A Phase I/II Study of GTI-2040 Plus Docetaxel as Second-Line Treatment in Advanced Non-small Cell Lung Cancer

A Study of the PMH Phase II Consortium

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Introduction: GTI-2040, an antisense oligonucleotide, targets the ribonucleotide reductase R2 subunit, critical for DNA synthesis. This study determined the recommended phase II dose (RP2D) of docetaxel plus GTI-2040, toxicity, and response rate in advanced non-small cell lung cancer (NSCLC).

Patients and Methods: Advanced solid tumor patients, preferably with platinum-treated NSCLC, performance status 0 to 2, no symptomatic central nervous system metastases, adequate organ and bone marrow function, and ≥1 prior chemotherapy regimen were treated with escalating doses of GTI-2040 given by 14-day continuous intravenous infusion (CVI) plus docetaxel every 21 days.

Results: Twenty-nine patients were treated, (24 NSCLC, 3 hormon-refractory prostate cancer, 1 head and neck, and 1 small cell lung cancer). GTI-2040 5 mg/kg as CVI for 14 days plus docetaxel 75 mg/m² intravenously every 21 days was determined as the RP2D. Dose-limiting toxicity was not seen. Two patients at RP2D developed grade 4/5 febrile neutropenia. One prostate specific antigen response was seen in phase I, but no objective tumor responses in the NSCLC patients. Median time to progression was 3.4 months, 3.2 months in the NSCLC patients treated at RP2D.

Conclusions: Activity of the combination at RP2D, GTI-2040 5 mg/kg/d × 14 days by CVI plus docetaxel 75 mg/m² does not seem superior to docetaxel alone in previously treated NSCLC.

Key Words: Antisense oligonucleotide, Lung cancer, Second-line, Docetaxel, GTI-2040, Ribonucleotide reductase, R2 subunit.

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Lung cancer is the most common cause of cancer-related mortality in North American men and women, and annually, it causes more deaths than colorectal, breast, and prostate cancer combined.1,2 The majority of patients are diagnosed with non-small cell lung cancer (NSCLC), and approximately two-thirds of these present with locally advanced or metastatic disease. Median survival in advanced NSCLC with systemic treatment is 8 to 10 months. After failure of platinum-based chemotherapy, second-line treatment with docetaxel in good performance status patients is associated with a median survival improvement of 3 months compared with best supportive care (7 versus 4 months), and improved symptom control.3 However, the response rate of second-line docetaxel, and agents like pemetrexed or erlotinib, is only 6 to 10% in randomized trials.3–6 There is a clear need for novel anticancer treatments to improve the outcome of this disease.

Ribonucleotide reductase (RNR) is an enzyme that is required in the reductive conversion of ribonucleotides to deoxyribonucleotides during G1/S phase, a rate-limiting step during DNA synthesis and repair. RNR is critical in cell proliferation, and inactivation of the enzyme results in inhibition of DNA synthesis, cell cycle arrest, and apoptosis.7,8 R2 can cooperate with ras, mitogen-activated protein kinase, and other signaling pathways to enhance malignant potential. R2 subunit overexpression seems to enhance oncogenic transformation through v-src, A-raf, c-myc, v-fms, and v-fes.9 Its expression may also increase drug-resistant properties of tumor cells.10 Thus, RNR and its R2 subunit are attractive targets for the anticancer drug development.

A GTI-2040 is an oligonucleotide antisense molecule complementary to the mRNA encoding the R2 subunit of RNR. It has been shown to inhibit growth of human lung and other tumor cell lines in vitro in a dose-dependent fashion.11
Its antitumor activity has been observed in various human tumor types using severe combined immune deficiency or nude mouse models, including lung cancer. Efficacy against chemotherapy-resistant tumors has also been documented, and it decreases the RNR R2 mRNA expression in cell lines, with maximal inhibition at concentrations of 0.2 μM, with arrest in early G1/S cell cycle progression. In the phase I study of single agent GTI-2040, the recommended phase II dose (RP2D) was 5 mg/kg given by continuous infusion for 21 of 28 days. Disease stabilization was seen in 4 of 21 evaluable patients. Dose-limiting toxicities included hyperbilirubinemia, transaminitis, and fatigue.

Docetaxel, a mitotic spindle poison, arrests cells in G2/M phase, and it is an accepted standard for the second-line treatment of advanced NSCLC. Although a phase I study of single agent GTI-2040 in lung cancer has not been performed, preclinical data suggest that it may have activity against NSCLC, even in the setting of chemotherapy-resistant tumors. Given the differing mechanisms of action and toxicity profiles of docetaxel and GTI-2040, we set out to examine the combination using a phase I/II trial design. The study objectives were to determine the RP2D of GTI-2040 in combination with docetaxel in recurrent, metastatic, or advanced NSCLC; to assess the objective tumor response rate of the combination in pretreated NSCLC; to assess toxicity, stable disease rate, time to disease progression, duration of response, and disease stabilization of the combination; to investigate the pharmacokinetic parameters of GTI-2040 when given in combination with docetaxel; to measure the baseline and posttreatment levels of RNR activity in peripheral blood mononuclear cells; and to explore the relationship between these potential correlative endpoints and clinical outcome.

PATIENTS AND METHODS

This multicenter study was sponsored by the National Cancer Institute (NCI) CTEP at three participating centers in the Princess Margaret Hospital Phase II Consortium, (Princess Margaret Hospital/University Health Network, Toronto; Juravinski Cancer Centre, Hamilton; Ottawa Hospital Regional Cancer Centre, Ottawa). All participating institutions received institutional research ethics board approval to conduct this study.

Patient Selection

For the phase I dose escalation portion of the study, patients with histologic or cytologic confirmation of advanced solid malignancies were eligible to participate if they had received up to one line of prior chemotherapy for advanced disease. For the phase II portion, eligible patients were required to have recurrent, metastatic, or advanced NSCLC, which was not amenable to curative or radical treatment. They were required to have received one regimen, (but not more than one), of prior chemotherapy for NSCLC. Prior endothelial growth factor receptor inhibitor therapy, endocrine therapy if appropriate (phase I), radiotherapy, and surgery were permitted, but therapy must have been discontinued at least 4 weeks before study entry. Prior docetaxel therapy was not permitted. Patients were required to have measurable disease, Eastern Cooperative Oncology Group performance status ≤2, age ≥18 years, life expectancy >3 months, adequate hematopoietic (neutrophils ≥1.5 × 10^9/L), hepatic and renal function, and normal coagulation parameters. Patients with symptomatic or progressive brain metastases, coagulopathy or therapeutic anticoagulation, pre-existing neuropathy > NCI common toxicity criteria grade 2, uncontrolled comorbid illness, contraindication or allergy to study treatment, HIV infection receiving antiretroviral therapy, and pregnant or lactating women were excluded. All patients provided written informed consent to participate in the study according to institutional guidelines.

Study Design

The GTI-2040 was administered as a continuous intravenous infusion (CVI) for 14 days starting on day 1 of each cycle, followed by a 7-day break. This was amended from the single-agent administration of 21 days by CVI followed by a 7-day break, to synchronize with standard 3-weekly docetaxel administration, and to permit recovery from potential overlapping toxicity. Docetaxel was administered intravenously more than 1 hour on day 3 of cycle 1 (for pharmacokinetic assessment), but on day 1 for subsequent cycles, with standard dexamethasone premedication. Each cycle was defined as 21 days, and dose escalation was based on safety data from the first cycle of each cohort. The GTI-2040 was supplied by the NCI CTEP, Division of Cancer Treatment and Diagnosis, under a Clinical Trials Agreement with Lorus Therapeutics Inc. (Toronto, Canada), and it was provided as injection in glass vials containing 500 mg per vial. Docetaxel is commercially available (Sanofi-Aventis Pharmaceuticals, Inc.) and was sourced locally for this study. The planned dose levels are shown in Table 1. Based on the GTI-2040 single agent RP2D of 5 mg/kg/d, dose escalation to this maximum dose was planned, in combination with standard dose docetaxel 75 mg/m^2 IV every 21 days.

For phase I, three patients were enrolled in each dose level. If no dose-limiting toxicities were seen during the first 21-day cycle, three patients were enrolled at the next dose level. If one patient experienced dose-limiting toxicity, an additional three patients were to be enrolled at that dose level. If two or more of six patients experienced dose-limiting toxicity at any dose level, this would be considered the

<table>
<thead>
<tr>
<th>TABLE 1. Dose Escalation Scheme</th>
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<td>Level</td>
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<tr>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
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DLT, dose-limiting toxicity; SD, stable disease; PD, progressive disease; NE, not evaluable; NSC, non-small cell lung cancer; SC, small cell lung cancer; HRPC, hormone refractory prostate cancer; H&N, head and neck cancer.
maximum tolerated dose, and the dose level below would be considered the RP2D. If no dose-limiting toxicity occurred at the highest planned dose level, this would be considered the RP2D.

Toxicities were graded according to the NCI common toxicity criteria Version 2.0. To be considered dose-limiting, toxicity had to occur during the first cycle of therapy and be deemed at least possibly related to protocol treatment. Dose-limiting toxicity was defined as following; grade 4 neutropenia lasting more than 7 days; febrile neutropenia ≥ grade 3; platelet count <25 x 10^9/L; thrombocytopenia resulting in grade ≥2 hemorrhage; grade ≥3 infection with grade ≥3 neutropenia (<1.0 x 10^9/L); grade 3 or 4 nonhematologic toxicity except alopecia, nausea, emesis, diarrhea (unless persistent despite preventive therapy); and inability to administer cycle 2 day 1 of combination within 2 weeks of completing previous cycle.

**Patient Evaluation**

All patients were required to have baseline history and physical examination, performance status assessment, hematology, biochemistry, coagulation, pregnancy test for women of childbearing potential, and toxicity assessment within 7 days of starting treatment. Computed tomography of chest and abdomen and other scans as necessary to document disease were required within 28 days of starting therapy.

On treatment, patients underwent a history, physical examination, and toxicity evaluation on day 1 of each cycle, and weekly hematology and biochemistry during cycles 1 and 2, and on day 1 of subsequent cycles. Tumor imaging was repeated every 6 weeks or sooner if clinically indicated.

All patients who completed at least one treatment cycle were considered evaluable for response, and all patients who received at least one dose of either GTI-2040 or docetaxel were evaluated for toxicity. Tumor response and progression were evaluated using the response evaluation criteria in solid tumors. Complete or partial responses required confirmation at least 4 weeks after initial documentation.

**Dose Modifications**

To receive full dose treatment on day 1, patients were required to have an absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, bilirubin ≤1.5 x upper limit of normal, aspartate transaminase/alanine aminotransferase ≤3.5 x upper limit of normal, and nonhematologic toxicity grade ≤2. Treatment was withheld until any toxicity resolved to grade 2 or less. Patients could be rechallenged on recovery with reduced doses of therapy at the investigator’s discretion, even after dose-limiting toxicity.

Treatment was discontinued in the case of serious or unacceptable toxicity, or by patient request. Otherwise duration of therapy depended upon best response, with termination of treatment if progression, ongoing treatment if partial response or stable disease, until evidence of progressive disease, and if complete response was documented, a maximum of two cycles after confirmation of complete response.

**Pharmacokinetics**

Plasma samples for analysis of GTI-2040 were collected during the first 3 cycles of therapy, at the following time points: cycle 1 day 1 pretreatment at 2, 4, 8, 24, and 48 hours, (predocetaxel), day 15 (end of GTI-2040 infusion); cycles 2 and 3, day 1 pretreatment (trough), day 15 (end infusion), and cycle 4, day 1 pretreatment. These samples were analyzed by high-performance liquid chromatograph methodology developed by Zhang et al., and plasma pharmacokinetic variables calculated using noncompartmental methods.

**Pharmacodynamics**

Peripheral blood mononuclear cells were collected at baseline from fresh blood samples for patients treated at RP2D and on day 3 of GTI-2040 single-agent therapy in cycle 1. Total RNA was extracted and analyzed for mRNA expression of RNR subunits (ribonucleotide reductase M1 (RRM1) and RRM2) and for housekeeping genes (HuPo and TATA box binding protein) by real-time polymerase chain reaction using the ABI 7900 HT Sequence Detection System 2.1, and these methods are further described in Juhasz et al. The RNA extracted from patient’s peripheral mononuclear blood cells was quality assured by Agilent 2000 Bioanalyzer. Only higher quality RNA samples were used for Real Time polymerase chain reaction assay.

**Statistical Methods**

It was estimated that approximately 12 to 18 patients would be required to complete the dose-escalation or phase I portion of the study. The phase II portion of the study was designed to declare the treatment active if the true objective response rate was at least 20%, and to declare the treatment inactive if the true objective response rate was at most 5%. Thus, the design parameters were set to be P0 = 0.05, P1 = 0.20, α = 0.10, and β = 0.10 and the optimal design of Simon used. The treatment would be declared active if 4 or more of 32 evaluable patients responded. Only NSCLC patients treated at the RP2D in the dose-escalation phase would be included in response assessment for the phase II component of the study. The study was to be stopped early if none of the first 18 patients assessed in phase II responded.

Descriptive statistics, such as the median, frequency, and proportion, were used to summarize the cohort of patients along with 95% confidence intervals (CIs) where possible. The Kaplan-Meier method was used to estimate time to progression and survival statistics. Overall survival was calculated from the date the patient first received study treatment until the date of death or last date the patient was known to be alive. Time to progression was calculated from the date the patient first received study treatment until the first date of progression. Patients who were removed from treatment due to an adverse event were censored in the time to progression analysis on the date they came off of treatment.

**RESULTS**

**Patient Characteristics**

Twenty-nine patients entered the study, 15 in the dose escalation phase including four NSCLC patients treated at RP2D, (Table 1), and an additional 14 NSCLC patients treated at RP2D in phase II. Two centers (Princess Margaret...
Hospital, Ottawa Hospital Regional Cancer Centre) participated in the dose escalation phase, and all three centers in the phase II portion. Patient characteristics are listed in Table 2. All NSCLC patients had received prior platinum-based therapy, one as adjuvant treatment. Two NSCLC patients treated at the RP2D had received prior therapy with endothelial growth factor receptor tyrosine kinase inhibitors. All three patients with prostate cancer in the dose escalation phase were chemonaive.

Dose Escalation

Three patients were enrolled into the first dose level, four into the second, and eight were treated at the RP2D in the phase I portion of the study. No patient experienced toxicity that was defined as dose limiting. The maximum tolerated dose was not reached, and the RP2D was declared as 5 mg/kg/d of GTI-2040 for 14 days by CVI plus docetaxel 75 mg/m² intravenously on day 1 for every 21 days. One patient in the second cohort experienced a malfunction of the CVI pump and may have received treatment at an accelerated rate. This patient was followed up for toxicity but not considered evaluable for response, and so a replacement patient was enrolled to that cohort.

Treatment Received

A total of 93 cycles of therapy were delivered to the 29 patients on treatment, 49 in the dose escalation phase (15 patients), and 44 cycles to the additional 14 NSCLC patients treated in the phase II portion. The median number of cycles received was 2 (range 1–7).

Safety

Adverse events during the first cycle of the dose escalation or phase I portion are listed in Table 3, with toxicity in all cycles of the first 15 patients listed in Table 4. As the doses of docetaxel and GTI-2040 increased during phase I, so did the incidence of fatigue, and grade 3/4 leukopenia and neutropenia. Significant toxicities beyond cycle 1 included two patients treated at RP2D who experienced febrile neutropenia. One patient developed *Enterobacter* bacteremia after three cycles of therapy; another patient with hormone refractory prostate cancer and obstructive uropathy developed urosepsis and expired in hospital after two cycles. Another developed grade 3 anemia, two had grade 3 hyperglycemia presumed secondary to dexamethasone premedication, and three developed central catheter-related thromboses. Based on the two patients with sepsis at RP2D beyond cycle 1, it was felt that the dose of GTI-2040 combined with docetaxel should not be escalated further to avoid incremental bone marrow suppression. Of the 18 NSCLC patients treated at the RP2D, 49 (89%) cycles were complicated by grade 3 or 4 toxicity (Table 5).

Efficacy

Twenty-six of twenty-nine patients were evaluated for response. One patient in the dose finding portion of the study (dose level 2) was not evaluated because of deviation from treatment administration (pump malfunction). One patient with prostate cancer treated at dose level 3 developed febrile neutropenia during cycle 2 was removed from study and was not evaluated for response. Another patient progressed clinically after cycle 1 and stopped therapy. No objective tumor responses were seen in either portion of the study. One prostate cancer patient treated at RP2D had a PSA response, and four others treated in the dose escalation phase had minor tumor shrinkage that did not meet partial response criteria by RECIST.

Twelve of eighteen NSCLC treated at RP2D had stable disease as their best response after cycle 2. Three had minor tumor regression that did not meet response criteria by RECIST (11–14% decrease).

The median time to progression was 3.4 months (95% CI: 2.6 months–not reached, Figure 1) in both portions of the trial. For NSCLC patients treated in the phase II, median time to progression was 3.2 months, (95% CI: 1.5 months–not reached).
Thirteen of the entire sample discontinued therapy for reasons of disease progression, five for reasons of toxicity, four stopped at patient request, six at investigator discretion, and one was withdrawn for incorrect treatment administration. Five patients completed six cycles of treatment, two at dose level 1, and three at dose level 3, including one patient with prostate cancer.

All patients have died. Median survival for the entire cohort was 8.6 months, (95% CI: 6.7–10.0 months) and 7.9 months (95% CI: 3.2–10.0 months) for NSCLC patients treated at RP2D. Survival at 6 months was 61.1% (95% CI: 42.3–88.3%), and 11.1% (95% CI: 3.0–41.0%) at 1 year for those treated at RP2D (Figure 2).

Pharmacokinetics

The average steady-state concentration of GTI-2040 during cycle 1 was 0.5 ± 0.2 μg/ml (range: 0.2–1.0 μg/ml) for patients at 3mg/kg dose level, and 1.6 ± 0.9 μg/ml (range: 0.2–4.7 μg/ml) for patients at 5 mg/kg dose level, (Figure 3). Given preclinical evidence of decreases in RRM2 subunit mRNA expression in human tumor cell lines at concentrations of 1.2 μg/ml, the steady-state concentration of GTI-2040 at the 5 mg/kg dose level seems to be sufficient, although intratumoral concentrations have not been assayed. There was no clear evidence that GTI-2040 levels were influenced by docetaxel administration.

### TABLE 4. Phase I Adverse Events, All Cycles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of Patients (n = 15)</th>
<th>No. of Cycles (n = 49)</th>
<th>No. of Cycles ≥ Grade 3 (n = 49)</th>
<th>No. of Patients Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>15 (100%)</td>
<td>45 (92%)</td>
<td>1 (2%)</td>
<td></td>
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<tr>
<td>Edema</td>
<td>3 (20%)</td>
<td>6 (12%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>9 (60%)</td>
<td>29 (59%)</td>
<td>0</td>
<td></td>
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<tr>
<td>Hyperglycemia</td>
<td>13 (87%)</td>
<td>37 (76%)</td>
<td>8 (16%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (47%)</td>
<td>10 (20%)</td>
<td>0</td>
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</tr>
<tr>
<td>WBC</td>
<td>14 (93%)</td>
<td>34 (69%)</td>
<td>15 (31%)</td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>12 (80%)</td>
<td>28 (57%)</td>
<td>18 (37%)</td>
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</tr>
<tr>
<td>Hemoglobin</td>
<td>14 (93%)</td>
<td>43 (88%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td>5 (33%)</td>
<td>8 (16%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Infection with neutropenia</td>
<td>3 (20%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3 (20%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

WBC, white blood cell; ANC, absolute neutrophil count.

### TABLE 5. Selected Adverse Events, in Patients Treated at RP2D (N = 18)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of Patients (n = 18)</th>
<th>No. of Cycles (n = 55)</th>
<th>No. of Cycles ≥ Grade 3 (n = 55)</th>
<th>No. of Patients ≥ Grade 3 (n = 18)</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>15 (83%)</td>
<td>47 (85%)</td>
<td>4 (7%)</td>
<td>4 (22%)</td>
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<tr>
<td>Nausea</td>
<td>12 (67%)</td>
<td>25 (45%)</td>
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<td>0</td>
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<tr>
<td>Dyspnea</td>
<td>10 (56%)</td>
<td>28 (51%)</td>
<td>5 (9%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9 (50%)</td>
<td>28 (51%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>5 (28%)</td>
<td>14 (25%)</td>
<td>14 (25%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (17%)</td>
<td>6 (11%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>3 (17%)</td>
<td>5 (9%)</td>
<td>1 (2%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Infection with neutropenia</td>
<td>1 (6%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>17 (94%)</td>
<td>49 (89%)</td>
<td>2 (4%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>WBC</td>
<td>16 (89%)</td>
<td>43 (78%)</td>
<td>24 (44%)</td>
<td>10 (56%)</td>
</tr>
<tr>
<td>ANC</td>
<td>12 (67%)</td>
<td>34 (62%)</td>
<td>26 (47%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Platelet</td>
<td>8 (44%)</td>
<td>14 (25%)</td>
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<td>1 (6%)</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1 (6%)</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>15 (83%)</td>
<td>36 (65%)</td>
<td>7 (13%)</td>
<td>3 (17%)</td>
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</tbody>
</table>

WBC, white blood cell; ANC, absolute neutrophil count; RP2D, recommended phase II dose.

FIGURE 1. Time to progression, non-small cell lung cancer (NSCLC) patients at RP2D (n = 18). RP2D, recommended phase 2 dose.

FIGURE 2. Overall survival, non-small cell lung cancer (NSCLC) patients treated at RP2D. RP2D, recommended phase 2 dose.
Pharmacodynamics

Peripheral blood mononuclear samples were collected from eight patients treated at RP2D, 7 with NSCLC, one with hormone refractory prostate cancer. There did not seem to be any relationship between RRM2 levels and duration of therapy, response, or toxicity in these eight patients.

DISCUSSION

The combination of GTI-2040 and docetaxel resulted in manageable toxicity, and it is unlikely that the dose of GTI-2040 could be escalated further without severe overlapping toxicities with docetaxel. The combination did not yield objective responses in pretreated NSCLC patients, although one prostate cancer patient had a PSA response. The time to progression of 3.2 months in the NSCLC patient cohort is consistent with the published literature in the setting of second-line single-agent docetaxel. The lack of objective responses is also consistent with docetaxel therapy, with an historical response rate of only 6 to 9% in the randomized trials of second-line treatment in NSCLC.3–6 The pharmacokinetic data suggest that although plasma levels of GTI-2040 achieved in this study would be expected to suppress RRM2 subunit activity, there is evidence of significant interpatient variability. Thus, higher doses of GTI-2040 may be required to ensure sufficient levels in all patients. Despite the small number of pharmacodynamic samples available, only one of eight patients demonstrated evidence of reduced RRM2 activity, again raising the question of insufficient dosing of GTI-2040.

It may be possible to further escalate dose by shortening the duration of GTI-2040 exposure, for example to 5 or 7 days by continuous infusion. It has been reported that RRM2 down-regulation occurs within 24 hours of GTI-2040 administration and is sustained over at least 7 days with continuous infusion.15,17 Marcucci et al. have been able to escalate to 7 mg/kg/d, in combination with cytarabine, over a shorter period in elderly patients with acute myeloid leukemia without significant additional toxicity.18 Achieving significant levels of R2 down-regulation over a 6-day infusion may render longer infusion periods unnecessary. Alternately, combination with less toxic agents like pemetrexed or erlotinib could permit further dose escalation of GTI-2040.5,6

Another question is whether the sequence of agents may impact on efficacy. Although initial preclinical studies suggested synergy with concurrent administration of GTI-2040 and taxanes, hence the concurrent administration used in the clinical trial, more recent studies suggest that the potential for chemosensitization by RRM2 down-regulation persists for up to 72 hours after the end of GTI-2040 treatment. Additional preclinical studies suggest that sequential rather than concurrent administration of the two agents may yield superadditive effects.19 However, this hypothesis would need to be tested clinically.

Antisense technology in drug development has the advantage of high specificity and selective gene inhibition, with the potential to maximize target inhibition while minimizing toxicity and off-target effects. However, the clinical development of antisense oligonucleotides has been limited by their short plasma half life, poor stability in physiologic fluids, and limited intracellular uptake. Although prolonged infusion may address the short half life of these compounds, these are inconvenient and may not ensure adequate tumor delivery of drug for target inhibition. Other antisense oligonucleotides have been evaluated in lung cancer, including aprinocarsen and oblimersen, antisense to protein kinase C-alpha and bcl-2, respectively.20–22 Despite promising preclinical data and minimal toxicity when added to chemotherapy, neither has yet been shown to improve lung cancer outcomes.

Finally, it may be that the RRM2 subunit is not an important target in NSCLC. Although critical for DNA synthesis, it is overexpressed in cancer cells and seems to facilitate signal transduction and oncogenic transformation through several pathways, it may not be a critical target in NSCLC. Other RNR inhibitors have met with variable success, such as hydroxyurea, which has minimal activity...
in lung cancer. By contrast, gemcitabine, which primarily inhibits function of the R1 subunit, has impressive single agent activity, and it is used as a standard agent in the first-line setting.

GTI-2040 combined with docetaxel at the tested dose and schedule demonstrates evidence of disease stabilization with some minor tumor responses. However, the addition of GTI-2040 does not show significant incremental benefit over docetaxel alone in pretreated NSCLC, though the numbers treated in this study are small. Further testing of this interesting compound should focus on differential sequencing, shorter duration of higher dose treatment, or an alternate agent for combination strategies.

ACKNOWLEDGMENTS

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