A Phase I Trial of a Guadecitabine (SGI-110) and Irinotecan in Metastatic Colorectal Cancer Patients Previously Exposed to Irinotecan

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Abstract

Purpose: Chemotherapeutic resistance eventually develops in all patients with metastatic colorectal cancer (mCRC). Gene silencing through promoter demethylation is one potential reversible mechanism of resistance with administration of hypomethylating agents. We evaluated the safety and tolerability of guadecitabine and irinotecan in patients with mCRC previously treated with irinotecan.

Patients and Methods: In this 3+3 dose-escalation study, patients with mCRC previously exposed to irinotecan received guadecitabine days 1 to 5 of a 28-day cycle and irinotecan 125 mg/m2 days 8 and 15 [dose level (DL) 1, guadecitabine 45 mg/m2; DL –1: guadecitabine 30 mg/m2; DL –1G: guadecitabine 30 mg/m2 with growth factor support (GFS); DL 1G: guadecitabine 45 mg/m2 with GFS].

Results: Twenty-two patients were treated across four DLs. Dose-limiting toxicities were neutropenic fever (DL 1 and –1G), biliary drain infection (DL –1), colonic obstruction (DL –1), and severe dehydration (DL 1G). Most common toxicities were neutropenia (82% any grade, 77% Grade 3/4), neutropenic fever (23%), leukopenia (73% any grade, 50% Grade 3/4), and injection site reactions (64% total, 0% Grade 3/4). Patients received a median of 4.5 cycles of treatment; 12/17 evaluable patients had stable disease as best response, with one having initial disease progression but subsequently durable partial response. Circulating tumor DNA showed decrease in global demethylation by LINE-1 after treatment.

Conclusions: We report the first study of chemo-priming with epigenetic therapy in gastrointestinal cancers. Guadecitabine 45 mg/m2 and irinotecan 125 mg/m2 with GFS was safe and tolerable in patients with mCRC, with early indication of benefit. These data have provided the basis for an ongoing phase II randomized, multicenter trial.

Clin Cancer Res; 24(24); 6160–7. ©2018 AACR.

Introduction

Overall survival (OS) of patients with metastatic colorectal cancer (mCRC) has improved to median 2.5 years over the past two decades with addition of irinotecan, oxaliplatin, bevacizumab, and EGFR inhibitors to fluorouracil based therapy (1). Although primary chemoresistance is a concern, even among patients with excellent response to therapies, resistance and intolerance to chemotherapeutic agents inevitably develops. In RAS wild-type mCRC, anti-EGFR antibodies combined with irinotecan results in increased response rate and progression-free survival (PFS) compared with anti-EGFR therapy alone; no such option exists for RAS mutated disease (2). The remaining FDA approved third-line treatment options (regorafenib and TAS-102) provide less than a 2-month OS benefit over placebo, highlighting the need for additional therapeutic options (3, 4).

Epigenetic therapy with DNA methyltransferase inhibitors (DNMTi) show success in hematologic malignancies, but little benefit in solid tumors, including non–small cell lung cancer (NSCLC), mCRC, and breast cancer (5–7). However, follow-up of patients with NSCLC treated in a phase I/II study of 5-azacitidine and entinostat, showed that 30% of these heavily pretreated patients had Response Evaluation Criteria in Solid Tumors (RECIST) responses to subsequent therapies, with another half with stable disease. Similar preclinical and early phase clinical studies in ovarian cancer have shown DNMTi reversing resistance to platinum agents (8). In preclinical CRC models, DNMTis can induce re-expression of tumor suppressor genes (9). Our group has reported DNMTi can both induce sensitivity and reverse chemoresistance to irinotecan in in vitro and in vivo models (10).

Guadecitabine (SGI-110) is a subcutaneously administered dinucleotide of decitabine and deoxyguanosine. Decitabine is an FDA approved DNMTi for treatment of myelodysplastic syndromes. Pharmacokinetic studies of guadecitabine demonstrate a prolonged half-life of the metabolite decitabine, compared with intravenous decitabine, with resultant higher exposures to decitabine and more potent global hypomethylation. When administered to patients with acute myeloid leukemia and myelodysplastic syndrome in a phase I study, dosing of guadecitabine...
monotherapy at 60 mg/m² daily ×5 in a 28-day cycle was tolerable and led to potent dose-related DNA demethylation (11). This dosing was intolerable in sorafenib-refractory patients with hepatocellular carcinoma (HCC) due to myelosuppression. However, although guadecitabine dosed at 45 mg/m² in patients with HCC had 67% grade 3/4 neutropenia and 11% febrile neutropenia, treatment maintained demethylation in both intratumoral and circulating DNA (12).

The primary objectives of this phase I dose-escalation study were to evaluate the safety and tolerability of guadecitabine in combination with irinotecan in patients with mCRC, and to determine the MTD. Secondary objectives were to assess changes in global methylation in the tumor and circulating cells after administration of combination therapy, assess pharmacokinetics (PK) of guadecitabine, and assess for disease response.

**Patients and Methods**

**Study population**

Patients were ≥18 years old, with histologically/cytologically confirmed mCRC, with prior exposure to irinotecan. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, intact organ and marrow function (leukocytes ≥3,000/mкл, absolute neutrophil count ≥1,500/mкл, platelets ≥100,000/mкл, total bilirubin <1.5 times the upper limit of normal [ULN], AST/ALT ≤3 times ULN, creatinine <1.5 times ULN, or creatinine clearance ≥50 mL/min/1.73 m²), measurable disease according to the RECIST (version 1.1), and biopsiable disease. Major exclusion criteria included patients with known brain metastases and prior therapy, hypomethylating agents, and recent (<6 months) small bowel obstruction.

**Study design**

This phase I, open-label, nonrandomized, dose-escalation study was conducted at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in the USA and the Cancer Center Amsterdam, VU University Medical Center in the Netherlands (NCT01896856). Patients were escalated per the 3+3 design, and at each dose level (DL; Table 1) patients were administered guadecitabine subcutaneously on Days 1 to 5 and irinotecan (intravenously) on days 8 and 15 of a 28-day cycle.

The study protocol and all amendments were approved by the independent institutional review boards or ethics committees for each study site and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided informed consent.

**Evaluations**

All patients who received at least one dose of guadecitabine were considered evaluable for toxicity. Safety evaluation included laboratory assessments, physical examinations, and adverse events (AE) were graded according to the NCI Common Terminology Criteria for Adverse events (CTCAE) version 4.0. Follow-up examinations and laboratory studies were done within 30 days of study completion. Dose-limiting toxicities (DLT) were defined as cycle 1 AEs attributable to study treatment defined as grade 4 thrombocytopenia or neutropenia last >7 days, any incidence of grade 3 or 4 febrile neutropenia, grade ≥3 nonhematologic toxicity unless it could be appropriately managed by supportive treatment, or any other clinically significant AE, which would place the subjects at undue safety risk or resulted in discontinuation of treatment.

Patients who completed at least one cycle of treatment and underwent repeat assessment of disease were considered evaluable for response. Responses were determined according to RECIST 1.1, include complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

The MTD was the highest DL at which less than 33% of patients experienced a DLT during cycle 1.

**PK analyses**

Pharmacokinetics of guadecitabine were assessed from plasma concentrations on cycle 1, day 1, at nine time points: pre-dose, and 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours, 6 hours, and 8 hours post-dose. Plasma concentrations were determined using a validated LC/MS-MS method with LLOQ of 1 and 0.5 ng/mL for guadecitabine and decitabine, respectively. Calculations were made of total exposure as determined by area under the plasma concentration–time curve, maximum concentration (Cmax), time to maximal concentration (Tmax), and terminal half-life (t1/2).

Table 1. Dosing levels of guadecitabine and irinotecan

<table>
<thead>
<tr>
<th>DL</th>
<th>Guadecitabine (mg/m²)</th>
<th>D1–D5</th>
<th>Irinotecan (mg/m²)</th>
<th>D8 and 15</th>
<th>Growth factor support</th>
</tr>
</thead>
<tbody>
<tr>
<td>–1G</td>
<td>30</td>
<td></td>
<td>125</td>
<td></td>
<td>Filgrastim 5 mcg/kg/day CID9–14 CID16 pegfilgrastim 6 mg C2 and beyond per clinical judgment</td>
</tr>
<tr>
<td>1G</td>
<td>30</td>
<td>45</td>
<td>125</td>
<td></td>
<td>Per clinician judgment, not allowed cycle 1</td>
</tr>
<tr>
<td>1 (starting dose)</td>
<td>45</td>
<td>125</td>
<td></td>
<td></td>
<td>Per clinician judgment, not allowed cycle 1</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>125</td>
<td></td>
<td></td>
<td>Filgrastim 5 mcg/kg/day CID9–14 CID16 pegfilgrastim 6 mg C2 and beyond per clinical judgment</td>
</tr>
</tbody>
</table>

Translated Relevance

Acquired resistance to cytotoxic chemotherapy invariably develops in all patients with metastatic colorectal cancer, and tracks with poor survival. Epigenetic changes in the methylation of tumor DNA have been implicated in acquired chemoresistance and may be reversible with DNT methyltransferase inhibitors. We tested this hypothesis in a phase I clinical trial of guadecitabine and irinotecan in patients with colorectal cancer who had previously been treated with irinotecan. We showed the combination to be tolerable and that a majority of the patients had disease benefit. We demonstrated pharmacodynamic effect with circulating tumor DNA showing decreased global demethylation. Our data support further development of this combination in mCRC and a randomized phase II trial is ongoing. Future directions include applying the technology to other classes of agents and in other tumor histologies.
neutropenia, the investigative team decided to expand the cohort to six patients total; one of these six patients developed neutropenic fever and was removed from the study. Dose was de-escalated to DL-1 with guadecitabine at 30 mg/m², during which two patients suffered DLTs (biliary drain infection in setting of neutropenia and colonic obstruction secondary to disease progression). Among the nine patients on DL 1 and –1, six received growth factor support (two who suffered from neutropenic fever recovered prior to administration of growth factor support). At this time, an amendment was made to add mandatory growth factor support and re-enroll the DLs starting with DL –1G. Seven patients were enrolled at DL –1G (one patient withdrew consent after two doses of guadecitabine), with one DLT of neutropenic fever. After recovering, the patient was resumed on therapy and remained on trial (requiring growth factor support) at the time of data lock. The study was escalated to DL 1G, with enrollment of six additional patients, of whom one suffered severe dehydration and renal failure leading to death after receiving cycle 1 day 8 irinotecan; review of the case suggested non-compliance with supportive care medication. However, after review of the toxicities observed across the study as well as the pharmacodynamics data described below, the investigative team agreed to conclude dose escalation at DL 1G even though the trial had not exceeded the MTD as defined in the protocol. The phase II dose was defined as DL 1G, guadecitabine 45 mg/m² days 1 to 5 and irinotecan 125 mg/m² days 8 and 15 of a 28-day cycle with mandatory growth factor support during cycle 1.

Most common attributable toxicities were neutropenia [18 (82%)], nausea [16 (73%)], injection site reactions [14 (64%)], fatigue [14 (64%)], and anemia [13 (59%)]. The most common attributable toxicities were neutropenia [17 (77%)], including five episodes neutropenic fever (23%), anemia [3 (14%)], diarrhea [4 (18%)], and thrombocytopenia [2 (9%)]; (Table 3).

### Results

Twenty-two patients were recruited between October 2013 and October 2015. Toxicity attributable to treatment was censored as of April 8, 2016, and follow-up data for OS was last censored as of January 1, 2017, at which time one patient was still on study. Patients were enrolled across four DLs (six at DL1, three at DL-1, seven at DL-1G, and six at DL1G). An amendment was made due to the high rates of neutropenia to add DL -1G and 1G (which specified mandatory growth factor support for the first cycle that could be discontinued for subsequent cycles based on provider choice). Patients were heavily pretreated, receiving a median of 2.5 prior lines of treatment, 14 of 22 (64%) with prior progression on irinotecan as determined by treating physician (Table 2).

Patients received a median of 4.5 cycles of therapy (range 0–18), 16 patients received more than one cycle, of whom seven required dose reductions of guadecitabine, irinotecan, or both. Of the twenty-one patients who had discontinued treatment at data-lock, 12 were due to disease progression (57%), six were due to toxicity (29%), and two patients withdrew consent, one after receiving two doses of guadecitabine, the other after 12.5 cycles (9%), and a patient was taken off trial after developing renal insufficiency from uroteral stones unrelated to treatment. At a median follow-up of 20 months, the median OS for the 22 patients on study is 10.7 months. Six, 12-, and 18-month OS is 68% (95% CI, 51%–91%), 47% (95% CI, 30%–75%), and 35% (95% CI, 19%–65%), respectively.

### Safety

No DLTs were noted in the first DL, but due to prolonged neutropenia, the investigative team decided to expand the cohort to six patients total; one of these six patients developed neutropenic fever and was removed from the study. Dose was de-escalated to DL-1 with guadecitabine at 30 mg/m², during which two patients suffered DLTs (biliary drain infection in setting of neutropenia and colonic obstruction secondary to disease progression). Among the nine patients on DL 1 and –1, six received growth factor support (two who suffered from neutropenic fever recovered prior to administration of growth factor support). At this time, an amendment was made to add mandatory growth factor support and re-enroll the DLs starting with DL –1G. Seven patients were enrolled at DL –1G (one patient withdrew consent after two doses of guadecitabine), with one DLT of neutropenic fever. After recovering, the patient was resumed on therapy and remained on trial (requiring growth factor support) at the time of data lock. The study was escalated to DL 1G, with enrollment of six additional patients, of whom one suffered severe dehydration and renal failure leading to death after receiving cycle 1 day 8 irinotecan; review of the case suggested non-compliance with supportive care medication. However, after review of the toxicities observed across the study as well as the pharmacodynamics data described below, the investigative team agreed to conclude dose escalation at DL 1G even though the trial had not exceeded the MTD as defined in the protocol. The phase II dose was defined as DL 1G, guadecitabine 45 mg/m² days 1 to 5 and irinotecan 125 mg/m² days 8 and 15 of a 28-day cycle with mandatory growth factor support during cycle 1.  

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Pharmacokinetics

Pharmacokinetics was assessed in 15 subjects (6 from 30 and 9 from 45 mg/m² dose) who contributed evaluable data. After guadecitabine subcutaneous injection, both guadecitabine and its active metabolite decitabine were detected in plasma from subjects at both DLs. Plasma concentrations of guadecitabine subcutaneous injection, both guadecitabine and decitabine were still present in circulation at 8 hours in most subjects, suggesting an exposure window for active metabolite decitabine were detected in plasma from 45 mg/m² dose) who contributed evaluable data. After conversion to the active metabolite was efficient.

Clinical response

Seventeen patients were evaluable for response, 12 patients (70.6%; 95% CI, 44.0%–89.6%) had SD as best response, and five had PD (29.4%; 95% CI, 13%–55.9%) at first evaluation (Fig. 1). The exposure of guadecitabine and the extent of formation of decitabine appeared to increase in a roughly dose proportional manner for the DLs studied (Supplementary Table S1). Based on the ratio of mean decitabine to mean guadecitabine systemic AUC values on molar basis, conversion to the active metabolite was efficient.

disease, seven of eight patients had stable disease at first evaluation (87.5%), and received a median of 7.5 cycles (range 2–12). One patient on DL – 1G withdrew consent after receiving only two doses of guadecitabine, and was considered evaluable for toxicity (and thus included in the analysis for toxicity), but not evaluable for response.

Clinical response

Seventeen patients were evaluable for response, 12 patients (70.6%; 95% CI, 44.0%–89.6%) had SD as best response, and five had PD (29.4%; 95% CI, 13%–55.9%) at first evaluation (Fig. 1). The exposure of guadecitabine and the extent of formation of decitabine appeared to increase in a roughly dose proportional manner for the DLs studied (Supplementary Table S1). Based on the ratio of mean decitabine to mean guadecitabine systemic AUC values on molar basis, conversion to the active metabolite was efficient.

### Table 3. Toxocities

<table>
<thead>
<tr>
<th>Grade</th>
<th>DL 1 (N = 6)</th>
<th>DL −1 (N = 5)</th>
<th>DL −10 (N = 7)</th>
<th>DL 1G (N = 6)</th>
<th>All (N = 22)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3</td>
<td>All</td>
<td>&lt;3</td>
<td>All</td>
<td>&lt;3</td>
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<tr>
<td>Hematologic</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
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<td>6 (100)</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Neutropenia</td>
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<td>6 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>5 (72)</td>
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<td>5 (83)</td>
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<td>0 (0)</td>
<td>1 (14)</td>
</tr>
<tr>
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<td>4 (67)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (29)</td>
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<td></td>
<td></td>
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<tr>
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<td>Dysgeusia</td>
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<td>Infections and fevers</td>
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<td>3 (50)</td>
<td>0 (0)</td>
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NOTE: One patient in DL – 1G withdrew consent after receiving only two doses of guadecitabine, and was considered evaluable for toxicity (and thus included in the analysis for toxicity), but not evaluable for response.
with PD and SD responses had similar mean and median changes in circulating LINE-1 methylation by cycle 2 day 15 (Mann-Whitney $P = 1.0$).

**Discussion**

The role of epigenetic agents in solid tumors is still being defined, but shows promise for reversing chemoresistance. Recent studies of combination DNMTi and histone deacetylase inhibitors (HDACi) in solid tumors has revealed little clinical response in patients with mCRC (no responses out of 47 enrolled) or in triple-negative breast cancer (no responses in thirteen enrolled); a single response was observed in hormone receptor positive breast cancer (6, 7). Similar results were seen in the phase I/II trial of combination DNMTi and HDACi in lung cancer, where only two of 19 patients treated showed objective responses. However, long-term follow-up showed possible prolonged median OS compared with historical controls, and further assessments revealed that multiple patients among this heavily pretreated cohort had major objective responses to subsequent systemic treatments, suggestive of a priming mechanism for chemotherapies (5). The reversal of treatment resistance has been best demonstrated in patients with ovarian cancer. In early-phase trials, treatment with low-dose decitabine leads to global demethylation in tumor cells, alongside changes in specific cancer pathways, including mismatch repair, WNT, and apoptotic pathways (16). When epigenetic agents were combined with platinum-based therapy in phase I/II studies, both decitabine and belinostat led to PR/stable disease in 46% and 44% in platinum-resistant ovarian cancer patients, recommending studies on a larger scale to better understand the clinical effect (17, 18). A randomized phase II study of guadecitabine with carboplatin in ovarian cancer compared with physician choice showed a non-significant trend to improvement in 6 month PFS (37% vs 15%), median PFS (16.3 vs 10.9 months) and OS (11 vs 7.4 months) (19). In advanced, pretreated colorectal cancer, Overman and colleagues reported 65% stable disease rate for a hypermethylator-phenotype enriched population with azacitidine and oxaliplatin and fluorouracil therapy (20). A second study of decitabine and the anti-EGFR targeted agent panitumumab in KRAS wild-type patients showed similar benefit rate in 20 patients, but no differences based on prior anti-EGFR exposure (21).

For this trial we targeted a patient with mCRC based upon work in our group demonstrating the ability of DNMTi to reverse irinotecan resistance in both resistant colon cancer cell lines and mouse models (10, 22). There is no well-accepted upon mechanism
that has explained irinotecan resistance (23, 24). It has been hypothesized that that methylation of DCR1 and WRN, the latter being a DNA helicase, may affect sensitivity to irinotecan, but confirmatory studies to validate these findings in clinical data sets have not been successful (9, 25–27). The multifocal effects of epigenetic therapies, such as guadecitabine, that result in widespread changes in gene expression across hundreds of cellular pathways, may well be responsible for reversing resistance to cytotoxic chemotherapies, but also create great barriers in understanding the mechanisms behind these effects (28–30).

Expected hematologic and gastrointestinal toxicities were seen throughout the trial, but treatments were better tolerated when combined with mandatory growth factor support. Notably for this refractory group of patients with prior oxaliplatin and irinotecan exposure, subjects remained on trial for a median of 4.5 cycles and had a median OS 10.7 months. Based upon this information, the decision was made between participating investigators, with the support of the Stand Up 2 Cancer Van Andel Research Institution and Astex Pharmaceutics to move to a randomized phase II study comparing this regimen to regorafenib or TAS-102 (NCT01896856).

Figure 2.
Percent change in RECIST lesions as compared with baseline. Tumor responses were measured every 8 weeks. The values shown are the percentage change in the sum of the longest diameters from baseline measurements of each measurable tumor. One patient (who remained on trial for 18 cycles by the time of data-lock) developed multiple new liver lesions on first scan, which were thought to have developed between scan and initiation of trial due to profound decrease in CEA. The patient continued to have a partial response but developed growth of a single liver lesion that was subsequently radiated. One patient had an increase of RECIST target lesions from 12 to 24 mm upon first reevaluation; however, the burden of disease was in a nontarget lesion (omental caking) and so decision was to proceed for two further cycles until disease progressed.

Figure 3.
Mean percent change in LINE-1 methylation in circulating DNA at CpG1-3 as compared with baseline levels on C1D1. LINE-1 methylation is measured at CpG1-3 in circulating tumor DNA on days 1, 8, and 15 of cycles 1 and 2, and on the first day of cycle 3 for 20 patient specimens. Average methylation changes as compared with baseline were calculated according to dose of guadecitabine (30 or 45 mg/m², whereby DLs –1 and –1G, and 1 and 1G have been combined). Standard deviation for 30 mg/m² was 3.7, and for 45 mg/m² was 4.6.
Phase I trials also allow for preliminary biomarker evaluations to assess molecularly targeted effects. While allowing for proof-of-concept studies, the role of biomarker studies in early oncology trials is difficult in part due to the hardship of obtaining tissue samples and the high cost of analysis (31). For epigenetic agents the global impact upon multiple targets makes it particularly difficult to identify which pathways are most relevant. Additionally, as seen in our trial, appropriate timing of sampling biopsies can potentially alter the apparent effectiveness of biomarker evaluation. Although there was no specific demethylation patterns in tumor samples by day 8 of treatment, the circulating DNA showed delayed and dose-dependent demethylation by the middle of cycle 2. These data recommended amendments to our phase II protocol for scheduling later biopsies, which will potentially allow for more useful comparisons of on-target epigenetic mechanisms of action with clinical response (32–34). Our experience reflects the importance of preliminary biomarker studies for helping to inform studies in subsequent trials.

The future of epigenetic therapy is wide ranging and a number of trials evaluating their efficacy in combination with systemic chemotherapy in other disease types are now underway. In particular, the impact of epigenetic therapy upon a wide number of gene targets may make it a strong companion treatment to checkpoint blockade and other immunotherapies (35–37). Multiple groups including ours have reported on the potential of DNMTi, HDACi, and emerging epigenetic modulating agents to modulate the tumor microenvironment, including increased co-stimulatory molecule expression, MHC class I/II and neoantigen expression, and affecting polarity of immune cells to a proinflammatory phenotype (16, 35, 36, 38, 39). Clinical trials using epigenetic drugs to prime for immunotherapy agents are ongoing as a major research area for this class of agents, including in mCRC. In breast cancer, the epigenetic modulator entinostat, a histone deacetylase inhibitor, has been shown to significantly improve survival in combination with hormonal therapy in hormone-resistant disease in a pivotal randomized phase II study, now being validated in a large, randomized phase III study (NCT02115282; ref. 40). However, epigenetic therapy is unlikely to play a role in all disease groups, and it will be important to identify molecular and clinical characteristics of patients likely to respond in order to better personalize future therapies (41–43).

We report the results of a phase I study evaluating safety, pharmacokinetics, and activity of the combination guadecitabine and irinotecan in mCRC. We determined that the phase II dose was guadecitabine at 45 mg/m² on days 1 to 5 and irinotecan at 125 mg/m² on day 8 and 15 with mandatory growth factor. A phase II study of guadecitabine and irinotecan versus standard of care (TAS-102 or regorafenib) supported by the Van Andel Research Institute-SU2C Dream Team is currently underway.

**Disclosure of Potential Conflicts of Interest**

J.S. Wang reports receiving speakers bureau honoraria from AstraZeneca. H.M.W. Verheul is a consultant/advisory board member for GlycoTrend. G.J. Rosner reports receiving other remuneration from Novartis. N. Ahuja reports receiving commercial research grants from Astex and holds ownership interest (including patents) in Cepheid. No potential conflicts of interest were disclosed by the other authors.

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**Acknowledgments**

We would like to thank all the patients and their caregivers that participated in this study and Ross Donehower for his clinical care of patients on the study. Van Andel Research Institute-SU2C Epigenetics Dream Team, Astex Pharmaceuticals, R3S Grant: R3S/CA209859

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Received February 5, 2018; revised April 29, 2018; accepted August 7, 2018; published first August 10, 2018.

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A Phase I Trial of a Guadecitabine (SGI-110) and Irinotecan in Metastatic Colorectal Cancer Patients Previously Exposed to Irinotecan

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