adds toxicity without additional activity. Based on these observations, a series of experiments was conducted to test the hypothesis that a capecitabine dosing schedule of 7 days of treatment followed by 7 drug-free days (7/7) will enable delivery of higher doses and improve efficacy. The specific objectives of the study were to determine the antitumor activity and tolerability of capecitabine at 2/3 maximum tolerated dose (MTD) administered using either 14/7 or 7/7 schedules alone and in doublet and triplet combinations with irinotecan at 2/3 MTD and optimally dosed bevacizumab in mice bearing HT29 colorectal xenografts.

Materials and Methods

Animals. Athymic nude mice (CrI:NU-Foxn1nu), 13 to 14 weeks old and weighing approximately 23-25 g, were purchased from Charles River Laboratories (Wilmington, DE, USA). The health of all animals was monitored daily by gross observation and analyses of blood samples of sentinel animals. All animals were allowed to acclimatize and recover from any shipping-related stress for a minimum of 72 hours prior to experimental use. Autoclaved water and irradiated food (5058-ms Pico Chow; Purina, Richmond, IN, USA) were provided *ad libitum* and the animals were maintained on a 12-hour light and dark cycle. Cages, bedding and water bottles were autoclaved before use and were changed weekly. All animal experiments were performed in accordance with protocols approved by the Institutional Animal Care and Use Committees.

Tumors. HT29 colorectal cancer cells (ATCC®) were chosen based on their moderate thymidine phosphorylase (TP) activity and moderate sensitivity to the traditional continuous daily administration regimen of capecitabine (22, 23). The HT29 cells were cultured using McCoy's 5A 10% (v/v) heat-inactivated fetal bovine serum and 1% (v/v) 200 nM L-glutamine.

Test agents. Capecitabine (Xeloda®; Roche Laboratories, Nutley, NJ, USA) was formulated as a suspension in 2% Klucler LF, 0.1% Tween 80, 0.09% methylparaben and 0.01% propylparaben, and administered orally (*p.o.*) every day at 2/3 MTD. The MTD of capecitabine was previously determined in tumor-bearing mice as 400 mg/kg per day (*q.d.*) with the 14/7 schedule (2/3 MTD=267 mg/kg) and 700 mg/kg *q.d.* with the 7/7 schedule (2/3 MTD=467 mg/kg) (41). Clinical-grade bevacizumab (Avastin®; Genentech

Inc., South San Francisco, CA, USA) was obtained as a stock solution of 25 mg/ml, diluted with sterile saline, and given intraperitoneally (*i.p.*) at the optimal dose (5 mg/kg twice per week). Clinical-grade irinotecan (Camptosar®; Pfizer Inc., New York, NY, USA) was provided in a stock sterile saline solution of 20 mg/ml, which was diluted as required with sterile saline and given *i.p.* every 4 days for 5 doses (days 1, 5, 9, 13, 17; q4dx5) at a dose of 40 mg/kg (2/3 MTD). The dose of irinotecan was selected based on a dose-finding study of monotherapy in mice bearing HT29 xenografts in which the MTD was 60 mg/kg administered q4dx5 *i.p.*

Study design. HT29 cells (3×10⁶ in 0.2 ml of phosphate-buffered saline) were injected into the right lateral flank. Treatment was started approximately 14 days after HT29 cell implantation and was designed to compare the following doublet and triplet 14/7 and 7/7 regimens with appropriate vehicle control: I. Capecitabine 14/7 at 267 mg/kg *p.o. q.d.* + irinotecan at 40 mg/kg *i.p. q4dx5* ("capecitabine 14/7 doublet"); II. Capecitabine 7/7 at 467 mg/kg *p.o. q.d.* + irinotecan at 40 mg/kg *i.p. q4dx5* ("capecitabine 7/7 doublet"); III. Capecitabine 14/7 at 267 mg/kg *p.o. q.d.* + irinotecan at 40 mg/kg *i.p. q4dx5* + bevacizumab at 5 mg/kg 2x/week *i.p.* ("capecitabine 14/7 triplet"); IV. Capecitabine 7/7 at 467 mg/kg *p.o. q.d.* + irinotecan at 40 mg/kg *i.p. q4dx5* + bevacizumab at 5 mg/kg 2x/week *i.p.* ("capecitabine 7/7 triplet").

Each treatment group included 10 animals. The health status of animals was checked daily by veterinary staff and tumor volume and weights were recorded 2-3 times/week.

Efficacy and safety endpoints. Tumor growth inhibition (TGI) was calculated from the percentage change in mean tumor volume. Survival was calculated using a cut-off of 1,500 mm³ and the mean increase in lifespan (ILS) was calculated using the formula: [(Median day of death in treated tumor-bearing mice) – (median day of death in control tumor-bearing mice)]/Median day of death in control tumor-bearing mice

Average percentage weight change was used as a surrogate endpoint for tolerability in all experiments.

Statistical methods. Statistical analysis consisted of Mann-Whitney Rank Sum Test, 1-way ANOVA, and *post-hoc* Bonferroni *t*-test (SigmaStat, version 2.0; Jandel Scientific, San Francisco, CA, USA). Survival was analyzed by the Kaplan-Meier method. Treated groups were compared with the vehicle group and survival comparisons between groups were analyzed by log-rank test (GraphPad Prism, version 4.3). Differences between groups were considered significant when the probability value (*p*) was ≤0.05.

Results

Monotherapy with 14/7 and 7/7 schedules of capecitabine at 2/3 MTD, irinotecan, and bevacizumab. Capecitabine 14/7 and 7/7 administered at 2/3 MTD and optimally dosed bevacizumab showed moderate monotherapy activity of between 60-77% TGI (data not shown), as previously reported (42). Irinotecan monotherapy administered at MTD (60 mg/kg *q4d*) produced 84% TGI, while more moderate activity of 56% TGI was seen at 2/3 MTD (data not shown).

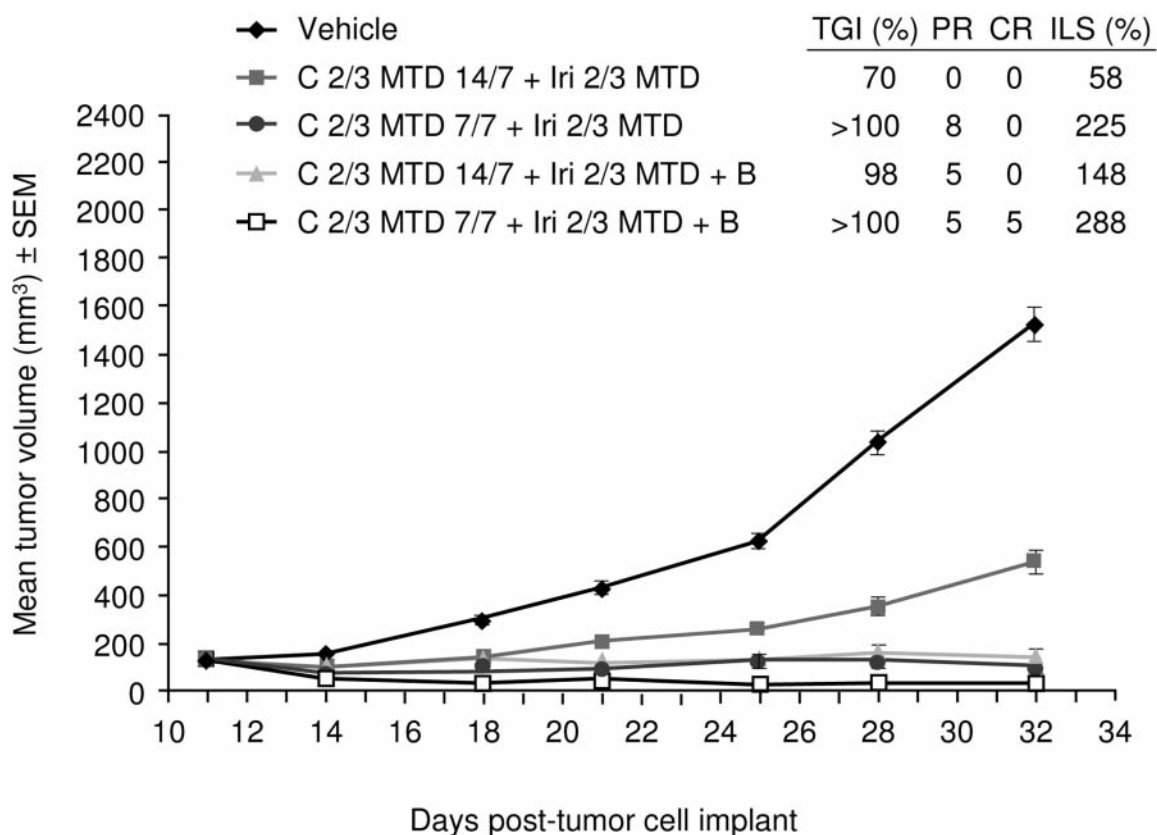


Figure 1. Antitumor activity of different capecitabine (C) schedules in combination with irinotecan (Iri) with or without bevacizumab (B) in athymic mice bearing HT29 colorectal cancer xenografts compared with vehicle control. MTD, Maximum tolerated dose; TGI, tumor growth inhibition; ILS, increase in lifespan; PR, partial response; CR, complete response.

Table I. Statistical comparisons (treatment 1 versus 2) of different capecitabine schedules in combination with irinotecan with or without bevacizumab in athymic mice bearing HT29 colorectal cancer xenografts.

Schedule*	Treatment 1	Treatment 2	TGI p-value**	ILS p-value†
Capecitabine (C) 7/7 versus 14/7 + irinotecan (Iri) at 40 mg/kg ± bevacizumab (B) at 5 mg/kg	C 14/7 at 2/3 MTD + Iri	C 7/7 at 2/3 MTD + Iri	<0.05	<0.0001
	C 14/7 at 2/3 MTD + Iri	C 14/7 at 2/3 MTD + Iri + B	<0.05	<0.0001
	C 14/7 at 2/3 MTD + Iri	C 7/7 at 2/3 MTD + Iri + B	<0.05	<0.0001
	C 7/7 at 2/3 MTD + Iri	C 14/7 at 2/3 MTD + Iri + B	>0.05	0.0075
	C 7/7 at 2/3 MTD + Iri	C 7/7 at 2/3 MTD + Iri + B	>0.05	0.0003
	C 14/7 at 2/3 MTD + Iri + B	C 7/7 at 2/3 MTD + Iri + B	<0.05	<0.0001

*Capecitabine 14/7 at 2/3 MTD = 267 mg/kg qd; 7/7 at 2/3 MTD = 467 mg/kg qd. **One-way ANOVA, *post-hoc* Bonferroni. †Log-rank test. MTD, Maximum tolerated dose; TGI, tumor growth inhibition; ILS, increase in lifespan.

Antitumor activity of 7/7 versus 14/7 schedules of capecitabine at 2/3 MTD in combination with irinotecan at 2/3 MTD with or without bevacizumab. In all treatment groups, TGI was significantly different from that of the vehicle control ($p < 0.001$) (Figure 1). The antitumor activity of capecitabine 14/7 plus irinotecan was statistically inferior to all other doublet and triplet regimens (Table I).

Addition of bevacizumab. The triplet regimen comprising capecitabine 14/7 plus irinotecan and bevacizumab was statistically more active than the corresponding doublet without bevacizumab (TGI 98% versus 70%, respectively; $p < 0.05$). In contrast, the triplet combination of capecitabine 7/7 plus irinotecan and bevacizumab was not significantly better than its corresponding doublet (TGI values >100% in

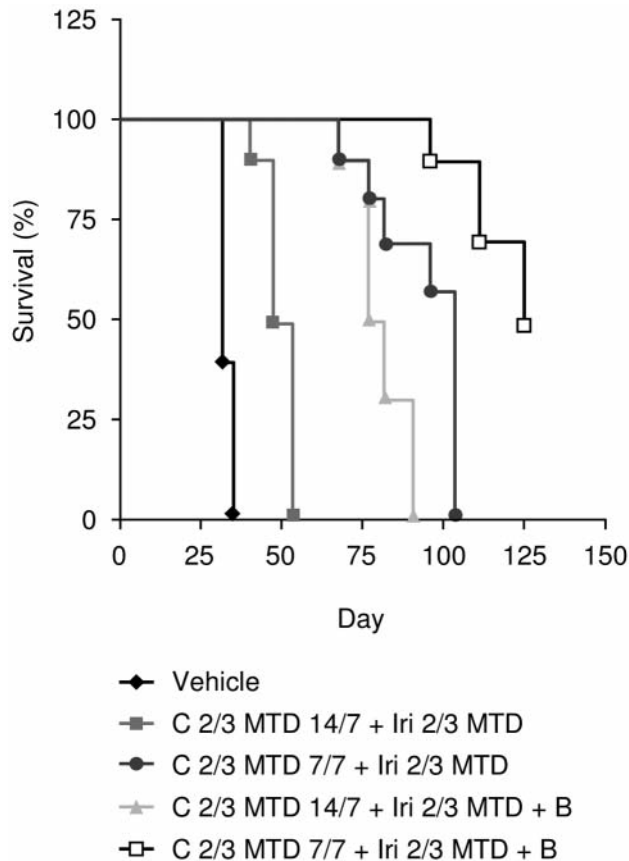


Figure 2. Kaplan-Meier curves for different capecitabine (C) schedules in combination with irinotecan (Iri) with or without bevacizumab (B) in athymic mice bearing HT29 colorectal cancer xenografts.

both groups), although there was a trend towards greater regression with the triplet; there were 10 objective responses (5 partial and 5 complete) with the triplet compared with 8 (all partial) with the doublet. In addition, survival was significantly greater with the triplet combination of capecitabine 7/7 plus irinotecan and bevacizumab compared with the doublet without bevacizumab (ILS 288% versus 225% , respectively; $p < 0.0001$).

Capecitabine 7/7 versus 14/7. The capecitabine 7/7 triplet regimen resulted in significantly greater tumor inhibition than the corresponding 14/7 triplet (TGI values of >100% versus 98% , respectively; $p < 0.05$) and improved survival (ILS 288% versus 148% , respectively; $p < 0.0001$). Survival was also significantly greater with capecitabine 7/7 in combination with irinotecan than with the corresponding doublet regimen using the 14/7 schedule (ILS 225% versus 58% , respectively; $p < 0.0001$). The significantly increased survival with the capecitabine 7/7 schedules compared with the corresponding 14/7 schedules in triplet and doublet

combinations is shown as a Kaplan-Meier plot in Figure 2. **Tolerability.** There was no toxicity with any of the capecitabine 7/7 and 14/7 doublet and triplet combination regimens tested. Data for average percentage weight change showed no significant changes during the treatment course and no significant differences between the treatment groups (Figure 3).

Discussion

This study was designed to determine whether the efficacy of capecitabine plus irinotecan combination therapy can be improved by modifying the schedule of capecitabine from 14/7 to 7/7 and/or by adding bevacizumab in nude mice bearing HT29 colorectal xenografts. TP-expressing HT29 cells provide a logical model in which to test novel capecitabine regimens because this enzyme is required for the pharmacological activation of capecitabine. However, TP levels in xenografts may not reliably reflect those in patients with advanced CRC, therefore, caution is required when extrapolating these experimental findings to the clinical setting (43). These experimental studies demonstrated that the addition of bevacizumab to capecitabine and irinotecan improved both TGI and ILS in the HT29 xenograft model. Modifying the capecitabine schedule from 14/7 to 7/7 also improved the antitumor efficacy of doublet and triplet combination regimens.

The 14/7 schedule of capecitabine in combination with irinotecan (both administered at 2/3 MTD) showed moderate antitumor activity (70% TGI), similar to previously published results (22, 23). Addition of bevacizumab to the 14/7 schedule resulted in a TGI value of 98% , however, the greatest antitumor effect of capecitabine-based treatment was achieved with the 7/7 schedules in both doublet and triplet regimens (TGI values >100%). Although TGI with the capecitabine 7/7 triplet regimen was not statistically superior to the corresponding doublet, the addition of bevacizumab clearly improved antitumor efficacy, as shown by a trend towards greater regression, which translated into significantly better survival ($p < 0.0001$). The survival benefits of 7/7 versus 14/7 schedules and the addition of bevacizumab to capecitabine and irinotecan were biologically significant according to NCI criteria (>25% ILS) (44).

Data from a breast cancer model (KPL-4 human estrogen-receptor negative) have also shown that a capecitabine 7/7 schedule is superior to a corresponding 14/7 schedule when used in combination with bevacizumab (45), or bevacizumab plus trastuzumab (38). These results in the HT29 CRC xenograft model suggest that the 7/7 schedule has the potential to improve the therapeutic index of capecitabine in combination with irinotecan and bevacizumab. Using the 7/7 schedule allowed the dose of capecitabine to be increased from 267 mg/kg to 467 mg/kg, representing an increase in total dose

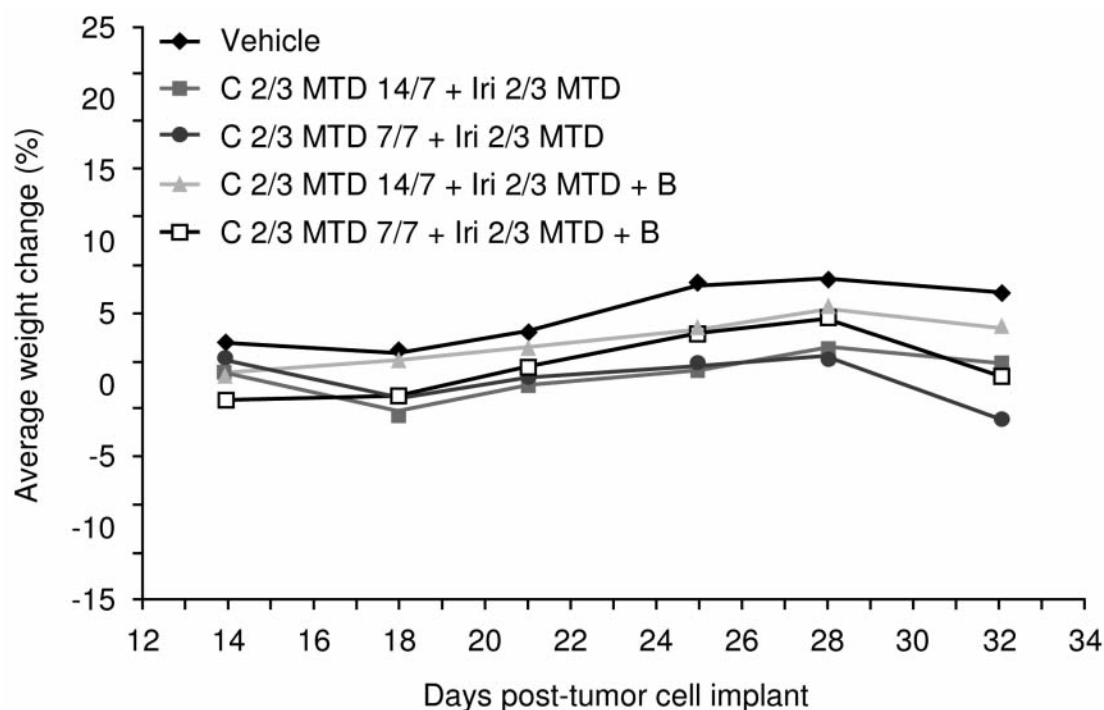


Figure 3. Tolerability to capecitabine (C) plus irinotecan (Iri) regimens with and without bevacizumab (B).

intensity from 3738 to 6538 mg/kg calculated over a 3-weekly cycle. The increase in delivered dose of capecitabine resulted in improved antitumor efficacy without additional toxicity. No toxicity was observed with any of the regimens studied, using changes in weight as a surrogate endpoint.

It has been suggested that increased toxicity with XELIRI compared with FOLFIRI observed in the BICC-C Study (14) may reflect a greater propensity for fluoropyrimidine-related toxicity among US patients compared with European or Asian patients, as described by Haller *et al.* (46). In addition, clinical studies have shown that irinotecan is associated with high rates of toxicity as monotherapy (6), or when combined with fluoropyrimidines (47). Gastrointestinal adverse events are a particular concern with irinotecan and the potential for overlapping toxicity needs to be managed effectively with dose modification when this agent is combined with capecitabine (26). However, the results of the BICC-C (13) and EORTC (35) trials on the toxicity of XELIRI are in contrast to data from the Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer (CAIRO) trial, which included the largest first-line XELIRI-treated patient cohort to date (2). In this study, the incidence of grade 3 to 4 diarrhea was consistent with the incidence of between 19% and 26% seen in four phase II studies involving a total of 210 patients (26, 29, 33, 34). These data suggest that XELIRI is a feasible and effective treatment option for patients with advanced colorectal cancer and dose modification should be

used in patients who are considered at risk for severe diarrhea. Although schedules of FOLFIRI in general have a lower incidence of diarrhea than XELIRI, this must be balanced against the use of ambulatory infusion devices and more frequent patient visits (48). Conceivably, alternative doses and schedules of capecitabine and irinotecan could provide a superior efficacy and tolerability profile than the traditional regimen used in the BICC-C trial (14).

A phase I dose-escalation study investigated a 7/7 schedule of capecitabine in combination with irinotecan in 27 patients with solid tumors. The recommended doses for further study were irinotecan 100 mg/m² and capecitabine 1,000 mg/m² *bid*, although some patients tolerated a capecitabine dose as high as 1,250 mg/m² *bid* (49). Dose-intensified capecitabine (1,750 mg/m² *bid* given on a 7/7 schedule) and irinotecan (130 mg/m²) was shown to be active with a tolerable safety profile in patients with advanced gastric cancer (50). Conversely, a decrease in the dose of irinotecan has been proposed to improve tolerability without decreasing efficacy. In one study, a lower dose intensity of irinotecan (70 mg/m² days 1 and 8) appeared to maintain activity and improve tolerability when combined with capecitabine (1,000 mg/m² *bid* days 1-14) (31). Furthermore, the authors of a recent phase II study of XELIRI (irinotecan 250 mg/m² *i.v.* on day 1 plus capecitabine 1,000 mg/m² *bid* days 1 to 14, every 3 weeks) recommended upfront dose reductions of both capecitabine

and irinotecan in patients with risk factors for toxicity. This approach appeared to improve safety compared with previous studies of this regimen without such dose reductions (26). Further improvements in therapeutic index may be achieved by use of biomarkers to identify patients most at risk from adverse events (51), or most likely to benefit from capecitabine (52) or capecitabine plus irinotecan (53). The future development of XELIRI should therefore consider optimization of drug doses and schedules, patient selection, and management of adverse events.

In conclusion, this study has demonstrated that bevacizumab can increase the efficacy of capecitabine plus irinotecan and that a 7/7 schedule of capecitabine is more effective than the standard 14/7 schedule. Based on these results in HT29 xenografts in athymic mice, the combination of capecitabine 7/7, irinotecan and bevacizumab merits further clinical investigation in patients with advanced CRC.

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