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ORIGINAL ARTICLE

# Treatment of Intractable Cancer Pain with Resiniferatoxin — An Interim Study

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## Abstract

**BACKGROUND** A substantial number of patients with advanced cancer suffer from refractory pain despite comprehensive medical management. In this article, we evaluate a nonopioid analgesic, resiniferatoxin (RTX), a potent agonist of the transient receptor potential vanilloid 1 (TRPV1) ion channel, which selectively interrupts nociceptive activity transmitted by a subpopulation of dorsal root ganglion neurons.

**METHODS** In this interim analysis of a first-in-human, open-label, Phase 1 study, 19 patients with refractory cancer pain localized to the abdomen and/or lower extremities received one dose of intrathecal RTX. The primary outcome was safety. Secondary outcomes were efficacy assessed over the course of the study using a numerical rating scale measuring the "worst pain" over a 24-hour period. This is a 0 to 10 scale where 0 is "no pain" and 10 is the "worst pain imaginable." Opioid consumption was measured as morphine equivalents used to control pain.

**RESULTS** Over 188 days after RTX injection, a total of 213 treatment-emergent adverse events (AEs) were reported among 19 patients treated, including 37 serious adverse events in 14 patients. Nine deaths occurred an average of 70 days after treatment (range from 11 to 140 days). Many of these events, including death, are consistent with the course of advanced cancer. At least one AE occurred in all 19 patients. Three patients experienced loss of heat sensitivity in the dermatomes exposed to RTX (grades I and II). Seven patients experienced urinary retention lasting more than 24 hours (three were grade III). Five patients had AEs related to a transient increase in the electrocardiographic QT interval that resolved within 24 hours (grades I and II). The only grade IV AE was an unstageable decubitus ulcer. RTX was associated with decreased "worst" pain intensity by 38% (pretreatment 8.4±0.4 vs. posttreatment 5.2±0.6) and reduced opioid consumption by 57% measured at posttreatment day 15.

**CONCLUSIONS** Intrathecal RTX is a single-administration, opioid-sparing analgesic in patients with intractable cancer pain. There were expected and unexpected AEs of various grades with an encouraging initial impact on pain. (Funded by the Intramural Research Program of the National Institutes of Health Clinical Center and others; ClinicalTrials.gov number, NCT00804154).

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# Introduction

Pain continues to be a primary concern and a major complication in up to 80% of patients with advanced cancer, with 25% of patients reporting unrelieved pain in the last week of life.[1,2] This pain is often refractory to standard of care treatments.[3] Most approved drugs for moderate to severe pain are nonsteroidal anti-inflammatory drugs and opioids, leaving a gap in pain control for patients unresponsive to these agents, and more effective treatments are needed.[4-6] This prompted the development of a new interventional palliative pain control agent, resiniferatoxin (RTX). RTX is a small, plant-derived molecule that is a highly specific agonist of the transient receptor potential vanilloid 1 (TRPV1) ion channel. TRPV1 is activated by noxious heat, capsaicin, inflammatory conditions, and tissue damage.[7,8] When administered intrathecally in the lumbar region, RTX produces a highly selective calcium overload in TRPV1+ sensory axons in the cauda equina that leads to a calcium-induced chemoaxotomy, thereby blocking peripheral nociceptive signals.[9-11] The high receptor specificity of RTX and the restricted expression of TRPV1 to a subpopulation of dorsal root ganglion neurons[12] lead to a selective analgesic action without affecting other peripheral nerve functions such as motor, touch, pressure, and proprioception. Similarly, central nervous system functions, such as respiratory functions or cognitive processes, are not impacted.[9,13] RTX has been shown to produce analgesia in preclinical animal models and veterinary pain studies[9,13-19] without noted adverse findings.

In this article, we report the interim results of a first-in-human Phase I clinical study in patients with intractable pain from advanced cancer to evaluate the safety and analgesic actions of the novel nonopioid agent RTX.

# Methods

## STUDY DESIGN AND OVERSIGHT

This report includes data from a pilot study and from a Phase I, single-site, non-randomized, open-label, dose escalation study using cohorts of three patients per dose tier (see dose escalation scheme, Supplementary Appendix, page 6). The starting dose was extrapolated from preclinical animal/toxicology studies and confirmed in the pilot study to evaluate feasibility and initial dosing (N=4 patients). The amount administered was escalated using a tapered dose escalation scheme, starting with a dose of 3 μg in the pilot, and 13 μg in the main study (0.1 μg of RTX/ml cerebrospinal fluid [CSF]), then increasing the dose in progressively smaller fractional increments to 26 μg, 44 μg, 64 μg, 92 μg, and 100 μg. Doses were planned for escalation in sequential groups of three patients until one escalation above the effective dose in 100% of patients ($ED_{100}$), completion of the 100-μg dose level, or the establishment of the maximum tolerated dose, whichever occurred first. If an effective dose was met in three of three patients without dose-limiting toxicity (DLT), the dose would be repeated, and if met in six of six patients, $ED_{100}$ would be reached, triggering a stopping rule. The maximum tolerated dose was defined as one dose level below the dose at which more than one patient demonstrated DLT. DLT was defined as the development of one grade III or higher agent-related toxicity in a patient, or two or more grade II agent-related toxicities in the same patient, occurring at any time from dosing through the day 15 visit. In addition, DLT was deemed to have occurred if all three patients in a cohort experience the same grade II agent-related adverse event (AE) of special interest lasting more than 24 hours: either thermal sensitivity reduction above the mid-chest level or transient urinary retention. Procedural hypertension was considered expected based on the preclinical observations,[15] and was not considered an agent-related AE for the determination of a DLT. The study was conducted in and sponsored by the Clinical Center at the National Institutes of Health (NIH). The study protocol was approved by the NIH Institutional Review Board (ClinicalTrials.gov number, NCT00804154). An independent data and safety monitoring board reviewed the study outcomes and safety and adjudicated dose escalation decisions. All authors attest to the completeness and accuracy of the data and the fidelity of the study to the protocol.

## PARTICIPANTS

Informed consent was obtained for all participants with a clinical and histologically confirmed diagnosis of metastatic cancer unlikely to be cured (see diagnoses in Table S1). Patients were included if they had signs of progressive disease after standard therapies, were not seeking curative therapies (e.g., chemotherapy or immunotherapy), and were experiencing severe refractory cancer pain at or below the T6 dermatome (average "worst" pain rating ≥6 using a 0 to 10 verbal numerical rating scale [NRS], with higher numbers indicating more severe pain). Participants were further evaluated by the Pain and Palliative Care and Medical Oncology Services to ensure that their pain was intractable despite the optimal use of standard analgesic treatments. The patency of the intrathecal space was confirmed by magnetic resonance imaging (MRI). A full



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list of eligibility criteria is provided in the Supplementary Appendix, pages 3–5.

### STUDY DRUG AND PROCEDURES

The study drug was formulated by the Pharmaceutical Development Center, Department of Pharmacy, Clinical Center, National Institutes of Health. The drug product was also provided by Sorrento Therapeutics, San Diego, California. To manage the acute burning sensation that RTX elicits on intrathecal administration, patients were anesthetized for the procedure. A spinal catheter was placed in the lumbar region (L3-S1, depending on patient anatomy; Table S2), and advanced 5 cm rostrally for RTX administration and CSF sampling. The parameters of injection volume, rate, and dose were investigated during the course of the study. The fifteen patients in the Phase I study received a single intrathecal administration of 13 μg or 26 μg of RTX diluted in an aliquot of the patient's CSF in a volume of 1 ml or 2 ml and injected over a duration of 30 or 60 seconds. Initially, injections were administered by timed manual injection. Subsequently, a syringe pump (Medfusion Model 3500, Smith's Medical, St. Paul, Minnesota) was used to precisely specify the volume and rate of the injection. After treating the first six patients, the volume and rate were modified to reduce CSF spread. The administration protocol was adjusted to 13 μg or 26 μg diluted in CSF to a total volume of 1 ml, infused over 2 minutes. See Figure 1 for study overview. Respiration, heart rate, and blood pressure were continuously monitored, and anesthesia was maintained for 2 hours postinjection. On discontinuation of anesthesia, patients were observed for 2 hours in the Post-Anesthesia Care Unit and subsequently transferred to the Intensive Care Unit overnight. The patients had no restrictions on analgesic medications at any point in the study period (see Table S3 for postinjection pain management, when needed).

### SAFETY ASSESSMENTS

The primary study objective was to evaluate safety, which was assessed through AE monitoring using the Common Terminology Criteria for Adverse Events, version 4.0. The posttreatment evaluation included a follow-up electrocardiogram (ECG), eye examination, and MRI of the spinal cord and brain. Safety monitoring was recorded until protocol completion (day 188).

### EFFICACY ASSESSMENTS

Two major secondary outcomes were examined: reduction in pain ratings and reduction in opioid use. Daily pain ratings were verbally assessed by an NRS.[20] Specifically, the data used were the answer to the question, "On a scale of whole numbers from 0 to 10, with 0 being no pain and 10 being the worst pain you can imagine, how would you rate your worst pain at or below the level of your chest from yesterday morning until this morning?" This "worst pain" component of the scale has been validated for capturing severe pain.[21] Pain intensity scores were averaged for a 4- to 7-day baseline preinjection period, and compared with the average of days 8 to 14 postinjection. The prespecified criteria for success included a 50% reduction in the "worst" pain rating or a 50% reduction in opioid use (in oral morphine equivalents) at day 15 relative to the 5 days prior to RTX injection. For pain ratings, this threshold is greater than the minimal clinically important difference, which is a reduction of either 2 points or 30% of the rating.[22]

Additional exploratory end points evaluated affective and sensory dimensions of pain captured for pretreatment versus day 15 (Figs. S2 and S3) as well as assessments of quality of life, functional impairment, cognitive abilities, and CSF neuron–specific enolase as a marker of target engagement (Figs. S4–S8).

## Results

### STUDY PARTICIPANTS

Thirty-four patients were recruited and provided informed consent. Nineteen patients were injected with RTX, the first four of whom were enrolled in a pilot feasibility study. All 15 study participants completed prespecified efficacy evaluations. The mean age of the study participants was 55.8 years (range 43 to 68 years); seven participants were female and eight participants were male. Entry pain intensity scores and cancer diagnoses are shown in Table 1. Of the 15 patients who were not treated, the most common reason leading to exclusion was marked disease progression (Fig. 1).

### SAFETY

A total of 213 treatment-emergent AEs were reported over the study period of 188 days, including 37 serious adverse events (SAEs) (Table 2). All treatment-emergent AEs are presented in Table 2 and summarized in the following section. Preliminary relatedness of some AEs is summarized because the relatedness was a major component of determining DLT (see section on DLT determination in the Methods). At least one AE occurred in all 19 (100%) patients. Fifteen of 19 patients (79%) experienced at least



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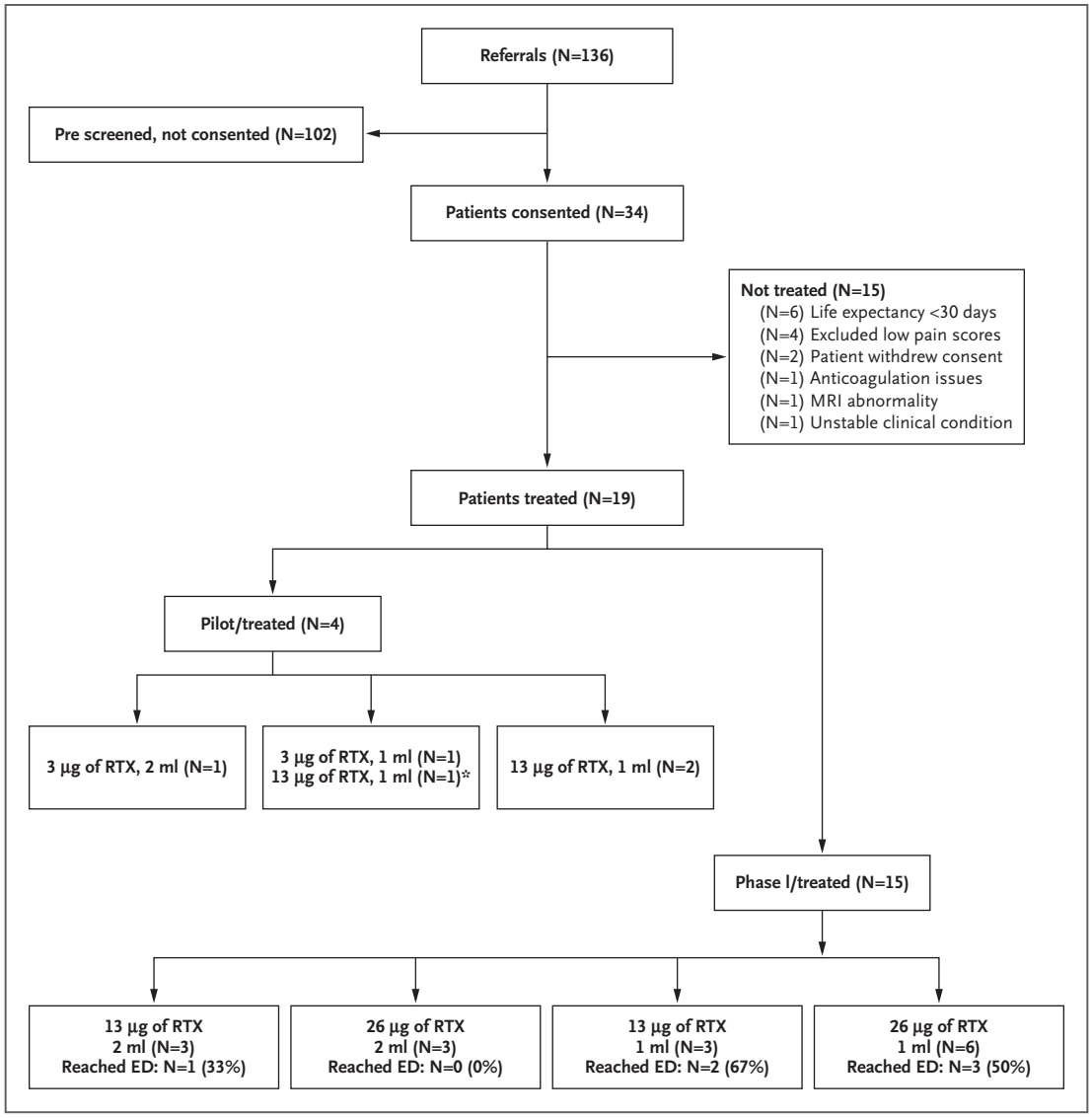


Figure 1. CONSORT Flow Diagram.

The first four patients were recruited to a pilot study to assess feasibility for the Phase I study. The first pilot patient received a 3-µg dose of resiniferatoxin (RTX). The second patient (marked with an asterisk) received an initial 3-µg dose, which was minimally effective, and per protocol was subsequently redosed at 13 µg. The remaining patients received only a single dose. After each set of three patients, dose escalation was considered if the effective dose was not met in all three patients, and no dose-limiting toxicity (DLT) was encountered. The effective dose was either a 50% reduction of "worst" pain ratings (measured pretreatment vs. days 8 to 14, averaged) and/or a 50% reduction in oral morphine equivalents during the same period. The first three patients in the Phase I study were dosed with a 2-ml formulation of 13 µg of RTX, followed by escalation to 26 µg in 2 ml. After these six patients, the volume was reduced to 1 ml and the dose escalation was restarted at 13 µg, proceeding to 26 µg in a 1-ml volume. DLT was met in one patient in the 26-µg dose (1-ml volume), leading to repeating this dose in three additional patients. CONSORT denotes Consolidated Standards of Reporting Trials; ED, effective dose; MRI, magnetic resonance imaging; RTX, resiniferatoxin.

one AE deemed to be possibly or probably treatment-related (Table S4). A common treatment-related expected AE was loss of heat sensitivity in the dermatomes exposed to RTX (lumbar distribution; grades I and II). This AE was classified as an AE of special interest when the loss of thermal heat sensation extended above the mid-chest region and lasted more than 24 hours. Three patients experienced this AE of special interest (each of the three had a different maximum



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**Table 1. Demographics of Patients.***

| Characteristic | 1 ml, 3–13 μg (N=4) | 2 ml, 13–26 μg (N=6) | 1 ml, 13–26 μg (N=9) | Total (N=19) |
|---|---|---|---|---|
| Median age (range) — years | 53 (45–61) | 57 (49–68) | 58 (43–63) | 57 (43–68) |
| Sex | | | | |
| Female — no. (%) | 2 (50) | 2 (33.3) | 5 (55.6) | 9 (47.4) |
| Male — no. (%) | 2 (50) | 4 (66.7) | 4 (44.4) | 10 (52.6) |
| Race or ethnic group — no. (%)† | | | | |
| Asian | 1 (25) | 0 (0) | 1 (11.1) | 2 (10.5) |
| Black | 1 (25) | 2 (33.3) | 2 (22.2) | 5 (26.3) |
| White | 1 (25) | 4 (66.7) | 6 (66.7) | 11 (57.9) |
| Hispanic or Latino | 1 (25) | 0 (0) | 0 (0) | 1 (5.3) |
| "Worst" pain intensity at entry — Mean±SD‡ | 7.5±1§ | 8.3±1.2 | 8.3±0.6 | 8.4±0.9 |

* Cancer diagnosis and lumbar level for resiniferatoxin injection are found in Supplementary Tables S1 and S2.
† Race was reported by participants.
‡ Pain scores were collected using the numerical rating scale, "worst" pain rating (or Brief Pain Inventory for the first four patients). These are both scales from 0 to 10 with 0 meaning no pain and 10 meaning the worst pain imaginable (2 points or 30% reduction from baseline, whichever is greater, is thought to be clinically meaningful). Higher numbers indicate more pain.
§ For the first four patients the "worst" pain scores were using a different instrument (the Brief Pain Inventory). The individual subscale ("worst pain") has similar characteristics to the numerical rating scale "worst" pain reported for other patients but cannot be directly compared.

severity: one grade I, one grade II, and one grade III). The second AE of special interest was urinary retention lasting more than 24 hours. Seven patients experienced urinary retention, two patients experienced grade I, two patients experienced grade II, and three patients exhibited grade III urinary retention (one patient with preexisting benign prostatic hyperplasia required readmission and a surgical procedure). Five AEs were related to a transient increase in ECG QT interval that resolved within 24 hours (grades I and II).

Two events in the study triggered changes in dose escalation. The first was a DLT determined by the data and safety monitoring board and study team to be possibly related to the volume and speed of administration. DLT was not reached in more than one patient in any three-patient cohort. For the dose of 26 μg given in a 2-ml volume, there was one grade III urinary retention requiring intervention. Following the recommendation of the data and safety monitoring board, the study team reduced the RTX injection volume to 1 ml and restarted dosing at 13 μg. For the 26 μg, 1-ml dose, one event (grade III urinary retention) met DLT as defined in the Methods, leading to a repeat of this dose tier in three patients, who did not experience additional DLT, and, therefore, 26 μg was not considered to be the maximum tolerated dose.

Acute hypertension and tachycardia are a known physiological response to RTX administration[15] and were monitored every 15 minutes in the operating room, and hourly thereafter for the first 20 hours after the procedure. Five AEs of hypertension were recorded in three patients, including three grade II events and two grade III events. These events resolved spontaneously or with standard care within 10 to 20 hours. The mean (95% confidence interval [CI]) systolic systemic arterial pressure was 106 mmHg (95% CI, 90 to 123) in the 1-ml group pre-RTX, reaching a maximum mean systemic arterial pressure of 147 mmHg (95% CI, 135 to 159) at 3 hours post-RTX; for the 2-ml administration volume pre-RTX the mean was 121 mmHg (95% CI, 106 to 136) and 161 mmHg (95% CI, 138 to 183) at 3 hours post-RTX (Fig. 2A). Diastolic blood pressure was 72 mmHg (95% CI, 60 to 84) in the 1-ml group pre-RTX, reaching a maximum of 94 mmHg at 15 minutes post-RTX (95% CI, 84 to 107); for the 2-ml administration volume pre-RTX the mean was 77 mmHg (95% CI, 58 to 95) and a maximum of 93 mmHg (95% CI, 70 to 115) at 15 minutes (Fig. 2B). Tachycardia did not trigger any AEs, but heart rate increased alongside blood pressure from an average of 74 beats per minute (bpm) (95% CI, 62 to 85) pre-RTX in the 1-ml group to a maximum of 88 bpm (95% CI, 75 to 101) at 3 hours post-RTX; in the 2-ml administration volume, heart rate increased from an average of 78 bpm (95% CI, 65 to 92) pre-RTX to a maximum of 93 bpm (95% CI, 76 to 111) at 3 hours post-RTX (Fig. 2B). Individual patient data are shown in Figure S1.

In total, 14 patients (74%) experienced an SAE (a total of 37 SAEs). The following SAEs were not considered to be DLT: one patient experienced multiple seizures in the postinjection period (see Discussion). There was a grade II decubitus ulcer approximately 10 days after RTX, which



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**Table 2. Adverse Events Occurring during the Study.***

| Event | Pilot | | 2 ml/13 μg | | 2 ml/26 μg | | 1 ml/13 μg | | 1 ml/26 μg | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Events | No. pt (%) | No. of Events | No. pt (%) | No. of Events | No. pt (%) | No. of Events | No. pt (%) | No. of Events | No. pt (%) | No. of Events | No. pt (%) |
| Any adverse event† | 28 | 4 (100) | 20 | 3 (100) | 20 | 3 (100) | 26 | 3 (100) | 119 | 6 (100) | 213 | 19 (100) |
| Mild | 7 | 4 (100) | 6 | 2 (67) | 11 | 3 (100) | 13 | 3 (100) | 34 | 5 (83) | 71 | 17 (89) |
| Moderate | 9 | 4 (100) | 5 | 2 (67) | 5 | 2 (67) | 9 | 3 (100) | 63 | 5 (83) | 91 | 16 (84) |
| Severe | 10 | 4 (100) | 7 | 3 (100) | 4 | 2 (67) | 3 | 2 (67) | 17 | 4 (67) | 41 | 15 (79) |
| Life-threatening | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 1 | 1 (17) | 1 | 1 (5) |
| Death‡ | 2 | 2 (50) | 2 | 2 (67) | 0 | 0 (0) | 1 | 1 (33) | 4 | 4 (67) | 9 | 9 (47) |
| Any serious adverse event | 12 | 4 (100) | 8 | 3 (100) | 4 | 2 (67) | 2 | 1 (33) | 11 | 4 (67) | 37 | 14 (74) |
| Adverse events of special interest§ | 0 | 0 (0) | 2 | 2 (67) | 4 | 3 (100) | 2 | 1 (33) | 10 | 4 (67) | 18 | 10 (53) |
| Common adverse events¶ | | | | | | | | | | | | |
| Anemia | 6 | 4 (100) | 1 | 1 (33) | 1 | 1 (33) | 1 | 1 (33) | 3 | 2 (33) | 12 | 9 (47) |
| Fever | 0 | 0 (0) | 1 | 1 (33) | 4 | 3 (100) | 2 | 1 (33) | 5 | 3 (50) | 12 | 8 (42) |
| Urinary retention | 0 | 0 (0) | 1 | 1 (33) | 4 | 3 (100) | 2 | 1 (33) | 5 | 2 (33) | 12 | 7 (37) |
| Dysesthesia | 3 | 2 (50) | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 5 | 5 (83) | 8 | 7 (37) |
| Abnormal liver enzymes | 3 | 2 (50) | 2 | 1 (33) | 0 | 0 (0) | 5 | 2 (67) | 7 | 2 (33) | 17 | 7 (37) |
| Urinary tract infection | 0 | 0 (0) | 3 | 2 (67) | 1 | 1 (33) | 0 | 0 (0) | 3 | 3 (50) | 7 | 6 (32) |
| Fatigue | 0 | 0 (0) | 1 | 1 (33) | 0 | 0 (0) | 0 | 0 (0) | 7 | 4 (67) | 8 | 5 (26) |
| Decreased thermal sensitivity | 0 | 0 (0) | 1 | 1 (33) | 2 | 1 (33) | 0 | 0 (0) | 4 | 3 (50) | 7 | 5 (26) |
| Prolonged QTC | 0 | 0 (0) | 1 | 1 (33) | 1 | 1 (33) | 2 | 2 (67) | 1 | 1 (17) | 5 | 5 (26) |
| Nausea/vomiting | 1 | 1 (25) | 2 | 1 (33) | 0 | 0 (0) | 0 | 0 (0) | 4 | 2 (33) | 7 | 4 (21) |
| Upper respiratory infection | 0 | 0 (0) | 0 | 0 (0) | 1 | 1 (33) | 0 | 0 (0) | 6 | 2 (33) | 7 | 3 (16) |
| Hypertension | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 5 | 3 (50) | 5 | 3 (16) |
| Headache | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 0 | 0 (0) | 4 | 3 (50) | 4 | 3 (16) |

* Treatment-emergent adverse events were categorized and recorded for the pilot and Phase I participants from patient consent through the post-dosing phase (day 188) using Common Terminology Criteria Adverse Events v4.0 event grading. Adverse events were graded as 1, mild; 2, moderate; 3, severe; 4, life-threatening; or 5, death. Relatedness of adverse events was determined by the principal investigator in conjunction with the data safety monitoring board. Full characteristics, including a number of events by relatedness to the study drug/procedure, are found in Supplementary Table S4. Pt denotes patient; QTC, corrected QT interval.

† This includes treatment-emergent adverse events.

‡ Deaths were reported between 1 and 4 months postinjection and were not considered dose-limiting toxicity. One patient in the pilot was unable to complete the day 15 assessments due to disease progression, was discharged to hospice one week after resiniferatoxin (RTX) injection, and died 1.5 weeks after RTX injection.

§ Adverse events of special interest include thermal sensitivity reduction above the mid-chest for greater than 24 hours or transient urinary retention lasting more than 24 hours.

¶ Common adverse events included those that occurred in three or more (>15%) of participants, except in case of death, which is listed above, remaining adverse events are included in the supplement.

progressed to a grade III/IV unstageable decubitus ulcer at approximately 2 months after RTX injection. Of the 19 patients, 9 died during the study period, and these deaths were attributed by the investigators to the underlying cancers and not considered DLT. The average time from RTX injection until death was 70 days (range of 11 to 140 days); see Table S5 for a description of these deaths.

## EVALUATIONS OF ANALGESIC EFFICACY BY PATIENT-REPORTED OUTCOMES

Daily pain ratings from the pretreatment baseline were compared with days 0 to 14 posttreatment, showing pain ratings with both volumes used for RTX treatment (Fig. 3A). Overall mean "worst" pain intensity for the 15 patients was 8.4 (95% CI, 7.8 to 8.9) before treatment and 5.8 (95% CI,



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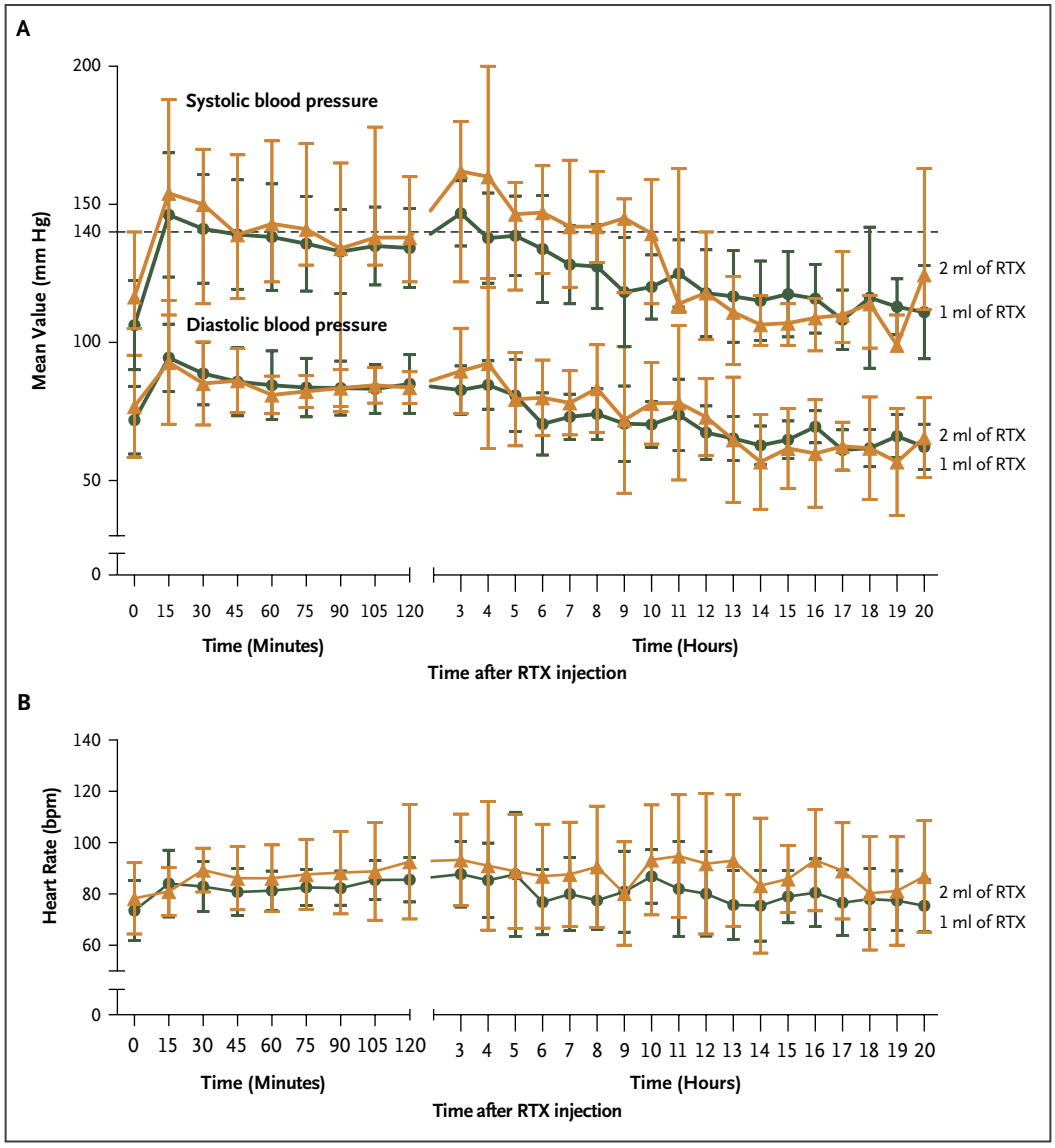


Figure 2. Hemodynamic Monitoring during the First 20 Hours after Intrathecal Injection Procedures.

For the first 20 hours, respiratory rate, heart rate, and blood pressure were monitored at 15-minute increments in the first 120 minutes, and approximately once an hour for between 3 and 20 hours. These measurements increased acutely after injection of resiniferatoxin, leading to three transient hypertension adverse events occurring in the 120-minute epoch. Panel A demonstrates that systolic and diastolic pressure increased within 15 minutes, peaking acutely, and at 3 hours when the patient was transferred to the Post-Anesthesia Care Unit, returning to preinjection baseline by 10 to 20 hours in all patients. Panel B shows heart rate in the first 20 hours after RTX injection. Hemodynamic effects were expected due to the burning sensation elicited by receptor activation on acute administration.[23,24] Data for each volume of injectate are plotted (orange triangles, 2-ml injection volume; green closed circles, 1-ml injection volume). Data are plotted as mean±95% confidence interval. bpm denotes beats per minute; RTX, resiniferatoxin.

4.8 to 6.8) at the day 15 time point. The effect of the volume of the infusion on the "worst" pain rating is reflected in the pain scores at the 8 to 14 day time point, as patients treated with 1-ml volume had an average pain rating of 8.4 (95% CI, 7.6 to 9.3) before treatment and 5.2 (95% CI, 3.8 to 6.6) after (N=9, Cohen's $d$=1.48), whereas patients treated with 2 ml of RTX had an average pain rating of 8.3 before treatment (95% CI, 7.7 to 8.9) and 6.6 (95% CI, 4.9 to 8.2)



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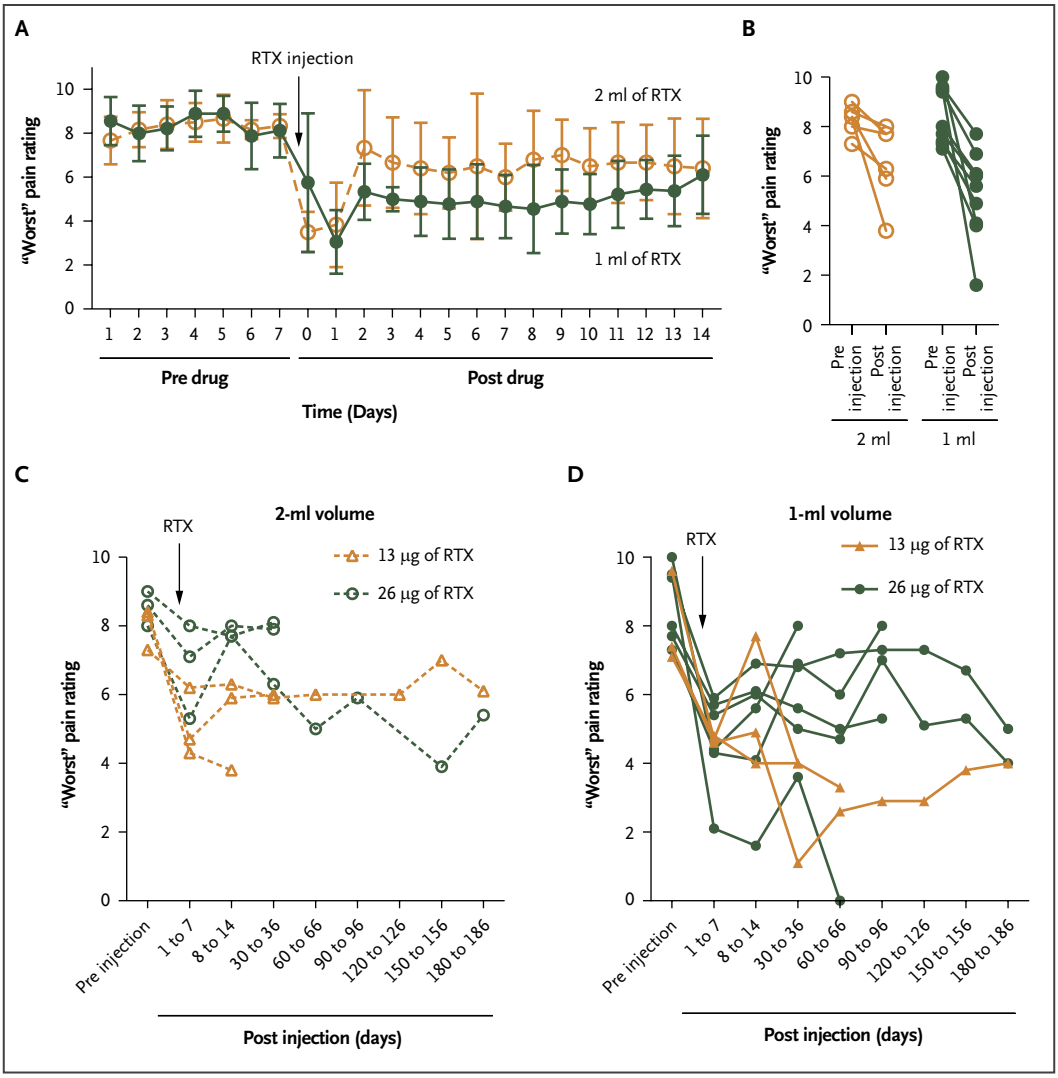


Figure 3. Patient-Reported Outcomes of Pain after Treatment with Intrathecal Resiniferatoxin.

Pain responses in patients treated with resiniferatoxin (RTX) were measured by patient-reported outcomes of pain. Pain scores were collected for 7 days before the procedure (predrug) using a numerical rating scale, capturing the "worst" pain rating, which is a scale from 0 to 10, with 0 meaning "no pain" and 10 meaning "the worst pain imaginable" (2 points or 30% reduction from baseline is thought to be clinically meaningful, whichever is greater). Panel A demonstrates the mean (95%CI) pain ratings that were collected daily for the first 14 days after administration. The major factor impacting treatment response was the volume of administration (1 ml or 2 ml). Panel B demonstrates for each patient the "worst" pain intensity measurements in the last 24 hours (specifically, binned average value at the 8- to 14-day epoch) these data were the primary end point for analgesia. "Worst" pain intensity decreased for all 15 patients over this epoch. Specifically, patients showing a 50% reduction in "worst" pain intensity at this time point met the primary outcome (3 out of 15 patients; 22%). Panel C and Panel D demonstrate the pain ratings that were collected across the entire study duration. Note that the attrition in participant numbers after day 30 is due to disease progression. Error bars show a 95% confidence interval. RTX denotes resiniferatoxin.

after (N=6, $d$=1.37) (Fig. 3B). These data led to our decision to use a smaller volume for the RTX infusion. Observations for "worst" pain intensity for the full 188-day evaluation period are plotted for each individual patient in the 2-ml (Fig. 3C) and 1-ml (Fig. 3D) administration volumes.

Additional pain ratings including "least" and "average" pain intensity are shown in Figure S2 as well as confirmatory observations using other pain scales (Figs. S3 and S4). Pain ratings for the four patients from the pilot study are included in Figure S5.



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### CHANGES IN OPIOID USE IN RESPONSE TO RTX

After the injection, patients were allowed to self-regulate their opioid use, resulting in an overall reduction in opioid use (reported as a median with 95% CI; pre-RTX median=306 [95% CI, 123 to 1140] morphine equivalents vs. post-RTX median=209 morphine equivalents, 15 days post-injection of RTX [95% CI, 90 to 660]). To avoid withdrawal symptoms, patients were given guidance on tapering their opioid medications. Among the patients in the 1-ml treatment group, oral morphine equivalents decreased in all participants (nine out of nine), whereas in the 2-ml group, morphine equivalents decreased in two out of six participants (Fig. 4A and 4B).

### PRESPECIFIED EFFICACY OUTCOMES

The prespecified efficacy outcome was defined as either an equal to greater than 50% reduction in "worst" pain intensity (met by 3 out of 15 patients, or 20%) or an equal to or greater than 50% reduction in oral morphine equivalents (met by 6 out of 15 of patients, or 40%) for study days 8 to 14 compared with pretreatment (Fig. 4B). The three patients who met the criteria for pain ratings also met the criterion for oral morphine equivalents.

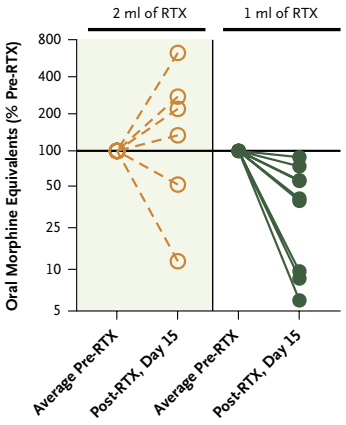
### OTHER EXPLORATORY STUDY OUTCOMES

Several additional exploratory outcomes that assessed functional impairment, mental function, quality of life, and other aspects of patient experience are found in Figure S6–Figure S8. CSF neuron–specific enolase measurement (ng/ml protein measured in CSF) showed elevations at 24 hours after injection and reached the "elevated range" (>30 ng/ml) in 3 of the 14 patients, consistent with acute chemoaxotomy by RTX (Fig. S9).

## Discussion

This Phase I study of RTX reports on a new interventional agent for pain palliation to reduce suffering in patients with intractable cancer pain. Our experience suggests confining the drug substance using a 1-ml volume and an infusion rate of 0.5 ml/minute; we were able to administer the drug without DLT in eight of nine patients so treated. As expected, almost all treated patients experienced treatment-emergent AEs; as noted below, some of these AEs were likely related to the patients' underlying disease. Our interim data show that considering these treatment-emergent AEs, a single RTX injection was associated with favorable changes in pain scores and opioid use. The chemoaxotomy mechanism of action produced analgesic effects that were durable

A




B

| Pt | Dose (μg) | Volume (ml) | % Change Worst NRS | % Change OME | Met Criteria |
|---|---|---|---|---|---|
| 1 | 13 | 2 | –14% | –47% | No |
| 2 | 13 | 2 | **–54%** | **–87%** | **Yes** |
| 3 | 13 | 2 | –30% | 120% | No |
| 4 | 26 | 2 | –4% | 173% | No |
| 5 | 26 | 2 | –14% | 527% | No |
| 6 | 26 | 2 | –7% | 34% | No |
| 7 | 13 | 1 | –20% | **–61%** | **Yes** |
| 8 | 13 | 1 | –34% | –11% | No |
| 9 | 13 | 1 | –44% | **–91%** | **Yes** |
| 10 | 26 | 1 | **–59%** | **–94%** | **Yes** |
| 11 | 26 | 1 | **–83%** | **–90%** | **Yes** |
| 12 | 26 | 1 | –24% | –43% | No |
| 13 | 26 | 1 | –27% | –42% | No |
| 14 | 26 | 1 | –22% | –25% | No |
| 15 | 26 | 1 | –23% | **–59%** | **Yes** |

| | | | | |
|---|---|---|---|---|
| **Average** | 26 μg<br>–29% | 13 μg<br>–32% | 26 μg<br>42% | 13 μg<br>–30% |
| **Average** | 2 ml<br>–20% | 1 ml<br>–37% | 2 ml<br>120% | 1 ml<br>–57% |

Figure 4. Reduction in Oral Opioids (Oral Morphine Equivalents) after Intrathecal Resiniferatoxin.

An objective measurement of analgesia was opioid intake in oral morphine equivalents, which can decrease after successful analgesic intervention. Panel A demonstrates that, similar to pain ratings, response to resiniferatoxin (RTX) was considered separately according to the two administration volumes, with the 1-ml volume showing a greater magnitude of effect, and consistent reduction (nine out of nine patients; 57% average reduction). Panel B demonstrates that the primary outcome measures for efficacy were a decrease of 50% in numerical rating scale (NRS) "worst" pain intensity and a decrease in opioid intake. For each patient, the NRS "worst" pain intensity rating decrease is also included, as well as whether the patient met each of the two primary efficacy end points. The NRS is a 0 to 10 scale that measures the "worst" pain intensity over the preceding 24 hours, where a 2-point difference (or 30%) is approximately the minimal clinically important difference. NRS denotes numerical rating scale; OME, oral morphine equivalent; Pt, patient; RTX, resiniferatoxin.



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at all time points examined, consistent with expectations for interventional neurolytic approaches.[9,13,25,26]

Of the various AEs observed after treatment, some were likely due to the progression of advanced disease. The determination of relatedness included the timing and expectedness of the AE. For those events that were deemed to be related to RTX administration, many were expected, had a side-effect profile that had not yet limited dose escalation, and resolved spontaneously or with intervention (e.g., transient hypertension in the immediate postoperative period). For all patients dosed, their lifespan was expected to be shorter than the study period (188 days), although life expectancy was not formally estimated. The cause of death was not determined except in two cases where an autopsy was performed, although deaths were attributed to disease progression, consistent with the course of advanced cancer. In total, 4 of 19 patients reached the final assessment at study day 188 postinjection. A common AE after RTX was urinary retention, which occurred in both men and women, although all three of the grade III events occurred in men. This finding could be related to the exacerbation of a preexisting condition such as benign prostatic hyperplasia. During the study, we added consultation with a urologist and serial bladder ultrasound studies to better characterize and manage this AE. Normal urinary function resumed either spontaneously or with therapy, with the most severe case lasting approximately 3.5 months (grade III). In dermatomes exposed to RTX, permanent thermal sensory loss was expected,[9,13,15,27] and was observed in several patients. Patients were informed of this on-target side effect and instructed on precautions to avoid accidental burn injury. The only grade IV SAE was an unstageable decubitus ulcer that was not deemed to be a DLT. While not seen in other patients, RTX decreases painful sensory input, and it is possible that ulceration is a consequence of the treatment. A transient increase in QT interval was observed in five patients and resolved within 24 hours. The association of this electrocardiographic change with drug administration is not clear, as it was not dose related and transient QT changes can be seen with general anesthetics.[28] Some patients experienced a transient hypertensive and tachycardic response to RTX injection (Fig. 2), consistent with acute nociceptive stimulation. This expected response was recorded as an AE in three patients (one grade II and two grade III), and resolved in a maximum of 12 hours. This autonomic response was expected and was not considered DLT, which was consistent with the preclinical observations.[15] One patient experienced multiple seizures in the postinjection period, which were attributed to toxicity from a chronic high-dose opioid regimen (9376 oral morphine equivalents per day; grade II).[29] The patient's seizures resolved with rapid reduction of opioids and a 2-day administration of anticonvulsants.

One of the key findings of the study was the observation of seemingly increased efficacy with a smaller administration volume. We observed that a lower volume delivered slowly to prevent spread in the intrathecal space was associated with better clinical outcomes with RTX. This is consistent with a concentration-dependent lesion of TRPV1-containing axons in the intrathecal space by RTX and mirrors similar results with intrathecal opioids or anesthetic agents.[30,31] These results are consistent with the idea that confining the drug substance to the lumbar cistern delivers a high drug concentration with minimal intrathecal spread to other dermatomes, thereby reducing sensory loss in regions unrelated to the pain condition.

Our data provide evidence that supports continued investigations of RTX to improve pain management for patients with advanced cancer experiencing intractable pain, especially when opioids fail or are poorly tolerated. Although it requires an anesthetic for drug administration, the appeal of this intervention is that it has the potential to improve pain control with a single durable treatment, while potentially decreasing the need for other drugs or interventions.

## Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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