PUBLICATION SUMMARY – BONE

Cryoablation for Palliation of Painful Bone Metastases: The MOTION Multicenter Study

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OVERVIEW

- Multicenter, prospective, single arm, phase II study
- 11 centers: 4 in EU and 7 in US
- N= 66 patients with painful bone metastases
- Patient follow-up at 1, 4, 8, 12, 16, 20, and 24 weeks after the cryoablation procedure
- Treatment of 1 painful bone metastatic lesion for each patient
- Primary efficacy objective: change from baseline to 8 weeks after cryoablation in worst pain in the last 24 hours as measured by the BPI-SF scale
- Complications were monitored for 30 days post procedure
- Hospital stay: median of 26.6 hours (range 19.4 – 45.8 hours)

Bone is the most common site of metastatic cancer. Bone metastasis are associated with bone pain resulting in significant decreased physical function and quality of life (QOL). External beam radiation therapy is the standard for treatment of patients with painful bone metastases, along with opioids and non-opioid analgesics. Unfortunately, the time to pain relief for radiation therapy is 1-2 months and for many patients the pain can persist after radiation therapy. Cryoablation for painful bone metastases allows for rapid and durable pain palliation.

OBJECTIVES

To assess the effectiveness and safety of cryoablation for palliation of painful bone metastases in participants who were not candidates for traditional pain therapies or for whom traditional pain therapies had failed to provide adequate relief. The primary objective was to evaluate the efficacy of cryoablation for pain palliation of bone metastases from baseline to 8 weeks after cryoablation in worst pain in the last 24 hours as measured by the BPI-SF scale.

Separate evaluations of ancillary efficacy endpoints were also made through 24 weeks, including: (a) changes in worst pain scores and average pain scores from baseline; (b) change in analgesic use (both morphine equivalent daily dose (MEDD) and nonsteroidal anti-inflammatory drugs); (c) use of additional therapies for persistent or recurrent pain associated with the index tumor or new metastases; (d) quality of life (as indicated by change from baseline in overall average BPI-SF); and (e) change in Karnofsky performance status as a measure of functional impairment. The safety endpoint was the incidence and severity of procedure or device-related adverse events

METHODS

This multicenter, prospective, single-arm, phase 2 study included 66 patients with painful bone metastases treated with percutaneous cryoablation, with follow-up at weeks 1, 4, 8, 12, 16, 20, and 24. Cryoablation was performed with the Visual ICE™ Cryoablation System (Boston Scientific) to a single metastatic bone lesion within 14 days of screening. In participants with multiple osseous lesions, the most painful lesion was selected as the index lesion.

Study sites used a standard cryoablation protocol including two freeze-thaw cycles. If the operator felt that another cycle would improve coverage and local control, it was performed in select cases. CT images were obtained at intervals throughout the freeze cycles. Freeze duration varied to encompass the entire tumor or as much of the tumor as could be safely treated. Participants were not denied needed therapy for pain; however, those who received additional targeted therapies to the index tumor were excluded. Participants could receive concomitant pain medications and chemotherapy for treatment of recurrent or new tumor pain. Opioid medication doses were converted to a standardized morphine equivalent daily dose.

Pain improvement was evaluated using a single item from the BPI-SF questionnaire completed by participants which asked participants to evaluate the level of the “worst pain in the last 24 hours.” The primary effectiveness endpoint was the change from pretreatment baseline rating of worst pain in the last 24 hours to post treatment week 8 rating. A clinically meaningful change for this item was defined as a reduction of at least 2 points. A responder analysis was conducted with response to cryoablation defined as a reduction of at least 2 points

in worst pain score in the last 24 hours among participants with stable medication use, defined as less than or equal to 25% increase in MEDD.

Cryoablation was performed with a minimum of 3 freeze–thaw cycles (3-min freeze, 3-min passive thaw, 7-12 min freeze, 5-min passive thaw, 7-12 min freeze followed by active thawing). Each procedure was monitored with non-contrast CT imaging typically at 3 to 5 minutes intervals to visualize the evolving ablation zone with the goal of achieving a minimal margin beyond the tumor of 5 mm. After CA needle(s) were removed, CT images were obtained to assess the overall ablation zone and to identify any potential complications. Follow-up was done within the first week, and at 1, 3, 6, 12, 18, and 24 months.

RESULTS

OUTCOMES

Sixty-six patients were included in the intention-to-treat (ITT) population in which cryoablation was attempted. Cryoablation was not completed for one patient who was withdrawn from the study resulting in 65 participants who completed cryoablation (safety population), with one patient not completing follow-up leaving 64 completed cases. Baseline patient and tumor characteristics are shown in Table 1 with a mean patient age of 60.8 years and predominant primary cancers of lung (28/8%), breast (13.6%), and kidney (12.1%) cancer of targeted bone metastases. The majority of patients had received previous systemic therapies (75.8%) with 42.4% of patients previously receiving radiation therapy, and only 10.6% of patients with no prior cancer treatments.

Additionally, targeted bone lesions were predominantly located in the ribs (24.2%), ilium (19.7) and pelvis (12.1%) with a majority of the tumor composition being osteolytic disease (72.7%). The mean maximum tumor diameter was 5.7 ± 3.2 cm. Overall, the mean total procedure time was 100.1 ± 48.21 minutes with an average of 3 ± 2 needles/case. Post-ablation the mean and median total hospital stay was 40.7 ± 57.17 hours and 26.6 hours; respectively.

The primary efficacy endpoint of mean change in worst pain in last 24 hours from baseline to week 8 was -2.61 ± 0.43 points (95% CI: -3.45, -1.78) as shown in Figure 1. Clinically meaningful changes from baseline were observed at all time points after week 8. In the completed case analysis (n = 64), mean pain scores improved by 2 points as early as week 1 and continued through week 24 and the 92% of participants achieved palliation (59/64), with median time to maximal pain relief of 39.0 days (95% CI: 43.7, 72.4 days; n = 59). Most participants achieved their maximum palliation by week 1 (33.9%; 20 of 59), week 4 (25.4%; 15 of 59), or week 12 (15.3%; nine of 59).

Opioid medication use at baseline was reported by 48 of 66 (73%) participants, with a mean MEDD of 43.1 mg ± 79.0 (median, 12.6 mg). Opioid medication use was reported by 56%–69% of participants who attended visits at week 4 through week 24. The MEDD among complete-case participants decreased from week 4 to week 24. Opioid pain medication use was stable (ie, increased ≤ 25% over baseline) over week 4 through week 24 in 57% (21 of 37) of participants.

Quality of life consistently improved over 6 months (Fig 2). The overall treatment effect was rated "better than at the last visit" by 60.9% (39 of 64) and 30% (11 of 37) of participants at weeks 1 and 24, respectively; treatment effect was rated "worse than at the last visit" by 13% (eight of 64) and 11% (four of 37) participants at weeks 1 and 24, respectively.

Table 1: Patient and Tumor Characteristics

Characteristics	Participants (n = 66)
Primary cancer diagnosis	
Lung cancer	19 (28.8%)
Breast cancer	9 (13.6%)
Other*	13 (19.7)
Kidney cancer	8 (12.1%)
Colon cancer	5 (7.6%)
Prostate cancer	4 (6.1%)
Sarcoma	3 (4.5%)
Thyroid cancer	3 (4.5%)
Stomach cancer	2 (3.0%)
Prior cancer treatments	
No prior cancer treatment	7 (10.6%)
Prior systemic chemotherapy	50 (75.8%)
Prior radiation for bone metastases (index tumor)	28 (42.4%)
Prior hormonal treatment (not restricted to bone metastases)	12 (18.2%)
Prior targeted molecular therapy for bone metastases	9 (13.6%)
Prior ablation therapy for non-index bone tumor(s)	6 (9.1%)
Prior bisphosphonate treatment for bone metastases	5 (7.6%)
Index Tumor Location	
Rib	16 (24.2%)
Ilium	13 (19.7%)
Pelvis	8 (12.1%)
Other	6 (9.1%)
Chest wall (rib with non-rib soft tissue)	4 (6.1%)
Acetabulum	3 (4.5%)
Sacrum	3 (4.5%)
Scapula	3 (4.5%)
Ischium	3 (4.5%)
Sternum	3 (4.5%)
Humerus	2 (3.0%)
Femur	1 (1.5%)
Vertebra	1 (1.5%)
Index tumor composition	
Predominantly lytic (osteolytic) disease	48 (72.7%)
Mixed	11 (16.7%)
Predominantly sclerotic (osteoblastic) disease	6 (9.1%)

*Other cancers: hepatic (n = 3); other cancers of the gastrointestinal system (n = 2); and, bladder, melanoma, rectal, uterine, urothelial, urachus, penile, and unknown primary cancers (n = 1 for each).

RESULTS

COMPLICATIONS

Adverse events that occurred within 30 days of the procedure were captured and graded in accordance with the Common Terminology for Adverse Criteria for Adverse Events (CTCAE version 4.03) of the National Cancer Institute. Events ongoing after 30 days were followed to resolution or through 6 months from onset. The safety population comprised 65 participants. Possibly related adverse events occurred in 22% (14 of 65) of participants. Of these, 3.1% (two of 65) were hematoma, 3.1% (two of 65) experienced nausea, and 3.1% (two of 65) experienced tumor pain; 7.7% (five of 65) were described as "other." Each of the following was experienced by 1.5% (one of 65) participants: hypotension, pain at needle site, pleural effusion, skin burn and frostbite, and vomiting. Three of 65 participants (4.6%) each had one serious adverse event that was a grade 3 or 4 event (abdominal pain, hematoma, and skin frostbite). There were no device-, procedure-, or opioid-related deaths in the study.

CONCLUSION

Overall, the data shows a rapid and durable pain relief along with a decrease in MEDD and a corresponding increase in the quality of life for patients.

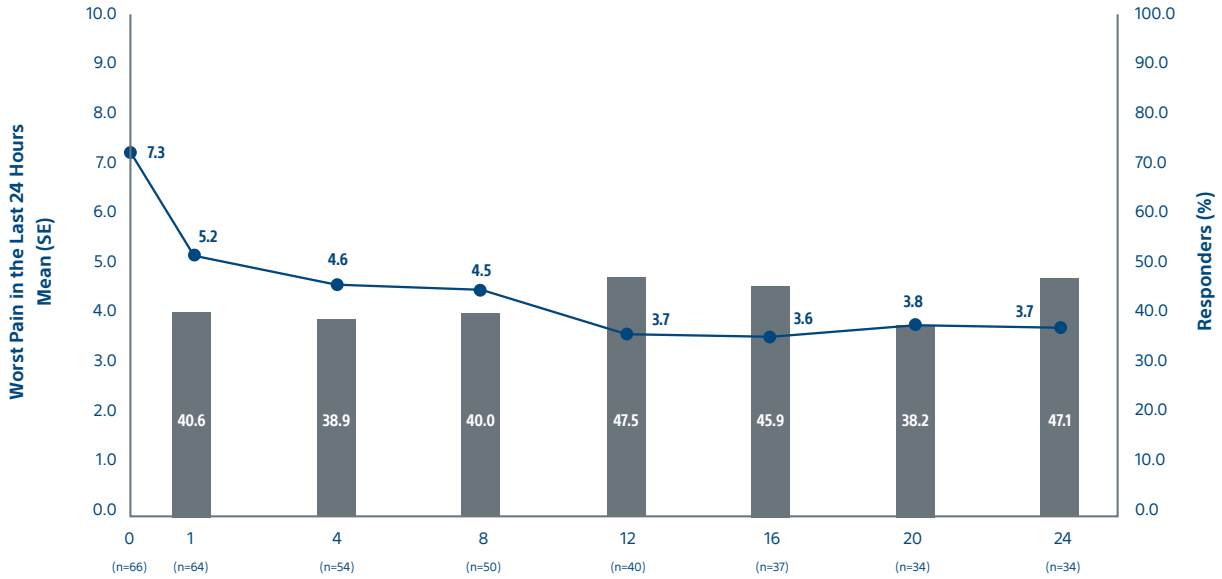

Figure 1: **Change in worst pain in last 24 hours through 24 weeks**

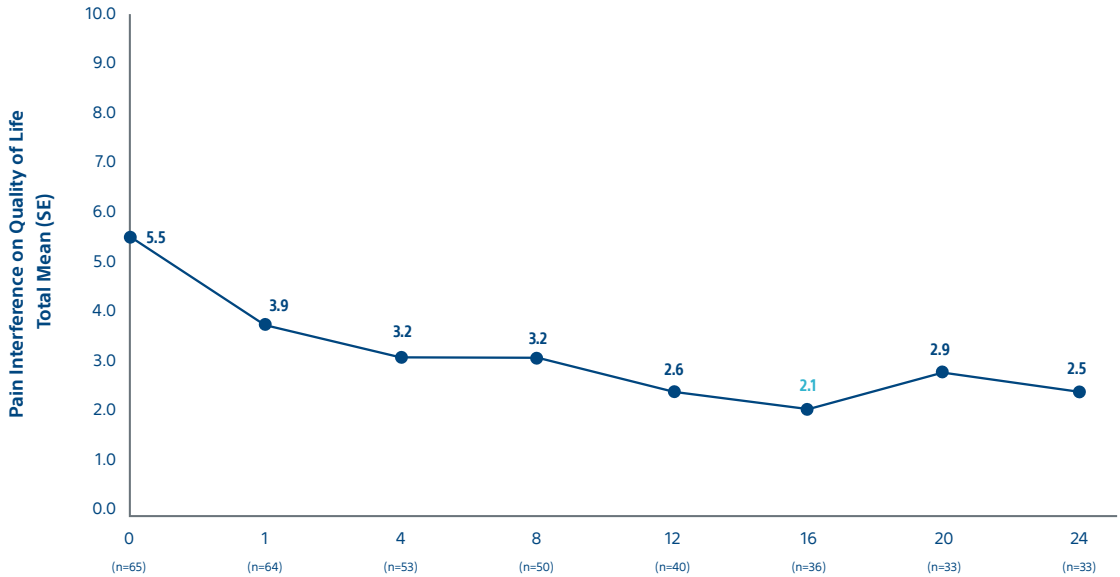

Figure 2: **Change in quality of life through 24 weeks**

CRYOABLATION NEEDLES (IceSeed 1.5, IceSphere 1.5, IceSphere 1.5 CX, IceRod 1.5, IceRod 1.5 PLUS, IceRod 1.5 i-Thaw, IceRod 1.5 CX, IcePearl 2.1 CX and IceForce 2.1 CX) and ICEFX and VISUAL ICE CRYOABLATION SYSTEMS

INDICATIONS: The Galil Medical Cryoablation Needles and Systems are intended for cryoablative destruction of tissue during surgical procedures. The Cryoablation Needles, used with a Galil Medical Cryoablation System, are indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery (with the exception of cardiac tissue), ENT, gynecology, oncology, proctology, and urology. Galil Medical Cryoablation Systems are designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors and skin lesions) by the application of extremely cold temperatures. A full list of specific indications can be found in the respective Galil Medical Cryoablation System User Manuals. **CONTRAINDICATIONS:** There are no known contraindications specific to use of a Galil Medical Cryoablation Needle. **POTENTIAL ADVERSE EVENTS:** There are no known adverse events related to the specific use of the Cryoablation Needles. There are, however, potential adverse events associated with any surgical procedure. Potential adverse events which may be associated with the use of cryoablation may be organ specific or general and may include, but are not limited to abscess, adjacent organ injury, allergic/anaphylactoid reaction, angina/coronary ischemia, arrhythmia, atelectasis, bladder neck contracture, bladder spasms, bleeding/hemorrhage, creation of false urethral passage, creatinine elevation, cystitis, diarrhea, death, delayed/non healing, disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT), ecchymosis, edema/swelling, ejaculatory dysfunction, erectile dysfunction (organic impotence), fever, fistula, genitourinary perforation, glomerular filtration rate elevation, hematoma, hematuria, hypertension, hypotension, hypothermia, idiosyncratic reaction, ileus, impotence, infection, injection site reaction, myocardial infarction, nausea, neuropathy, obstruction, organ failure, pain, pelvic pain, pelvic vein thrombosis, penile tingling/numbness, perirenal fluid collection, pleural effusion, pneumothorax, probe site paresthesia, prolonged chest tube drainage, prolonged intubation, pulmonary embolism, pulmonary insufficiency / failure, rectal pain, renal artery/renal vein injury, renal capsule fracture, renal failure, renal hemorrhage, renal infarct, renal obstruction, renal vein thrombosis, rectourethral fistula, scrotal edema, sepsis, skin burn/frostbite, stricture of the collection system or ureters, stroke, thrombosis/thrombus/embolism, transient ischemic attack, tumor seeding, UPJ obstruction/injury, urethral sloughing, urethral stricture, urinary fistula, urinary frequency/ urgency, urinary incontinence, urinary leak, urinary renal leakage, urinary retention/ oliguria, urinary tract infection, vagal reaction, voiding complication including irritative voiding symptoms, vomiting, wound complication, and wound infection. PI-719210-AA

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