Single Intratumoral Drug Injection Yields Complete Response (CR) in Metastatic Breast Cancer (MBC) Bone Lesions: Results from a Phase 2a Trial

Poster #3549

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Introduction

Survival and quality of life (QoL) are reduced for patients with destructive (lytic) lesions from metastatic breast cancer (MBC), affecting the axial skeleton in 70% of patients. MBC lesions can lead to debilitating pain, which is managed using opioids, palliative radiation therapy, or surgery. Skeletal-related events (SREs) are a collection of negative clinical outcomes associated with reduced survival that includes pain, pathologic fracture, and spinal cord compression. Further, SRE risk correlates with decreased QoL due to significant morbidity (e.g., pain and pathologic fracture) and decreased life expectancy (i.e., 7-months after SRE) [**3**].

Zeta-BC-003 is a first-in-class intratumoral (IT) drug therapy designed to better treat patients' MBC bone lesions. It is a novel biomaterial infused with the small molecule, N-allyl noroxymorphone. Zeta-BC-003 is designed to be administered via a minimally invasive percutaneous IT injection using fluoroscopic guidance.

N-allyl noroxymorphone *decreases tumor activity via antagonism of the newly discovered opioid growth factor receptor (OGFR) pathway* [**1**]. OGFR antagonism induces tumor cell death while stimulating mesenchymal stem cells (MSC) to become bone cells and inhibiting MBC directed differentiation of monocytes into osteoclasts, the cells that destroy bone and directly induce pain (**Figure 1A**).

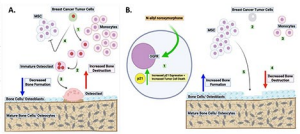


Figure 1: (**A**) Tumor mediated bone destruction. Tumor cells produce growth factors that increase monocyte cell proliferation [**1**], increase immature osteoclast numbers [**2**] that leads to increased bone destruction [**3**]. MSC/bone cells activity is blocked by the tumor cells [**4**], preventing bone healing. (**B**) N-allyl noroxymorphone increases p21 expression via the OGFR [**1**] (shown in a generic cell), which causes tumor cell death [**2**], decreases monocyte [**3**] and osteoclast numbers [**4**]. With no tumor activity, bone cells mediate healing [**5**].

When metastatic tumor cells reach bone, they subvert normal bone turnover by increasing osteoclast number and activity at the expense of new bone formation (**Figure 1A**). In contrast, N-allyl noroxymorphone antagonizes the OGFR leading to increased p21 expression (**Figure 1B**) [**1**]. OGFR antagonism stops MBC directed bone destruction by reducing monocyte numbers, which in turn leads to a fewer osteoclasts and a reduction in pain [**2**]. In addition, fewer osteoclasts, in parallel with increased bone cell numbers, directly promotes bone healing.

There were no SREs in this Phase 2a study while pain was reduced and QoL increased. A radiographic complete response (CR) was seen in the 9 treated lesions in 9 patients. Importantly, in 2 patients a radiographic CR was also seen in 4 non-treated lesions found adjacent to the treated lesions in the same vertebral body. Complete trabecular bone restoration was seen in 6 of lesions. These results are consistent with previous work [**3**], in which Zeta-BC-003 produced a CR, decreased pain, and increased QoL in 7 MBC lesions, for a patient treated via FDA's Compassionate Use/ Expanded Access program.

Methods

ZGMBC (NCT05280067) is a non-randomized, open label Phase 2a trial that was recently completed at the University of British Columbia. Ten (10) female patients were enrolled (8/23-3/25) with spinal MBC lytic bone lesions and a Spinal Instability Neoplastic Scale (SINS) score ≥3 and ≤9. Under sedation, one (1) lesion per patient was treated with a single intratumoral injection of Zeta-BC-003, using an 18-gauge spinal needle and fluoroscopic guidance. Patients were followed with CT and MRI at discharge and then at days 84 & 180. Primary endpoints were the occurrence of SREs, the bone defect size change (i.e., volumetric tumor analysis), pain measured using the Numeric Rating Scale (NRS); and the quantity of postoperative prescription opioid use. Secondary endpoints included an assessment of the QoL via SF-12v2 and the spinal stability was re-evaluated at the end of the study using SINS. In addition, treatment responses were assessed via the MD Anderson Criteria (MDAc) and RECIST v1.1 according to the following criteria:

Volumetric analysis of the change in tumor size was only assessed on CT by tracing the vertebral body and tumor defect through all of the slices in Osirix. Tumor response was assessed using CT in parallel with T2-weighted STIR and T1-weighted MRI images. Tumor response was determined based on the response observed in all 3 imaging modalities.

1. **Complete Response (CR):** Presence of the following criteria:
   - Complete 'fill-in' or bone sclerosis of the lytic lesion on XR and CT
   - Disappearance of hot spots or tumor signal on CT or MRI
   - Normalization of osteoblastic lesion on XR and CT
2. **Partial Response (PR):** Presence of one or more of the following criteria:
   - Sclerotic rim about initial lytic lesion or sclerosis of previously undetected lesion on XR or CT
   - Partial fill-in or sclerosis of lytic lesion on XR or CT
   - Regression of measurable lesion on XR, CT, or MRI
   - Decreased of blastic lesion on XR or CT
3. **Progressive Disease (PD):** Presence of one or more of the following criteria:
   - Increase in size of any existing measurable lesion on XR, CT or MRI
   - Increase in activity on blastic/lytic lesion on XR or CT
   - Presence of new lesion on XR, CT, or MRI
4. **Stable Disease (SD):** No evidence of new bone metastases on XR, CT or MRI, AND presence of one of the following criteria:
   - No change in measurable lesion on XR, CT or MRI
   - No change in blastic/lytic lesion on XR, CT or MRI

Results

Patients had a mean age of 52-yrs (range: 32.5 - 67.4) and 9 were pre/peri-menopausal. Six (6) patients had hormone receptor (**HR**) positive tumors while two (2) patients were **HR$^+$/HER2$^+$**, one (1) patient was **HER2$^+$/HR$^-$**, and one (1) patient had triple negative breast cancer (**TNBC**). Four (4) patients had non-surgically accessible bone MBC (e.g., ribs, ilium, skull), three (3) had liver MBC, one (1) patient had lung MBC, and three (3) patients had mediastinal lymph node MBC. Five (5) patients were given bisphosphonates to prevent bone metastases. All patients remained on standard of care systemic therapy.

In the nine (9) patients that completed the study (day 180), there were ***no treatment related SAEs, AEs, or SREs***. One patient died due to complications from pleural effusion (day 90). At day 180, we analyzed 9 treated lesions in 9 patients as well as 4 additional lesions within the same vertebral body in 2 patients, resulting in a total of 13 analyzed lesions. At day 180, the mean bone defect volume decreased 82.4% (±13.6%) at day 180 (range: 60% to 98.5%). Pain decreased 4.16% per the mean NRS. The Morphine Equivalent Dose (MED) was calculated for the three (3) patients treated with opioids, which showed a decrease of 66.9%, 66.7%, and 33.3%, respectively. At day 180, a 24.2% increase in the Physical Component Summary (PCS) and a 12.1% increase in the Mental Component Summary (MCS) showed improved QoL (SF-12v2; **Table I**). The patient QoL improved with decreased MED, with PCS increasing for those patients by 36.7%, 13.4%, and 58.4%, respectively. The decreased MED related to a lower MCS for two (2) patients (2.4% & 6.9%) while the third patient increased 47.1%. The mean SINS increased 18.5%, from 4.5 to 3.7, indicating increased stability.

Table I: SF12v2 Qol. Analysis

Patient Number	MCS-12 (Mental Component Score) Baseline	MCS-12 (Mental Component Score) Day 180	% Change	PCS-12 (Physical Component Score) Baseline	PCS-12 (Physical Component Score) Day 180	% Change
VAH-0004	25.18598	34.70977	36.73%	68.04520	67.09035	-2.83%
VAH-0007	46.77440	59.82586	27.90%	54.55675	46.90197	-14.03%
VAH-0008	53.85304	45.47771	-15.54%	42.09040	57.79843	37.32%
VAH-0009		40.06777			33.64733	
VAH-0010	28.87447	32.74013	13.39%	29.69048	43.67642	47.09%
VAH-0011	26.09298	41.33995	58.43%	35.83488	33.34625	-6.94%
Average	**36.195774**	**42.36007**	**24.18%**	**46.24354**	**47.07576**	**12.12%**

Table II: Relationship between Progressive Lesions in Adjacent and Non-Adjacent Vertebrae vs Systemic Therapy

Patient Number	Progressive Lesion Number and Location: Treated Vertebrae	Adjacent Lesion Number	Adjacent Lesion: Vertebrae	Non-Adjacent Lesion Vertebrae	Systemic Drug Therapy: Bisphosphonate	CDK4/6 Inhibitor
VAH-0004	T12	1	T11	T09, L2		
VAH-0007	T11	1	T10			Ribociclib
VAH-0008	T9	1		T11	Pamidronate	Ribociclib
VAH-0009	L3	2	T12	L3	Pamidronate	Ribociclib
VAH-0010	L3	2	L2, L4		Pamidronate	Ribociclib
VAH-0011	L5	1		L2	Pamidronate	Palbociclib
VAH-0012	L3	2	L2	L1		
VAH-0013	L5	2	L4	L2	Zometa	Ribociclib
VAH-0014	L5	3	L4	L2, L3	Zoledronic acid	
VAH-0015	L2	1	L1			
Average	**1.7 (19.6%)**					

Progressive lesions (N=17) were seen in adjacent (i.e., immediate inferior or superior vertebrae) or in non-adjacent (i.e., a vertebral bone separates the inferior or superior vertebrae with the progressive lesion). No correlation was seen between progressive lesions in adjacent and non-adjacent vertebral bones (**Table II**). There was also no relationship between progressive lesions in adjacent or non-adjacent vertebrae and systemic treatment with a bisphosphonate or a CDK4/6 inhibitor. For the 9 patients who completed the study, 7 of 13 MBC bone defects were completely healed, resulting in trabecular bone restoration and normal bone morphology (**Figures 2** and **3**). The 13 lesions assessed in the 9 patients were found to have a radiographic CR via the MDAc, which is defined as 'fill-in' of the bone defect via CT plus no active tumor ('hot spots') on MRI.

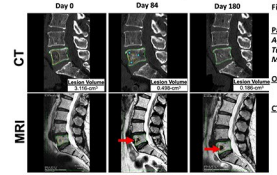


Figure 2:

Patient Demographics:
Age: 65.2
Tumor Phenotype: HR$^+$/HER2$^+$ breast cancer
Medical History: Dyslipidemia

Outcome:
- **Radiographic Complete Resolution**
- **Reconstitution of Trabecular Bone**
- **No SREs**

CT
- Tumor bone lesion decreased 94.0% (16.7-fold)
- **Day 84:** Trabecular reconstitution (Blue Arrowheads) indicative of bone healing after tumor inhibition of bone cells ceases
- **Day 180:** Complete trabecular bone reconstitution

MRI
- T2-weighted Fat Suppressed MRI = shows tumor signal
- **Day 0**: Tumor signal is observed
- **Day 84:** Tumor activity decreases significantly (**Red Arrow** = area absent of MRI signal)
- **Day 180:** No tumor activity detected - **Red Arrow** = area absent of MRI signal confirming tumor no longer present

Conclusion

At day 180 there were no SREs, and Zeta-BC-003 provided a radiographic CR in 9 patients (13 lesions), decreased MBC defect volume, increased stability (SINS), decreased pain (NRS/MED), and increased QoL. In contrast, 53% of patients reported an SRE by 6-months in previous work [4]. SRE risk decreases QoL and is correlated with significant morbidity (e.g., pain & fracture) and decreased life expectancy (i.e., <6-months after SRE) [**3**]. These data are consistent with a patient treated via Compassionate Use followed for 3-yrs [**3**], in which CR was observed in 10 lesions coupled with a 50% decrease in pain (NRS) and a 76% decrease in opioid drug use (MED – day 0: 250-mg vs 2-yrs: 60-mg). Zeta-BC-003, the first non-palliative IT treatment, reduces SRE risk, decreases pain, ceases MBC lesion activity, reconstitutes trabecular bone, and increases QoL. An unexpected finding was that both bisphosphonate and CDK4/6 inhibitor therapies were ineffective at preventing progressive lesions in superior and inferior adjacent and non-adjacent vertebrae. Further work will be needed to assess if Zeta-BC-003 will also increase overall survival.

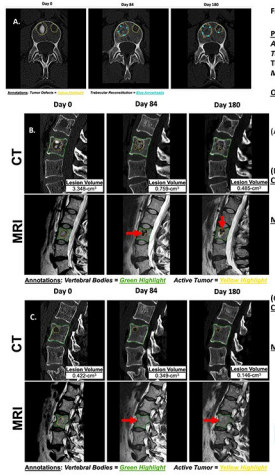


Figure 3:

Patient Demographics:
Age: 40.5
Tumor Phenotype: Triple negative breast cancer
Tumor Imaging Location: Left side tumor
Medical History: None

Outcome:
- **Complete Resolution (i.e., no tumor activity)**
- **Reconstitution of Trabecular Bone (i.e., healing)**
- **No SREs**

(A) Axial view showing the two adjacent lesions. The left-side lesion was treated while the right-side lesion was not. New bone is seen in the treated lesion at days 84 & 180 (blue arrowheads)

(B) Left-side Treated Lesion

CT
- Tumor bone lesion decreased 85.5% (6.9-fold)
- **Day 180:** Significant bone healing/ trabecular reconstitution
- Remaining bone defects likely to heal given enough time

MRI
- T2-weighted Fat Suppressed MRI = shows tumor signal
- **Day 0:** Tumor signal is observed
- **Day 84:** Tumor activity decreases significantly (**Red Arrow** = area absent of MRI signal)
- **Day 180:** No tumor activity detected - **Red Arrow** = area absent of MRI signal confirming tumor no longer present

(C) Right-side Non-treated Lesion Adjacent to Treated Lesion

CT
- Tumor bone lesion decreased 65.4% (2.89-fold)
- **Day 180:** Significant bone healing/ trabecular reconstitution
- Remaining bone defects likely to heal given enough time

MRI
- T2-weighted Fat Suppressed MRI = shows tumor signal
- **Day 0**: Tumor signal is observed
- **Day 84:** Tumor activity decreases significantly (**Red Arrow** = area absent of MRI signal)
- **Day 180:** No tumor activity detected - **Red Arrow** = area absent of MRI signal confirming tumor no longer present

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