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Clinical Trial Results

First-in-Human Phase I Study of MBC-11, a Novel Bone-Targeted Cytarabine-Etidronate Conjugate in Patients with Cancer-Induced Bone Disease

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02673060
- **Sponsor(s):** Osteros Biomedica Ltd.
- **Principal Investigator:** Alexander Alexandrov
- **IRB Approved:** Yes

Lessons Learned

- Results are consistent with MBC-11 targeting and treating cancer-induced bone lesions by concentrating cytarabine and etidronate at the site of disease.
- MBC-11 was well tolerated, with an maximum tolerated dose of 5 mg/kg per day and myelosuppression as the principal toxicity.
- Treatment significantly reduced cancer cell activity in over half of bone lesions detected at baseline.
- MBC-11 pharmacokinetic and pharmacodynamic parameters are consistent with the novel drug design goals, and encouraging results warrant further clinical development.

Abstract

Background. MBC-11 is a first-in-class conjugate of the bone-targeting bisphosphonate etidronate covalently linked to the antimetabolite cytarabine (araC). This first-in-human phase I dose escalation study assessed safety, tolerability, maximum tolerated dose (MTD), plasma pharmacokinetics, bone turnover, tumor biomarkers, and bone lesion activity by fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging.

Methods. Fifteen patients with advanced solid cancers and cancer-induced bone disease (CIBD) were treated with 0.5–10 mg/kg per day of MBC-11 administered daily for 5 days of every 4 weeks for up to four cycles.

Results. Grade 1–2 myelosuppression, involving all lineages, was the principal toxicity. Two of three patients treated with 10 mg/kg experienced dose-limiting grade 4 neutropenia and thrombocytopenia (adverse event [AE] duration ≤5 days); the MTD was 5 mg/kg. Four of five patients with pretreatment elevations of the bone resorption marker TRAP5b (tartrate resistant acid phosphatase-5b) had persistent decrements. Six of 13 patients who reported baseline pain noted a reduction after MBC-11. ^{18}F-FDG-PET/CT imaging demonstrated partial metabolic responses in three patients and stable metabolic responses in three other patients. SUV_{max} (standard unit of emission normalized to total uptake) was reduced by at least 25% in 110 (52%) of 211 bone lesions. Significant activity was noted across all doses, and myelosuppression increased with dose.

Conclusion. At MBC-11 doses that were well tolerated, substantial reductions in metabolic activity of bone-associated cancer cells provide a foundation for further disease-directed efficacy studies. ***The Oncologist*** 2019;24:303–e102

Discussion

MBC-11 is a conjugate of araC, linked through a phosphate group to an antiresorptive bisphosphonate, etidronate, designed to both target the conjugate to bone mineral and enable the concentration and release of drug to effectively kill cancer cells in bone lesions [1, 2]. In a subset of patients, MBC-11 was associated with stabilized or reduced bone turnover, with a more pronounced effect on resorption biomarkers (TRAP5b, C-telopeptide-CTX, deoxypyridinoline-DPD)

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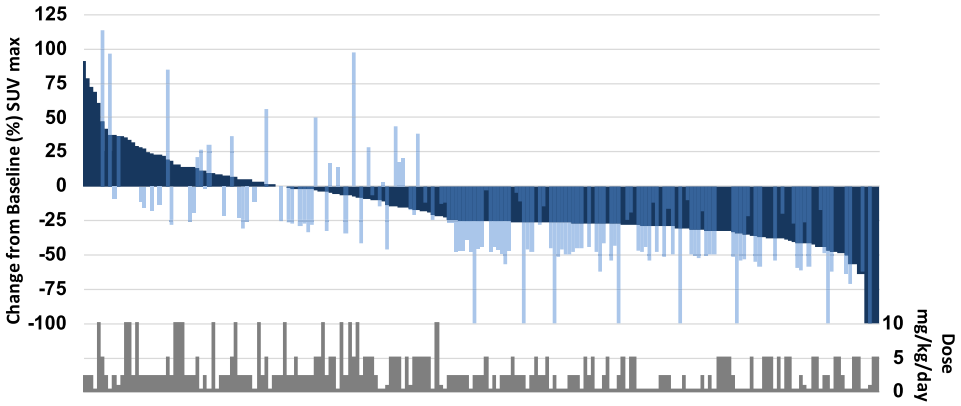

Figure 1. Of 14 patients, 211 bone lesions were detected at baseline using fluorodeoxyglucose positron emission tomography/computed tomography imaging. The change in SUV_{max} after 2 months (two cycles of therapy) are shown with dark-blue bars; −100% indicates reduction to below the limit of detection. Five patients continued on therapy for an additional 2 months (four cycles total); further changes from baseline are shown by light-blue bars overlapping their respective bone lesion at the two-cycle time point. Of the 211 lesions, 110 (52%) showed a reduction in SUV_{max} of ≥25% after two cycles of MBC-11. Of the 133 bone lesions present at baseline in the five patients who received four cycles, 85 (64%) showed a reduction. Six patients with progressive disease developed new bone lesions (Table 3). Five patients requested two additional cycles of therapy; at the end of 4 months two of these patients had new bone lesions appear. A total of six patients persisted without new bone lesions. The underlying grey bars correspond to their respective blue bars and indicate the dose-administered scale on right. Although not significant, it is interesting that the majority of responsive bone lesions correspond to the lower dosing.
Abbreviation: SUV_{max}, standard unit of emission normalized to total uptake.

than formation (bone-specific alkaline phosphatase-bALP, osteocalcine-OC, and procollagen 1NH2-terminal peptide-P1NH); this was consistent with observations in the canine osteosarcoma study [8]. A modest effect on tumor biomarkers was noted in a subset of patients.

MBC-11 is the first clinical demonstration of an araC delivery technology targeting bone and killing epithelial derived cancer cells. These observations indicate a significant fraction of MBC-11 is binding bone and releasing active concentrations of araC in the bone compartment. The MBC-11 MTD of 5 mg/kg results in a 1 μM systemic exposure to araC, notably 5–10-fold below the exposure needed in patients with leukemia. Despite the lower molar dosing of MBC-11 (at MTD) compared with araC regimens (2–20-fold higher), similar myelosuppressive AEs were observed, suggesting a relative concentration of the active form of araC in the bone compartment provided by MBC-11.

With PET Response Criteria in Solid Tumors (PERCIST) version 1.0 [3] criteria applied to ^{18}F-FDG-PET/CT imaging performed at baseline with 14 of the 16 patients, three patients displayed partial metabolic response (PMR), three patients displayed stable metabolic disease (SMD), and eight displayed progressive metabolic disease (PMD). Patients diagnosed with PMD often displayed significant reduction or stabilization of bone lesions; however, the appearance of a new lesion, including nonosseous lesions, defines PMD. Of the five patients receiving four cycles of therapy, two patients remained with SMD, and three showed PMD.

A non-PERCIST analysis of all measurable bone lesions with hypermetabolic cancer cell activity at baseline (Fig. 1) showed a significant reduction of 52% after cycle 2 and 64% after cycle 4. We observed both inter- and intrapatient variability, demonstrating that different lesions—even within the same patient—may regress below limits of detection, at a moderate level, or be unresponsive.

This study has demonstrated the dose-limiting toxicity (DLT; 10 mg/kg) and MTD (5 mg/kg) levels are driven by myelosuppression, and at doses below this MBC-11 is safe, well tolerated, and effective in treating CIBD lesions. Although reduction in bone lesion activity and antiresorptive activity occurs throughout the range of doses from 0.5 to 10 mg/kg, myelosuppression increases above 5 mg/kg. This is consistent with the wide therapeutic index of MBC-11 observed in animal models of multiple myeloma and breast cancer-induced bone disease [2]. The phase I clinical results of MBC-11 safety and activity on bone lesions, tumor biomarkers, and bone resorption markers demonstrate the effects of MBC-11 on treating cancer-induced bone lesions and warrant further clinical investigation.

Trial Information	
Disease	Breast cancer
Disease	Cervical cancer
Disease	Prostate cancer
Disease	Advanced cancer
Disease	Cancer-induced bone disease
Stage of Disease/Treatment	Metastatic/advanced

Prior Therapy	No designated number of regimens
Type of Study – 1	Phase I
Type of Study – 2	3 + 3
Primary Endpoint	Safety
Primary Endpoint	Tolerability
Secondary Endpoint	Maximum tolerated dose
Secondary Endpoint	Pharmacodynamics
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Efficacy

Additional Details of Endpoints or Study Design

Patients and methods. Patients with CIBD meeting the following criteria were included in the study: (a) men or nonpregnant, nonlactating women ≥18 years of age, having given written informed consent; (b) histologically confirmed malignant tumor with bone metastases or primary bone malignant tumor, documented by radiographs, bone scan, or bone biopsy (the presence of extraskeletal sites did not influence recruitment); (c) no available chemotherapy or indication for chemotherapy at screening, with an Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and expected survival ≥3 months; (iv) adequate bone marrow, liver, and renal function (defined below); and (v) men and women of childbearing potential in agreement to use contraception during and 2 months after study completion.

Exclusion criteria. Patients were excluded from the study if any of the following criteria were met at screening: (a) planned or concurrent use of radiotherapy, chemotherapy, or targeted (bio)therapy of cancer (bisphosphonates or denosumab were not allowed; hormonal therapy was allowed); (b) history of allergic reaction or intolerance to araC or to etidronate or other bisphosphonates; (c) fracture ≤6 months prior to inclusion in the study; (d) serious concomitant diseases, including HIV, hepatitis, diabetes mellitus, class II, III, or IV congestive heart failure as defined by the New York Heart Association, or central nervous system diseases with severe disturbance of intellectual and memory function; (e) known brain metastasis or a major surgery within 4 weeks prior to screening; (f) plasma calcium levels <8.5 mg/dL or a vaccination within 12 months prior to screening; (g) failure of vitally important organs in decompensation stage or any condition that, in the opinion of the investigator, increased the patient's risk for participating in the study; and (h) participation in another clinical study or use of systemic chemotherapy within 1 month before screening.

Study design. A phase I, open-label, nonrandomized multicenter clinical study of the safety, tolerability, pharmacodynamics, and pharmacokinetics of escalating doses of the drug MBC-11 in patients with malignant tumors with cancer-induced bone disease was approved by the Russian Ministry of Health (ClinicalTrials.gov NCT02673060). The trial was sponsored by Osteros BioMedica Ltd. and conducted in St. Petersburg, Russia. The study was approved by the Ethics Committee of the Ministry of Health, Russian Federation. All patients provided written informed consent that was reviewed by the local ethics committee prior to study initiation. The study was conducted in accordance with current Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki of the World Medical Association (latest edition Fortaleza, Brazil, October 2013), and applicable competent authority requirements including International Council for Harmonisation Guideline E6.

The study used a standard "three-by-three" dose escalation to define the MTD and to determine the recommended dose of MBC-11 for the further clinical studies. Five dose levels of MBC-11 were investigated sequentially: cohort 1 at 0.5 mg/kg, cohort 2 at 1 mg/kg, cohort 3 at 2.5 mg/kg, cohort 4 at 5 mg/kg, and cohort 5 at 10 mg/kg. The trial design did not allow patients to change dose cohorts or require expansion to six patients at the MTD.

Treatment began with a single administration of MBC-11, followed by a 7-day period of rest; treatment continued with a cycle of MBC-11, defined as 5 consecutive days of dosing followed by a 23-day period of rest (Fig. 2). Upon a cohort's completion of a cycle with acceptable safety and tolerability data, progression to the next dose was permitted. The progression from single to multiple administrations was applied to each successive cohort. Two cycles of MBC-11 were planned per patient, in the absence of unacceptable toxicity. Five patients choose to continue to cycle 3 and cycle 4 with investigator approval. The end of study visit was performed 23 days after the last dosing of MBC-11.

The study aims were to evaluate the safety and tolerability of MBC-11 in patients with CIBD, with the primary objectives of determining the DLT and MTD. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, were used to grade DLT, which was defined as any serious adverse event (SAE) or AE of at least grade 3 assessed if at least one of the following criteria were observed: (a) not resolving within 2 weeks after onset and requiring treatment interruption in the opinion of the investigator, or (b) any grade ≥ 4 toxicity, assessed as related to the MBC-11. In case of a DLT, the treatment of the respective patient was stopped immediately. Primary outcome measures of safety and tolerability were based on evaluation of adverse events; physical examination, laboratory parameters (complete blood count, clinical chemistry, coagulation, urinalysis), and 12-lead electrocardiogram were used to determine DLT and MTD.

The secondary pharmacodynamic outcomes included assessment of the following: (a) bone remodeling markers of formation (bone-specific alkaline phosphatase-bALP, osteocalcine-OC, and procollagen 1NH2-terminal peptide-P1NH) and resorption (C-telopeptide-CTX, tartrate resistant acid phosphatase-TRAP-5b, and deoxypyridinoline-DPD), (b) serum total and ionized calcium, and (c) serum tumor markers (CA15.3 for breast cancer, free prostate-specific antigen [PSA], total PSA for prostate cancer).

Exploratory efficacy assessments included (a) bone pain intensity measured by Numerical Rating Scale (NRS), (b) quality of life (QoL) measured by general QoL questionnaire SF-36, (c) ECOG performance status, (d) the number of skeletal-related events (pathologic fracture, radiation therapy or surgery to bone, spinal cord compression), (e) the objective response rate according to PERCIST criteria (see below) [3] using ^{18}F-FDG PET/CT, and (f) a bone-only analysis of all measurable bone lesions. This analysis defined a ≥ 25% reduction in SUV_{max} as responsive, <25% change as stable, and ≥ 25% increase as progressive. The two different image analyses allowed comparison of systemic with skeletal effects, as well as comparison with other publications that use either method. In addition, the bone-targeted nature of the MBC-11 drug design warranted a more thorough analysis of the impact on bone than PERCIST criteria would allow.

Statistical analysis. All patients receiving at least one dose of MBC-11 were included in all analyses. Statistical programming and analyses used the R software language and Statistica 10 software (TIBCO Software Inc., Palo Alto, CA). Demographics and baseline characteristics are presented as descriptive statistics as arithmetic means, standard deviations, median, minimum, maximum, and percentages as appropriate. Between-cohort comparisons were performed using the Kruskal-Wallis test. Between-cohort comparisons of categorical variable such as AEs—provided as incidence or tumor marker incidence rates—were performed using Fisher's exact test. Clinically significant deviations from the reference ranges were reported as adverse events, and the incidence rates for laboratory values outside of the normal range during the study were compared between treatment cohorts using Fisher's exact test. Quantitative variables were compared between subjects receiving different doses of the study medication at an individual visit using the Kruskal-Wallis H test. Tumor and bone-turnover biomarkers were summarized using descriptive statistics by cohorts, and the Friedman test was used to compare changes between baseline and end-of-cycles 1 and 2 visits for all patients and for cohorts.

The numbers of study participants within each objective response category, according to PERCIST criteria applied to ^{18}F-FDG-PET/CT image analysis, were calculated for each visit and cohort. Response rates were compared between cohorts at each visit using Fisher's exact test.

Bone pain intensity and ECOG performance status data were analyzed in the following way: descriptive statistics were provided for each corresponding visit and for each cohort. Between-cohort comparison was performed using the Kruskal-Wallis test. NRS data were compared within cohorts separately, using Friedman test. ECOG baseline values were compared with the data from the end of cycles 1 and 2, using the Wilcoxon *t* test.

Patient criteria definition of adequate functions included the following: adequate bone marrow function (hemoglobin ≥9 g/dL with or without transfusion requirement, absolute neutrophil count ≥1,500/mm^3, and platelets ≥75,000/mm^3), adequate liver function (bilirubin ≤2 × upper limit of normal [ULN], ALT ≤2.5 × ULN), and adequate renal function (creatinine ≤1.5 × ULN and creatinine clearance ≥50 mL/min).

PERCIST criteria restrict analysis to a total of seven lesions per patient and no more than two in one organ—we identified up to two predominant bone lesions per patient as the measurable target lesions and followed guideline [3] definitions of metabolic response: PMR (≥30% reduction in SUL_{max} [standard unit of emission normalized to lean body mass] of target lesions in the absence of new lesion formation or any lesion progression of ≥30% SUL_{max}), SMD (less than a 30% change in any lesion with no other signs of progression), PMD (≥30% increase in SUL_{max} of any lesion of the appearance of new lesions).

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	MBC-11
Trade Name	MBC-11
Company Name	Osteros Biomedica Ltd.
Drug Type	Small molecule
Drug Class	Bone-targeting conjugate of antiresorptive and antimetabolite
Dose	0.5, 1.0, 2.5, 5.0, 10 milligrams (mg) per kilogram (kg)
Route	IV
Schedule of Administration	Treatment began with a single administration of MBC-11, followed by 7-day period of rest; treatment continued with a cycle of MBC-11, defined as 5 consecutive days of dosing followed by a 23-day period of rest (Fig. 1). Upon a cohort's completion of a cycle with acceptable safety and tolerability data, progression to the next dose was permitted. The progression from single to multiple administrations was applied to each successive cohort. Two cycles of MBC-11 were planned per patient in the absence of unacceptable toxicity. Five patients choose to continue to cycle 3 and cycle 4 with investigator approval. The end of study visit was performed 23 days after the last dosing of MBC-11.

Dose Escalation Table

Dose level	Dose of drug: MBC-11	Number enrolled	Number evaluable for toxicity
1	0.5	3	3
2	1	3	3
3	2.5	3	3
4	5	4	4
5	10	3	3

Patient Characteristics	
Number of Patients, Male	8
Number of Patients, Female	8
Stage	All patients presented with bone metastases: eight with <6 metastases, three with 6–20 metastases, and three with >20 metastases. Two patients received one cycle of MBC-11, eight patients received two cycles of MBC-11, and five received four cycles of MBC-11
Age	Median (range): 62 ± 13 years
Number of Prior Systemic Therapies	Median (range): Not collected
Performance Status: ECOG	
	0 — 3
	1 — 11
	2 — 2
	3 — 0
	Unknown —
Cancer Types or Histologic Subtypes	
	Breast cancer — 7
	Prostate cancer — 8
	Cervical cancer — 1

Primary Assessment Method	
Title	^{18}F-FDG-PET/CT Metabolic Response
Number of Patients Enrolled	16
Number of Patients Evaluable for Toxicity	16
Number of Patients Evaluated for Efficacy	14
Evaluation Method	Other (PERCIST 1.0)
Response Assessment: Metabolic CR	*n* = 0 (0%)
Response Assessment: Metabolic PR	*n* = 3 (21%)
Response Assessment: Metabolic SD	*n* = 3 (21%)
Response Assessment: Metabolic PD	*n* = 8 (57%)

Outcome Notes

The term *metabolic*, which prefaces all response criteria (*mCR*, *m*PR, *m*SD, *m*PD), indicates the cancer cell activity within the seven target lesions per patient measured and evaluated as per PERCIST criteria. These results are illustrated in more detail in Table 3 and allow comparison of the per lesion effect of MBC-11, as illustrated in Figure 1, with the per-patient effect presented here by PERCIST based responses.

Adverse Events

All Cycles

Name	NC/NA	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades
Blood and lymphatic system disorders - thrombocytopenia	56	25	0	6	13	0	44
Anemia	25	38	31	6	0	0	75
Hematuria	94	0	0	6	0	0	6
Blood and lymphatic system disorders - lymphopenia	68	13	6	13	0	0	32
Neutrophil count decreased	68	0	19	0	13	0	32
Blood and lymphatic system disorders - leukopenia	18	56	13	13	0	0	82
Nausea	88	6	0	6	0	0	12

Febrile neutropenia	94	0	0	6	0	0	6
Rash maculopapular	94	6	0	0	0	0	6
Vomiting	94	0	6	0	0	0	6
Bone pain	75	0	19	6	0	0	25
Renal and urinary disorders - leukocyturia	94	6	0	0	0	0	6
Proteinuria	94	6	0	0	0	0	6
Fatigue	68	13	19	0	0	0	32
Pain in extremity	94	0	6	0	0	0	6
Nervous system disorders - hyporeflexia	94	0	6	0	0	0	6
Upper respiratory infection	94	0	6	0	0	0	6

Worst-grade toxicity recorded in all patients, across all cycles.

Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Neutropenia	4	Definite
Thrombocytopenia	4	Definite

Of all adverse events, 14 were severe, including seven SAEs (two grade 4, and one grade 3 thrombocytopenia; two grade 4, and one grade 3 neutropenia one; one hematuria). The hematuria was listed as a urinary bladder hemorrhage and occurred 7 days after a single injection, and the patient did not complete a full cycle or proceed in the study. The SAE resolved after 54 days and was not considered a DLT. Four of the seven SAEs listed as blood disorders were considered DLT: two patients with breast cancer receiving 10 mg/kg MBC-11 each developed a grade 4 thrombocytopenia and a grade 4 neutropenia; all resolved within 7 days.

Dose-Limiting Toxicities

Dose level, mg/kg	Adverse event	SAE grade	Number with a dose-limiting toxicity
10	Thrombocytopenia	4	2
10	Neutropenia	4	2

Abbreviation: SAE, serious adverse event.

Pharmacokinetics and Pharmacodynamics

Dose level	Dose of drug: MBC-11, mg/kg	Drug or metabolite	C_{max}, mean ± SD, ng/L	T_{max}, h	$AUC_{0–72}$, mean ± SD, h × ng/mL	$T_{½}$, mean ± SD, h (after infusion)	Cl F, mean ± SD, L/h	V_d, L
4	5	MBC-11	744 ± 550	1.75	1150 ± 424	≤0.25	402 ± 160	616 ± 326
4	5	araC	327 ± 120	2	605 ± 144	≤0.25	735 ± 277	1173 ± 438
4	5	araCMP	246 ± 225	1.25	418 ± 313	≤0.25	1866 ± 498	1179 ± 760
4	5	araU	3045 ± 212	3.25	44243 ± 14987	9.6 ± 2.8	10.7 ± 5	134 ± 40
4	5	Etidronate	3752 ± 771	2.75	15838 ± 7528	4.9 ± 2.5	32 ± 17	181 ± 36

Single 5 mg/kg dose plasma pharmacokinetic parameters derived from the four patients of cohort 4. The mean of the cohort dosed at 5 mg/kg is provided with standard deviation; calculations included the time points during the infusion. Note the T_{max} for MBC-11 and the two rapidly cleared metabolites (araCMP and araC) occurred during the infusion.Abbreviations: $AUC_{0–72}$, area under the concentration-time curve from 0 to 72 hours; Cl F, total plasma clearance; C_{max}, maximal concentration; $T_{1/2}$, half-life; T_{max}, time for maximal concentration; V_d, volume of distribution.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

This is one of two bisphosphonate conjugates tested in clinical trials and the first to demonstrate efficacy (ClinicalTrials.gov identifiers: MBC-11, NCT02673060; Osteodex, NCT01595087). Sixteen patients received at least one dose of MBC-11. Fifteen patients completed at least one cycle of MBC-11 (Fig. 2). The majority of adverse events were

blood and lymphatic disorders and were consistent with the myelosuppressive effects known for the araC moiety of the conjugate.

Pharmacokinetic parameters and a representative time course of plasma exposure to MBC-11 and its metabolites are presented in Figure 3 for the patients dosed at 5 mg/kg. During the 2-hour infusion period of MBC-11, araCMP (direct hydrolysis product), araC (metabolite of araCMP), and araU (metabolite of araC) remained at an approximate concentrations of 1 μM, whereas etidronate (direct hydrolysis product of MBC-11) increased up to 10 μM by the end of infusion and continued to increase another 40% over the next 30–60 minutes (as shown in Fig. 3's graph of patient 12). At the end of infusion of MBC-11, araCMP and araC were eliminated rapidly ($T_{1/2}$ < 30 minutes). Etidronate elimination after infusion was consistent with reported elimination half-life of 1–6 hours [4, 5]. During and after the infusion, the appearance of araU lagged behind that of etidronate (T_{max} 3.25 and 2.75 hours, respectively). The rapid conversion of araC into araU and the slow elimination of araU are consistent with published reports [6, 7].

In a subset of patients, MBC-11 was associated with stabilized or reduced bone turnover, with a more pronounced effect on resorption (TRAP5b, CTX, DPD) than formation (bALP, OC, P1NH); this was consistent with observations in the canine osteosarcoma study [8].

The changes in the breast cancer marker, CA15-3 antigen, are presented in Table 1. CA15-3 antigen serum level was decreased or unchanged in three of six patients at the end of cycle 2.

The changes in the prostate cancer markers, total prostate-specific antigen (PSA) and the ratio of free PSA to total PSA, are presented in Table 2. Four patients demonstrated a trend in stabilization, and one patient demonstrated an improvement in PSA status.

All patients from cohorts 1–5 had median Eastern Cooperative Oncology Group (ECOG) performance status of 1 at baseline and end of cycle 2. ECOG worsened in four patients; two went from 0 to 1, and two went from 1 to 3 ECOG status by the end of cycle 2. All other patients and the five patients treated through four cycles remained unchanged at ECOG status of 1.

Six of 13 patients reported a reduction in pain (Numerical Rating Scale) at the end of the first week of dosing that remained below baseline in four patients at the end of cycle 2; of five patients who continued through four cycles of treatment, two remained below baseline reports; this suggests a trend toward pain reduction in a subset of patients.

Skeletal related events were not observed throughout the duration of the study and are consistent with the overall stabilization or reduction in bone lesion activity observed by imaging.

Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging demonstrated a significant reduction in cancer cell metabolic activity in many bone lesions. Table 3 shows the results of 14 of the 16 patients who had ^{18}F-FDG-PET/CT performed at baseline and at the end of two cycles of treatment; five patients continued therapy and were imaged after completion of four cycles of therapy. PET Response Criteria in Solid Tumors (PERCIST) version 1.0 [3] criteria limited analysis to one or two target bone lesions and a total of seven lesions—including nonosseous lesions—per patient. After two cycles of MBC-11, three patients displayed partial metabolic response (requiring ≥30% reduction in a target lesion SUL_{max} [standard unit of emission normalized to lean body mass] and the absence of new lesions or increase of any lesions by ≥30% SUL_{max}), three patients displayed stable metabolic disease (SMD), and eight displayed progressive metabolic disease (PMD). It is important to note that patients diagnosed with PMD often displayed significant reduction or stabilization of bone lesions; however, the appearance of a new lesion, including nonosseous lesions, is defined as PMD by PERCIST. Of the five patients receiving four cycles of therapy, two patients remained with SMD, and three showed PMD.

Within PERCIST analysis, five patients had 14 sites of nonosseous cancer followed over the course of therapy. SUL_{max} for three nonosseous sites increased by >30%; the remaining 11 nonosseous sites remained stable or decreased—including three below the limits of detection after two cycles of therapy (see Table 5).

To further understand the impact of MBC-11 upon bone lesions, a non-PERCIST analysis included all measurable bone lesions, identifying a total of 211 bone lesions with hypermetabolic cancer cell activity at baseline. Of the 211 lesions, 110 (52%) showed a reduction in SUV_{max} (standard unit of emission normalized to total uptake) of ≥25% after two cycles of MBC-11 compared with baseline. Of the 133 bone lesions present at baseline in the five patients who received four cycles of treatment, 85 (64%) showed a reduction in SUV_{max} of ≥25%.

We observed both inter- and intrapatient variability, demonstrating that different lesions—even within the same patient—may regress below limits of detection, at a moderate level, or be unresponsive. Although the bone lesions of patient 02 were stabilized, significantly reduced, or reduced below the limits of detection (Table 3), the increase of ≥30% in activity in a prostate lesion defines PMD by PERCIST (Table 4) [3]. This example highlights the need in the case of bone-targeted drugs to analyze bone tissue specifically while separately applying PERCIST criteria to understand the impact across all tissues. It is interesting to note that significant benefit was observed in a subset of patients across all cohorts, and thus no dose response was observed with regard to efficacy, whereas dose response was obvious in regard to myelosuppression.

The phase I clinical results of MBC-11 safety and activity on bone lesions, tumor biomarkers, and bone resorption markers demonstrate the effects of MBC-11 on treating cancer-induced bone lesions and warrant further clinical investigation; an additional six patients at the maximum tolerated dose would be included if this study were to be repeated.

In summary, the pharmacokinetic results are consistent with a large fraction of MBC-11 being hydrolyzed in the blood, while a smaller but significant fraction—accounting for efficacy—binds the bone mineral and is subsequently hydrolyzed on the bone surface or presumably within osteoclasts to release araC for uptake by bone-localized cancer cells—as was the intent of the drug design. MBC-11 was

discovered and preclinically developed by MBC Pharma Inc (Aurora, CO) and subsequently licensed to Osteros Biomedica Ltd. (Moscow, Russia) for clinical development. MBC-11 active pharmaceutical ingredient was manufactured by Johnson Matthey Pharma Services (Devens, MS). Phase II work is planned for in a multisite open label study in Russia; with success, continued international development will be pursued.

The phase II study will investigate the effects of MBC-11 in patients with bone metastases as the dominant site of disease due to castration-resistant prostate cancer or breast cancer.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

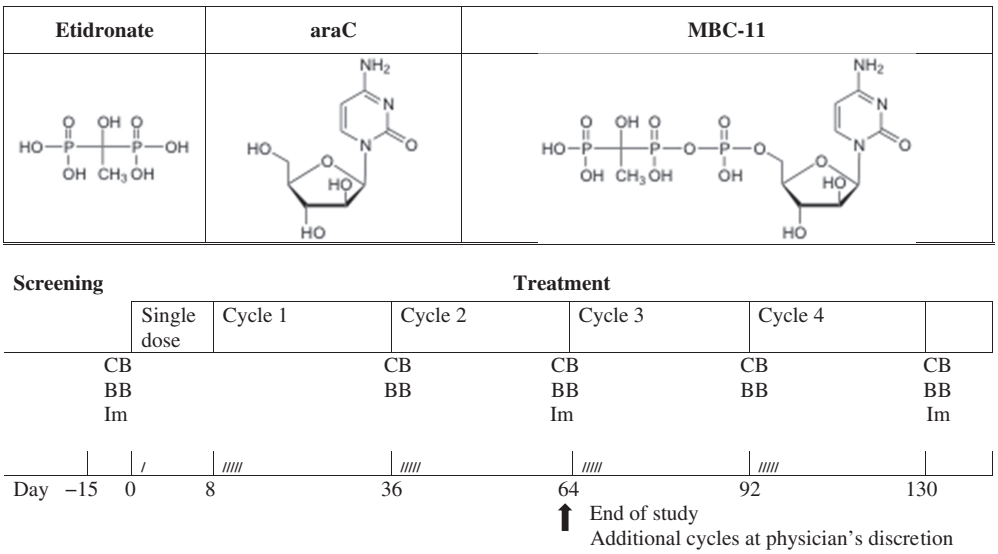
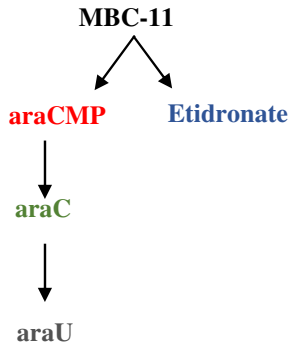


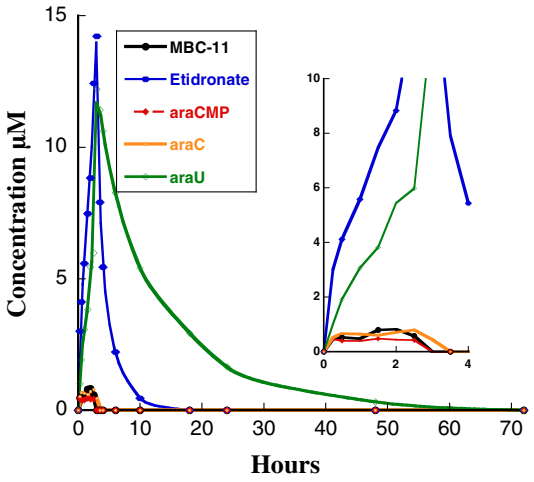
Figure 2. MBC-11 chemical structure and study design. **(Top row):** Chemical structures of active drug moieties, etidronate and araC, and MBC-11. **(Lower row):** Screening: Confirmed metastatic bone cancer and consistency with exclusion/inclusion criteria. Treatment: MBC-11 administered as a single 2-hour infusion followed by 7 days without drug prior to first cycle; subsequently, MBC-11 administered as 2-hour infusions on the first 5 days of a 28-day cycle. End of study defined as 1 week after the end of cycle 2, unless physician directed extension with cycles 3 and 4, defining end of study as 1 week after end of cycle 4.
Abbreviations: /, single dose; BB, bone biomarkers; CB, cancer biomarkers (PSA or CA-15-3); Im, 18F-FDG PET/CT.

A



B

Inset shows MBC-11 and nucleoside metabolites during the 2-hour infusion time and shortly thereafter.



C

PK parameter	MBC-11, mean ± SD	araC, mean ± SD	araCMP, mean ± SD	araU, mean ± SD	Etidronate, mean ± SD
C_{max}, ng/mL	743.5±549.9	326.8±119.6	246±225.3	3045±212.1	3752.5±771.2
$AUC_{0–72}$, ng/mL·h	1149.5±424.1	604.9±143.9	417.8±312.5	44242.8±14986.5	15837.9±7528.2
AUC_{0-00}, ng/mL·h	1149.5±424.1	604.9±143.9	557±173.5	44242.8±14986.5	16054.2±7947.2
AUMC, ng/mL·h^2	1611.89±319.7	1007.2±418.6	553.6±410.9	44780.5±15627.6	131171.9±129590.5
MRT, h	1.5±0.3	1.6±0.3	1.3±0.1	13.8±4.0	7.0±3.7
$T_{1/2}$, h (after infusion)	1.018±0.2 (<15 min)	1.13±0.21 (<15 min)	0.9±0.1 (<15 min)	9.6±2.8	4.9±2.5
T_{max}, h	1.75	2	1.25	3.25	2.75
Kel, h^{-1}	0.696±0.118	0.631±0.112	0.753±0.08	0.078±0.028	0.173±0.087
CL, mL/h	402173± 160187.9	734828.6±276736.7	866351.6±498196.8	10665.3±4946.5	31909.4±16941.0
V_d, mL	616379.3±326048.6	1173351.1±437660.4	1179477.5±759977	133741.7±39867.6	181408.3±36051.9

Figure 3. Plasma pharmacokinetics of MBC-11. **(A):** MBC-11 Metabolic breakdown pathway. MBC-11 is hydrolyzed to etidronate and araCMP. Etidronate does not break down further. AraCMP is rapidly dephosphorylated to araC, which is deaminated to araU. **(B):** Time course of plasma exposure in patient 12 to MBC-11 and its metabolites. **(C):** Single 5 mg/kg dose plasma PK parameters. The mean of the cohort dosed at 5 mg/kg is provided with standard deviation; calculations included the time points during the infusion.
Abbreviations: AUC_{0-00}, Area under the concentration-time curve from zero to infinity; $AUC_{0–72}$, Area under the concentration-time curve from zero to 72-hours; AUMC, Area under the concentration-time curve from the first moment to infinity; CL, clearance; C_{max}, maximal concentration; Kel, elimination rate; MRT, mean residence time; PK, pharmacokinetics; $T_{1/2}$, half-life; T_{max}, time for maximal concentration; V_d, volume of distribution.

Table 1. CA15.3 antigen in patients with breast cancer

Patient #	Dose, mg/kg	Baseline	End of cycle 2	End of cycle 4	Change, %
03	0.5	245	136	97	−60
09	2.5	**12**	**15**	—	Stable normal
10	2.5	72	133	—	+46
11	2.5	32	39	**25**	−22
19	5	1,050	1,246	—	+16
20	10	521	1,076	—	+52

Bolded values indicate values within the normal reference range ≤25 U/mL.
Abbreviation: —, data was not collected for patients that completed study after 2-cycles of treatment.

Table 2. Prostate-specific antigen in prostate cancer subgroup

Patient #	Dose, mg/kg	Baseline		End of cycle 2		End of cycle 4	
		Total	Free	Total	Free	Total	Free
01	0.5	427	30	15	5	—	
02	0.5	35	5	50	9	—	
04	1	**0.3**	**0.1**	**0.3**	**0.1**	**0.4**	**0.1**
07	1	21	8	27	6	—	
08	1	8	3	34	12	210	64
12	5	72	28	427	125	—	
15	5	10	1.2	9	1.1	—	

Bolded values indicate values within the normal reference.
Abbreviation: —, data was not collected for patients that completed study after 2-cycles of treatment.

Table 3. Results of ^{18}F-FDG-PET/CT image analysis using PERCIST criteria and independent assessment of all measurable bone lesions

				Analysis 2: All measurable bone lesions[c]												
		Analysis 1: PERCIST[b] diagnosis		Total			End of cycle 2					End of cycle 4				
							Responsive		Stable	Progressive		Responsive		Stable	Progressive	
Patient-cancer[a]	Dose, mg/kg	End cycle 2	End cycle 4	Base-line	End cycle 2	End cycle 4	BD	≤25%	±24%	≥25%	NL	BD	≤25%	±24%	≥25%	NL
01-P	0.5	PMD		2	3	—			1	1	1					
02-P	0.5	PMD		4	3	—	1	2	1							
03-B	0.5	PMR	PMD	54	54	54		44	10				40	12	2	
04-P	1.0	PMR	SMD	3	3	3		1	1	1			1	1	1	
07-P	1.0	PMR		1	0	—	1	1								
08-P	1.0	PMD	PMD	2	2	7			2				1	1		5
09-B	2.5	PMD		4	4	—		2	2							
10-B	2.5	PMD		16	30	—			10	6	14					
11-C	2.5	SMD	SMD	57	57	52		31	25	1		5	43	14		
12-P	5.0	PMD		33	35	—		25	8		2					
15-P	5.0	PMD		2	1	—	2	2			1					
19-B	5.0	SMD	PMD	17	17	20		2	14	1				9	8	3
20-B	10.0	PMD		15	30	—			12	3	15					
41-B	10.0	SMD		1	6	—			1		5					
			Totals	**211**	245	—	4	**110**	87	13	38	5	85	37	11	8

[a]Patient number and original primary cancer.
[b]PERCIST criteria define the following: PMR, ≥30% reduction in SUL_{max} (standard unit of fluorescence normalized to lean body mass) in up to two target lesions; SMD, ≤30 increase in SUL_{max} in any measurable lesion; PMD, if ≥30 increase in SUL_{max} in any measurable lesion or appearance of any new lesion.
[c]Measurable bone lesions were not restricted to the target lesions defined by PERCIST but included all measurable detected bone lesions; the change in SUV_{max} was grouped into Responsive (reduction of ≥25%, including lesions no longer detectable [BD]), Stable (no ± change >25%), and Progressive (increase of ≥25% or the appearance of a new bone lesion [NL]).
Abbreviations: —, data was not collected for patients that completed study after 2-cycles of treatment; B, breast cancer; BD, below the limit of detection; C, cervical cancer; NL, new lesion; P, prostate cancer; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PMD, progressive metabolic disease; PMR, partial metabolic response; SMD, stable metabolic disease.

Table 4. Nonosseous sites of cancer and metastases

		SUL_{max}		
Patient	**Site**	**Baseline**	**End of cycle 2**	**End of cycle 4**
01-P	Prostate	5.6	6.7	
	Lung	4.38	0	
02-P	Prostate	7.74	13.88	
	Skin	5.76	5.07	
	Lymph node	4.11	3.14	
	Body of V4	4.59	0	
	Lymph node	3.19	0	
03-B	Lymph node	9.6	2.8	2.59
20-P	Adrenal	6.05	5.84	
	Lymph node	5.56	5.7	
	Liver	5.46	7.18	
	Neck of femur	6.1	9.74	
	Lymph node	5.19	6.14	
41-B	Lung	1.69	1.93	

Imaging results provided as SUL_{max}; zero indicates below limit of detection, blank cell indicates data was not collected at that time point.
Abbreviations: B, breast cancer; P, prostate cancer; SUL_{max}, standard unit of fluorescence normalized to lean body mass.