A Phase II Study of Concurrent Chemoradiation with Weekly Docetaxel, Carboplatin, and Radiation Therapy Followed by Consolidation Chemotherapy with Docetaxel and Carboplatin for Locally Advanced Inoperable Non-small Cell Lung Cancer (NSCLC)

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Introduction: The current standard of care for good performance status patients with locally advanced non-small cell lung carcinoma is concurrent chemoradiation, although a clearly superior regimen has not been identified. Docetaxel has been shown to possess good single-agent activity against non-small cell lung cancer (NSCLC) and radiosensitizing properties, both alone and synergistically with carboplatin. We undertook this phase II study to determine the safety and efficacy of weekly docetaxel-carboplatin and concurrent radiation therapy followed by docetaxel-carboplatin consolidation for the treatment of locally advanced NSCLC.

Methods: Sixty-seven patients having previously untreated stage IIIA or IIIB unresectable NSCLC were enrolled, with 61 patients evaluated for endpoints. Docetaxel 20 mg/m^2 IV infusion over 30 minutes followed by carboplatin area under the curve = 2 over 30 minutes was administered weekly during concurrent thoracic radiotherapy. After 3 week rest, consolidation docetaxel 75 mg/m^2 IV infusion over 60 minutes and carboplatin area under the curve = 6 over 30 minutes was administered every 3 weeks for two cycles. Concurrent thoracic radiation consisted of 45 Gy (1.8 Gy fractions 5 d/wk for first 5 weeks) followed by 18 Gy boost (2.0 Gy fractions 5 d/wk for 2 weeks) for a total dose of 63 Gy.

Results: One and 2 years overall survival rates were 45 and 20%, respectively. Progression free survival at 1 year was 27%. Median survival time was 12 months. Median time to progression was 8 months. The primary hematologic toxicity was leukopenia. The primary nonhematologic toxicity was esophagitis.

Conclusion: The administered regimen of weekly docetaxel-carboplatin and concurrent radiation therapy followed by docetaxel-carboplatin consolidation has acceptable toxicity profile. However, the overall survivals at 1 and 2 years are somewhat disappointing.

Key Words: Chemoradiation, NSCLC, Concurrent chemoradiation, Consolidation, Chemoradiotherapy, Non-small cell lung cancer, Docetaxel, Carboplatin.

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Lung cancer is the third most common noncutaneous neoplasm and most common cause of cancer related deaths in the United States.[1] Non-small cell lung cancer (NSCLC) represents approximately 75 to 80% of lung cancer cases, and often presents at an advanced stage (stage III-IV) that is usually beyond surgical intervention. Previously, the standard of care for patients with such presentation was a 4 to 6 week course of thoracic radiation therapy. It allows for excellent local control of thoracic-related symptoms including hemoptysis, airway obstruction, dyspnea, and chest pain. However, radiation therapy alone is limited in its long-term effectiveness, with median survival times (MSTs) of less than 10 months after disease presentation, and 5-year survival rates of 5 to 8%.[2] Such low survival emphasizes the need for novel therapeutic regimens for the treatment of NSCLC. One strategy is the use of chemotherapy and radiation with the intent of rendering tumors resectable. However, when resection is not an option the challenge becomes to maximize the remaining therapeutic options to provide greater disease control and increase overall survival.

Many novel clinical investigations have sought to improve the survival of stage III NSCLC by combining chemotherapy with thoracic radiation. Early randomized trials failed to show any clear benefit of combined chemotherapy/radiation regimens over thoracic radiation alone. However, the introduc-

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tion of platinum-based chemotherapy regimens resulted in significant survival advantages when combined with thoracic radiation therapy versus radiation therapy alone. In patients with locally advanced, unresectable stage III NSCLC, such combinations resulted in MSTs of 13 to 14 months, and 5-year survival rates as high as 15 to 20%, almost tripling survival from radiotherapy alone.[3–6] Furthermore, a number of trials and a meta-analysis have shown that concurrent chemoradiation affords superior outcomes compared with sequential chemoradiation when using similar chemotherapy regimens, although the toxicity profile may be more severe in concurrent therapy.[7–11] Although no clearly superior treatment regimen exists for advanced NSCLC, combined modality treatment—particularly concurrent chemoradiation with a platinum-containing agent—is the current standard of care for unresectable stage III NSCLC. It is thought that the advantage conferred by concurrent treatment is due to radiosensitizing effects of chemotherapy and improved local control that translates into clinically significant increases in overall survival.

To that end, a number of other chemotherapeutics have been investigated for combined modality treatment. The taxanes are a novel class of chemotherapeutic agents that possess good activity as single agents in the setting of NSCLC.[12,13] The Locally Advanced Multimodality Protocol trial investigated the use of taxanes through three separate arms of sequential therapy, induction/concurrent therapy, or concurrent/consolidation therapy using a regimen of paclitaxel, carboplatin, and thoracic radiation. Results showed a median survival of 16.1 months for concurrent/consolidation arm, 12.7 months for induction/concurrent therapy, and 13.0 months for sequential therapy.[14] A number of other trials have investigated the use of paclitaxel and carboplatin in combined modality therapy for NSCLC with encouraging results and similar MSTs.[15–18]

Docetaxel has a mechanism of action similar to paclitaxel in its ability to stabilize microtubules by promoting microtubule assembly and inhibiting microtubule depolymerization. Several preclinical studies have shown docetaxel and paclitaxel to possess radiosensitizing effects.[19–22] It is thought that they exert their radiosensitizing effect by cell cycle synchronization at the G2/M phase, a particularly radiosensitive point of the cell cycle. However, docetaxel differs from paclitaxel in a number of important ways. Although both have been observed to induce p27, docetaxel causes greater phosphorylation of the proapoptotic Bcl-2.[23] Docetaxel exhibits activity in cisplatin-resistant and paclitaxel-resistant cell lines,[24–26] as well as higher uptake and accumulation in tumor cells, greater affinity for microtubulin, and slower cytoplasmic efflux than paclitaxel.[27–29] Docetaxel also possesses stronger antiangiogenic properties than paclitaxel.[30]

These observations have led to trials investigating the safety and efficacy of docetaxel in multimodality treatment. Trials have examined the use of docetaxel as consolidation therapy,[31,32] or for use in concurrent chemoradiation as single agent or part of platinum-containing doublets.[33–35] Here, we report the results of a phase II study designed to explore the potential benefits of concurrent weekly docetaxel/carboplatin and thoracic radiation therapy followed by consolidation docetaxel/carboplatin on overall response rate, survival, progression-free survival, safety, and toxicity in patients with locally advanced NSCLC.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically documented inoperable stage IIIA or IIIB NSCLC without evidence of malignant or exudative pleural effusion were eligible for this study. All patients had measurable or assessable disease. Further eligibility criteria included: patient age $\geq$18 years; Eastern Cooperative Oncology Group performance status $\leq$1; no prior chemotherapy or radiotherapy; platelet count $\geq$100,000/μl; absolute neutrophil count (ANC) $\geq$1500/μl; hemoglobin $\geq$9 g/dl; total bilirubin within normal limits; aspartate transaminase or alanine aminotransferase could be up to 5 $\times$ institutional upper limit of normal (ULN) if alkaline phosphatase was $\leq$ULN, or transaminase level up to 1.5 $\times$ ULN if alkaline phosphatase is $\leq$2.5 $\times$ ULN, or transaminase level $\leq$ULN if alkaline phosphatase is $\leq$5 $\times$ ULN; a calculated creatine clearance of $\geq$50 ml/min per Cockroft-Gault formula; and a forced expiratory volume in 1 second $>$800 ml. Exclusion criteria included: known hypersensitivity to drugs formulated with polysorbate 80; peripheral neuropathy grade $\geq$2; any concomitant malignancy, brain metastasis, or uncontrolled, clinically significant medical or psychiatric disorder; pregnant or nursing women; and weight loss $\geq$10% body weight over prior 3 months. All patients signed an informed consent and received medical oncology and radiation oncology consult and approvals before study entry. Before initiation of protocol therapy, all patients underwent a complete history and physical examination; pretreatment laboratory tests including complete blood cell count (CBC) with differential and platelet count, chemistry panel, and serum pregnancy tests for females of child-bearing potential; screening 12-lead electrocardiograph; assessment of lung function by forced expiratory volume in 1 second; computed tomography (CT) or magnetic resonance imaging (MRI) of chest and upper abdomen to determine location, type, and size of measurable lesions; and screening brain CT or MRI. Positron emission tomography (PET) scanning was encouraged but not required for protocol treatment.

Treatment Plan

Eligible patients received treatment in an outpatient setting beginning with concurrent chemotherapy and radiotherapy delivered over a 7-week period. CBCs including differential and platelet counts were obtained weekly during periods of active study treatment. In cases of grade 4 ANC, minimum bi-weekly CBCs were obtained until documented ANC recovery to $\leq$ grade 1. Routine serum chemistries were collected every 4 weeks during concurrent chemoradiation and before the start of each consolidation chemotherapy cycle. A chest CT or MRI scan was repeated before administration of consolidation chemotherapy. Full supportive care, including transfusion of blood, blood products, antibiotics, and antiemetics was provided.

Chemotherapy

Docetaxel was administered as a 30-minute intravenous infusion weekly starting on day 1 for 7 weeks as part of concurrent therapy. Docetaxel was given at a dose of 20 mg/m^2/wk. Patients were premedicated with dexamethasone 4 mg × 3 doses, given 12 hours before docetaxel infusion, 1 hour before infusion, and 12 hours after infusion. Carboplatin was administered as a 30-minute intravenous infusion during concurrent therapy at a dose of area under the curve (AUC) 2 immediately after docetaxel infusion.

Consolidation chemotherapy was started after a 3-week rest period after concurrent therapy. Docetaxel was given at a dose of 75 mg/m^2 once as a 1 hour intravenous infusion followed by carboplatin AUC 6 given as a 30 minute intravenous infusion every 3 weeks for two cycles (1 cycle = 3-week period). Dexamethasone was given at a dose of 8 mg PO beginning 24 hours before docetaxel administration and every 12 hours thereafter for five doses. Antiemetic therapy with 5-HT$_3$ was given 60 minutes before consolidation chemotherapy.

Radiation Therapy

Radiation therapy began on day 1 of chemotherapy for all patients, after infusions of docetaxel and carboplatin. The target volume consisted of an original volume and a boost volume. Volumes were based on a planning CT taken before treatment. The original volume consisted of the complete extent of visible primary tumor with margins of 2.0 to 2.5 cm; lymph nodes in the original volume included ipsilateral hilum, superior mediastinum, and subcarinal nodes with margins of 2.0 cm. The ipsilateral supraclavicular nodes were included only for primary tumors involving the upper lobes and/or mainstream bronchus lesions. Inferior mediastinal nodes were included for patients with primary disease of lower lobe(s) or inferior mediastinal involvement. Contralateral lymph nodes were only included in patients with mediastinal, subcarinal, or contralateral hilar involvement. The boost volume consisted of the primary tumor volume, involved nodes, and nodes ≥2.5 cm in diameter only. Radiation therapy was delivered to the original volume as a total dose of 45.0 Gy administered as 1.8 Gy daily fractions 5 days a week over 5 weeks, followed by an additional 18.0 Gy to the boost volume delivered as daily 2.0 Gy fractions. Total dose was 63.0 Gy in 34 fractions over 7 weeks. The maximal dose allowed to any point in the spinal cord was 49 Gy.

Response and Toxicity Criteria

All toxicities were graded using National Cancer Institute Common Toxicity Criteria, version 2.0. Assessment of disease response occurred before cycle 1 of consolidation therapy and 2 months after completion of consolidation therapy, or at any time clinical signs were suggestive of progressive disease (PD). Patients with PD before consolidation were taken off study. Complete response was defined as the disappearance of all measurable and evaluable disease for at least 4 weeks. Partial response required a reduction of 50% in the sum of the products of the perpendicular diameters of all measurable lesions, or a 50% decrease (for assessable disease) lasting at least 4 weeks in the area of the tumor mass estimated by two independent observers.

Dose Modifications

No more than one dose modification of docetaxel and carboplatin (concurrent therapy reduced to 15 mg/m^2/wk and AUC 1.5, consolidation therapy reduced to 56 mg/m^2 and AUC 5) was allowed for any patient during therapy. If reduced, dose was not reescalated for subsequent dosages or cycles.

Statistical Methods

Sample size estimation was completed using a log-rank test. MST for the historical control group was estimated as 17 months. Using a two-sided type I error rate = 5%, 84 patients were needed to detect relative risk of 1.65 between historical control group and this study with 80% power. This power analysis was based on the assumptions that accrual time was approximately 18 months with additional 3 years follow-up time. With an assumed dropout rate of 5% in this study, final sample size was determined to be 80 patients. Overall survival was measured using the Kaplan-Meier method. Statistical analyses were completed suing S-Plus 6 and/or SAS statistical software.

RESULTS

Patient Characteristics

Between October 2004 and January 2007, 67 patients with locally advanced stage IIIA or IIIB NSCLC were enrolled in this study. Of the original 67 patients, 63 were deemed evaluable. Characteristics are summarized in Table 1. The sample consisted of 37 men and 26 women, with a median age of 64 years, ranging from 48 to 83 years. The majority of patients were white (82%) followed by African

TABLE 1. Characteristics of Enrolled Patients

	Number (%)
No. patients	67
Age (yr)	
Median	64.2
Range	48–83
Sex	
Male	40 (60)
Female	27 (40)
Baseline PS	
PS = 0	28 (42)
PS = 1	39 (58)
Histology	
Squamous	14 (21)
Adenocarcinoma	19 (28)
Large cell	2 (3)
Poorly differentiated	6 (9)
Unclassified	19 (39)
Stage	
IIIA	32 (48)
IIIB	35 (52)

PS, performance status.

American (12%). Twenty-seven patients (42%) had a baseline Eastern Cooperative Oncology Group performance status = 0, whereas 36 patients (58%) had performance status = 1. Approximately 48% of patients presented with stage IIIA disease, whereas 52% of patients had stage IIIB disease. The most common histologies were adenocarcinoma and squamous cell carcinomas.

Response, Survival, and Patterns of Failure

Approximately 75% of enrolled patients completed the entire protocol treatment including concurrent chemoradiation and all cycles of consolidation chemotherapy. Patients with PD during treatment were removed from protocol treatment but included in response analysis. Patients were also removed from protocol treatment if during treatment toxicity was deemed to be intolerable to the patient, or if unrelated medical circumstance dictated need for removal, but patients were followed with intent-to-treat. Two patients were not evaluable because of withdrawal before initiation of protocol treatment and not included in statistical calculations. The final number of patients evaluated for response was 61 patients. Of patients evaluable for response, 11% (7 of 61) showed a complete response to treatment, whereas 56% (34 of 61) showed a partial response. Approximately 10% (6 of 61) showed PD, and 23% (14 of 61) showed stable disease.

The MST was approximately 12 months (95% confidence interval 10.8–13.2 months). The median time to disease progression was approximately 8 months. One and 2 years overall survival was 45 and 20%, respectively. Progression-free survival at 1 year was 27%. Unresolved pleural or pericardial effusions were considered evidence of PD for response evaluation, at the discretion of the treating physician, irrespective of the subsequent outcome. Kaplan-Meier plots of progression-free survival and overall survival are shown in Figures 1 and 2, respectively.

There were 44 reported sites of failure. Among these, 22 (50%) were distant failures. Five failures occurred in the brain, representing 11% of first failure, or 23% of patients with distant sites of first failure. Six (14%) were both local and distant failures and 16 (36%) were local-regional failures.

Toxicity

All toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. Hematologic and nonhematologic toxicities are summarized in Table 2. Concurrent chemoradiation was generally well tolerated. Both leucopenia and neutropenia was relatively uncommon during concurrent or consolidative chemotherapy. Grade 3 or higher, leucopenia occurred most frequently (approximately 16%) followed by neutropenia (approximately 13%). Of nonhematologic toxicities, esophagitis of grade 3 or higher occurred in approximately 22% of patients. Pneumonitis was documented in three patients, all at grade 3. There was one potential grade 5 GI toxicity that is not verifiable because of lack of autopsy, however, treating physicians felt toxicity was unrelated to treatment and instead to PD. There were no episodes of grade 3 or higher neuropathy.

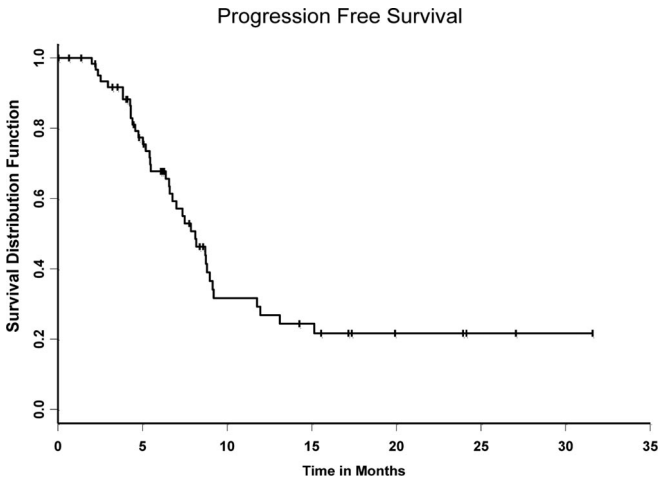

FIGURE 1. Kaplan-Meier plot of progression-free survival. Median time to disease progression was approximately 8 months.

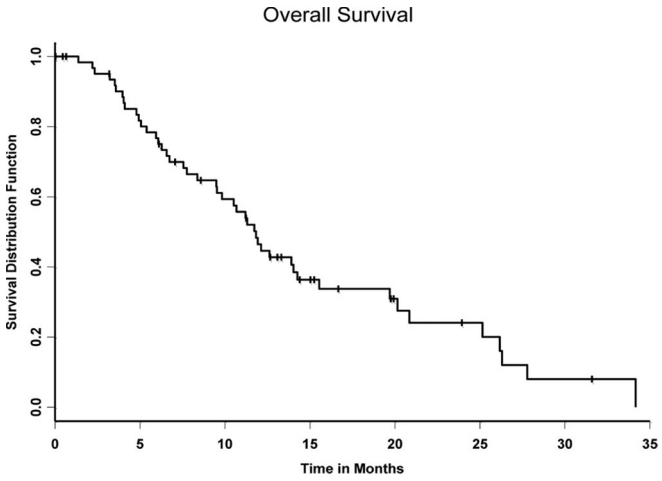

FIGURE 2. Kaplan-Meier plot of overall survival.

TABLE 2. Hematologic and Nonhematologic Toxicities

	Grade				
Acute Toxicity	**2**	**3**	**4**	**5**	**≥Grade 3 (%)**
Hematologic					
Anemia	10	4	0		5.97
Leukopenia	4	9	2		16.42
Lymphopenia	2	2	1		4.48
Neutropenia	2	4	5		13.43
Transfused: platelets		2			2.99
Nonhematologic					
Allergy	9	1			1.49
Skin		1			1.49
Dysphagia-esophagitis	2	12	3		22.39
Nausea	8	1			1.49
Vomiting	1	3			4.48
Diarrhea	1	1			1.49
GI-other		2	2	1	7.46
Infections	1	2	1		4.48
Pneumonitis	?	3			4.48

DISCUSSION

The treatment of locally advanced NSCLC remains a significant challenge to the clinician. Although a number of significant advances have been made in multimodality treatment of NSCLC, no clearly superior option has emerged for unresectable NSCLC. It is generally accepted that concurrent chemoradiation is the current standard of care, especially for patients with good performance status. However, there are many questions that remain to be answered, including the role of induction and consolidation chemotherapy. We undertook this study to investigate the safety and efficacy of a docetaxel-carboplatin doublet with concurrent thoracic radiation and consolidation docetaxel-carboplatin for the treatment of stage IIIA or IIIB NSCLC.

A number of trials have investigated the use of docetaxel and concurrent thoracic radiation therapy. Phase I studies have established 30 mg/m^2 docetaxel as the recommended dosage for use as single agent with concurrent radiation.[34,36,37] Phase I investigations of weekly docetaxel-carboplatin doublet chemotherapy and concurrent radiation recommended a lower dosage of docetaxel at 20 mg/m^2 and carboplatin AUC = 2 to maintain an acceptable toxicity profile.[35,38,39] We employed this dosage for use with concurrent thoracic radiation therapy, followed by 75 mg/m^2 docetaxel and carboplatin AUC = 6 for consolidation. One and 2 years overall survival rates were 45 and 20%, respectively. Progression free survival at 1 year was 27%. MST was 12 months. Median time to progression was 8 months. This outcome is less than anticipated for stage III NSCLC with combined modality therapy.

The use of induction or consolidation chemotherapy remains controversial. Two nonrandomized Southwest Oncology Group (SWOG) trials (9019, 9504) with identical enrollment criteria investigated the efficacy and safety of a cisplatin-etoposide chemotherapy regimen with concurrent thoracic radiation.[31,40] They differed in that SWOG 9019 followed concurrent therapy with cisplatin-etoposide consolidation, whereas 9504 used a three cycle docetaxel consolidation regimen. SWOG 9019 had a reported MST of 15 months and 5-year survival rate of 15%. However, SWOG 9504 had a MST of 26 months and a 5-year survival of 29%. It seemed that docetaxel consolidation conferred a significant and impressive advantage in survival. However, a recent phase III trial, HOG LUN 01-24/USO-023 randomized patients to cisplatin/etoposide concurrent chemoradiation and either docetaxel consolidation or observation, with primary endpoints of survival, and secondary endpoints of progression free survival and toxicity.[41] The results of this trial showed a median survival and 3-year survival rate of 24.1 months and 27.6% in the observation arm, and 21.5 months and 27.2% in the docetaxel arm, respectively. Additionally, there were significantly higher rates of febrile neutropenia, infection, pneumonitis, and hospitalizations in the docetaxel arm, thus bringing into question the efficacy and toxicity of docetaxel consolidation. The dosage of docetaxel used in the SWOG study was initially 75 mg/m^2, and allowed for dose escalation up to 100 mg/m^2 during the second and third cycles, whereas the HOG study used 75 mg/m^2 for three cycles.

In comparison, consolidation docetaxel-carboplatin has had limited evaluation. Sakai et al.[42] conducted a phase I/II investigation of bi-weekly docetaxel/carboplatin (30 mg/m^2 and AUC = 3)and concurrent TRT followed by consolidation docetaxel-carboplatin at same dosage. Results were encouraging with MST of 27 months, and 61% survival at 2 years, but more follow-up is needed. Our trial investigated the administration of docetaxel and carboplatin at dosages of 20 mg/m^2 and AUC = 2 during concurrent thoracic radiation followed by consolidation at dosage of 75 mg/m^2 and AUC = 6. The trials differed in a number ways. First, our trial evaluated a greater number of patients than the Sakai trial (61 versus 33 patients). Our results significantly differed in results of response and overall survival. There are a number of possible reasons for this difference. One potential factor is the accuracy in staging. Our trial enrolled during the PET era, unlike the Sakai trial. Our trial did not require PET scanning for enrollment, however, over 50% of patients enrolled in our trial were staged by PET, and of those staged by PET, there were approximately equal numbers of stage IIIA and IIIB patients. It is unlikely that the patients who did not receive baseline PET scanning were understaged. The Sakai trial enrolled a relatively high proportion of stage IIIB patients, equally distributed between T4 and N3 staging. Our trial had an approximately equal distribution between IIIA and IIIB patients, and of IIIB patients there was a slightly higher proportion of T4 staging as opposed to N3 staging. Our results were somewhat disappointing compared with the Sakai trial. It is possible that the higher dosages used during concurrent chemoradiation in their trial contributed to greater local control and impacted progression free and overall survival. However, the low number of patients evaluated in the Sakai trial argue against an absolute benefit. We used a higher dosage during the consolidation phase, still resulting in unacceptable response and survival. The advent of PET staging during the accrual of this trial would be expected to decrease the likelihood of previously unrecognized stage IV patients inadvertently entering the trial. There is no clear reason to explain the discrepancy in results between these two trials other than the lower sample size of the previous trial. Still, similar conclusions from these trials are reached in that the concurrent chemoradiation using traditionally available cytotoxic agents has unfortunately reached a plateau, highlighting the need for greater resources and investigation into novel treatment combinations, including targeted therapeutics.

In conclusion, our trial reported suboptimal response and overall survival outcomes. The regimen has acceptable toxicity profile, yet the overall survival and progression free survival is rather disappointing. This regimen does not seem to be active and we are not pursuing further investigation.

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