Immunotherapy development landscape for bone metastasis – need of predictive preclinical efficacy evaluation for de-risking clinical development

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Introduction

Most cancer deaths are caused by metastases. Bone metastases are a challenge especially in breast and prostate cancer, being developed in 70-90% of advanced-stage patients. Bone metastases remain incurable causing high mortality, skeletal-related effects and decreased quality of life. Only 5% of patients with bone metastases are alive 5 years after the diagnosis.

Currently approved immunotherapies are ineffective in bone metastases. Development of therapies for bone metastasis has been challenging due to lack of appropriate preclinical models, especially in the context of immuno-oncology. This creates a need to improve understanding immune microenvironment in bone metastases, namely interactions between tumor, immune and bone cells according to the osteoimmuno-oncology (OIO) concept, and ultimately to develop immunotherapies that primarily target bone metastases. In this study we used 1stOncology, a cancer drug development resource, to identify novel immunotherapies in development for breast and prostate cancer with data available for the effects on bone metastasis.

We aimed to 1) identify novel immunotherapies in development for breast and prostate cancer with clinical data available for bone metastasis; 2) describe how to improve preclinical evaluation of immunotherapies by introducing a preclinical Bone Metastasis Technology Platform (“The Platform”).

Materials and Methods

1stOncology database is a cancer drug development resource including information from 23 291 drugs, 2 056 targets (situation on March 13, 2024) and new data is added constantly. New data includes information obtained from abstracts/posters from scientific meetings, and companies' publications such as presentations and press releases. 1stOncology provides a tool to search for information or therapies in development, that would be difficult to obtain elsewhere.

The Platform utilizes human or mouse tumors growing in bone microenvironment resulting in a model that mimics the growth of bone metastases in patients. The Platform provides a predictive tool for studying unique biological features associated with different types of bone metastases and immune cell infiltration in cancer type -specific manner. When either syngeneic or humanized mouse models with tumor and immune cells of same species are used, interactions of tumor and immune cells in bone metastatic microenvironment can the studied and targeted with novel immunotherapies.

Results

1stOncology database and summary of findings

We used 1stOncology database, a cancer drug development resource, to identify novel immunotherapies in development for breast and prostate cancer bone metastasis (Table 1). Twenty-four immunotherapies that included evaluation of effects on bone metastasis were identified. Twenty of these drugs are in clinical development (Table 2), 1 is not under active development, and 3 are in preclinical stage. Efficacy of only 3 of the identified therapies have been evaluated in preclinical bone metastasis models, one reason being that such models have not been commonly available. The use of clinically relevant and predictive preclinical bone metastasis models would significantly de-risk decision making when moving to clinical development in bone metastasizing cancers.

Table 1. Summary of database searches performed.

Database search	Breast cancer	Prostate cancer
All drugs in active development	1,498 drugs	746 drugs
Limiting to drugs with development related to bone metastasis	242 drugs	206 drugs
Further Limiting to immuno-oncology drugs only	67 drugs	73 drugs
Further Limiting to immuno-oncology drugs in clinical development (phase 1-3)	36 drugs	47 drugs
Drugs with published data available about effects on bone metastasis	0 drugs	20 drugs*

* Of the 20 drugs, 6 included both breast and prostate cancer as indication, but bone metastasis data is published only in prostate cancer.

Table 2. Immuno-oncology drugs in clinical development for prostate cancer in the context of bone metastasis (data cut-off July 2023).

ASSET NAME	TARGET(S)	MODALITY	TRIAL	SELECTED ELIGIBILITY CRITERIA AND OUTCOME MEASUREMENT		TRIAL STATUS	DEVELOPER/ SPONSOR
				INCLUSION	OUTCOME		
Imifoplatin (PT-112)	Pyrophosphate-platinum conjugate	Small molecule	NCT02266745, ph1/2	Progressive disease measured by physical examination or imaging (RECIST v1.1 or PCWG3 or by informative tumor markers)	Secondary: rPFS, disease control rate, objective response rate, duration of response, OS	Recruiting	Promontory Therapeutics/ Pfizer, EMD Serono
P-PSMA-101	PSMA	CAR-T	NCT04249947, ph1 (in combination with rimiducid)	Measurable disease by RECIST 1.1 or bone only metastases with measurable PSA	Overall response rate, % of patients with complete or partial response	Recruiting	Poseida Therapeutics
Pasotuximab (BAY2010112)	PSMAxCD3	Bispecific antibody	NCT01723475, ph1	Appearance of one more new lesions in bone scan	Secondary: Tumor and PSA response	Completed	Bayer
MGC018	B7-H3	ADC	NCT03729596, ph1/2 (combination with anti-PD-1 will not enroll) NCT05551117, ph2/3	In prostate cancer cohort, patients with bone only disease are eligible One or more metastatic lesion, present MRI, CT or bone scan	Secondary: OS, PFS, rPFS, response rate Primary: rPFS	Active, not recruiting Not yet recruiting	MacroGenics
OS-7300a	B7-H3	ADC	NCT04145622, ph1/2	CRPC participants with bone only disease may be eligible on a case-by-case basis	Anti-tumor activity	Recruiting	Daiichi Sankyo
MVI-118	Encode AR LBD	DNA vaccine	NCT02411786, ph1 (+/- GM-CSF)	Soft tissue and/or bone metastases by radiographic imaging	Secondary: Median and 18-month PFS	Completed	Madison Vaccines
MVI-816 (pTVG-HP)	Encode AR LBD	DNA vaccine	NCT01706458, ph2 (in combination with sipuleucel-T) NCT02499835, ph1/2 (in combination with pembrolizumab)	Soft tissue and/or bone metastases in imaging studies	Secondary: PFS, time to radiographic progression	Completed Active, not recruiting	Madison Vaccines
Recombinant Ad5 vaccine	PSA/ MUC-1/ brachyury	Virus vaccine	NCT03481816, ph1	Metastatic bone disease in an imaging study	Secondary: OS, PFS	Completed	ImmunityBio/ NCI
Rilimogene glafolivec	PSA, CD48, CD80, ICAM1, KLK3	Virus vaccine	NCT01322490, ph3 (+/- GM-CSF)	Radiological progression (new or growing bone metastases or new/enlarging lymph node disease)	Primary: OS, number alive without event after 6 months (event is two new bone lesions or other metastases)	Completed	Bavarian Nordic
Bintrafusp alfa (M7824) and M9241	PD-L1- TGFβ NHS-IL12A	Fusion protein Fusion protein	NCT04633252, ph1/2 (in combination with androgen deprivation therapy, prednisone and docetaxel)	Metastatic disease, defined as at least one lesion on TC99 bone scan or at least one measurable lesion per RECIST 1.1.	Secondary: Radiographic response rates, radiographic and biochemical time to progression	Recruiting	Merck KGaA/NCI
Vudalimab (XmAb20717)	PD-1 x CTA-4	Bispecific antibody	NCT05005728, ph2 (in combination with carboplatin, cabazitaxel, olaparib)	Progression of bone disease (evaluable disease) or 2 or more new bone lesions by bone scan	Secondary: Objective response rate by PCWG3, bone scan and rPFS, duration of response	Recruiting	Vencor
Tremelimumab	CTLA-4	Monoclonal antibody	NCT03204812, ph2 (in combination with durvalumab)	Evidence of metastatic disease to the bone seen in most recent bone scan, CT scan and/or MRI	Secondary: rPFS, median OS	Completed	Pfizer/MDA
BMS-986249	CTLA-4	Conditionally activated antibody	NCT03369223, ph 1/2 (in combination with nivolumab)	Measurable disease or metastatic disease documented by bone lesions in radionuclide bone scan	Secondary: PFS, overall response, duration of response	Recruiting	CytomX Therapeutics/ BMS
Epacadostat and MVA-BN Brachyury	IDO1 TBXT	Small molecule Protein	NCT03493945, ph1/2 (in combination with M7824 and N-803)	Radiographically proven metastatic or locally advanced solid tumor of any type	Secondary: PFS	Recruiting	Incyte/NCI Bavarian Nordic
Talabostat mesylate (BXCL701)	DPP4, DPP8, DPP9, FAP	Small molecule	NCT03910660, ph1/2 (in combination with pembrolizumab)	RECIST 1.1 measurable disease or detectable bone metastases by whole body bone scintigraphy	Secondary: rPFS, median OS, duration of response	Recruiting	BioXcel Therapeutics
Dendritic cell vaccine	CTAG1B, MAGEC2, MUC1	Cell vaccine	NCT02692976, ph2	Bone disease progression defined by two or more new lesions in bone scan as described in PCWG2 criteria	Secondary: rPFS, OS	Completed	Radbound University
MB-105	PSCA	CAR-T	NCT03873805, ph1	Radiographic evidence of new metastatic foci in computed CT or bone scan	Secondary: rPFS, OS	Recruiting	Fortress Biotech/ City of Hope
Reolysin (pelareorep)	N/A	Virus	NCT01619813, ph2 (in combination with docetaxel and prednisone)	Metastatic or locally recurrent disease, clinically and/or radiologically documented disease	Primary: Disease progression, OS	Completed	Oncolytic Biotech

‘Developer” refers to the original developer/owner, “Stage” refers to the highest development stage. “Inclusion” and “Outcome” columns include selected parameters relevant in the context of bone metastasis. Detailed description of the drugs and the results are provided in the chapters below. All listed trials are for prostate cancer. Abbreviations: AR = androgen receptor, B7-H3 = B7 homolog 3, CAR-T = chimeric antigen receptor, T cell, CD = cluster of differentiation, CRPC = castration-resistant prostate cancer, CTAG1B = cancer/testis antigen 1B, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, DPP = dipeptidyl peptidase, FAP = fibroblast activation protein, ICAM 1 = intracellular adhesion molecule 1, IL12A = interleukin 12 A, KLK3= kallikrein related peptidase 3, LBD = ligand binding domain, MAGEC2 = MAGE family member C2, MRI = magnetic resonance imaging, MUC-1 = mucin-1, OS = overall survival, PCWG3 = prostate cancer working group 3, PD-1 = programmed cell death 1, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, PSA = prostate-specific antigen, PSCA = prostate stem cell antigen, PSMA = prostate-specific membrane antigen, RECIST = response evaluation criteria in solid tumors, rPFS = radiographic progression-free survival, TBTX = T-box transcription factor T, TGFβ = transforming growth factor beta.

Overview of the Preclinical Bone Metastasis Technology Platform

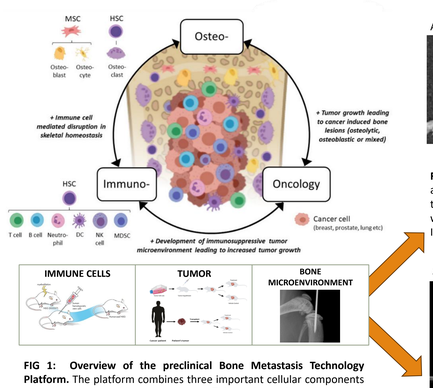

FIG 1: Overview of the preclinical Bone Metastasis Technology Platform. The platform combines three important cellular components that affect growth of bone metastases. This can be achieved by the use of syngeneic models with mouse immune and tumor cells or human immune cells from Human Immune System (HIS) mouse models and human tumor cells from cell line -derived xenografts (CDX) or patient-derived xenografts (PDX). Most importantly, in both cases the tumors need to grow in bone microenvironment to allow tissue-specific interactions in a bone metastasis specific microenvironment. This can be achieved for example by intratibial (see figure on the right) or intracardiac inoculation of tumor cells. Images from Kähkönen et al., 2021.

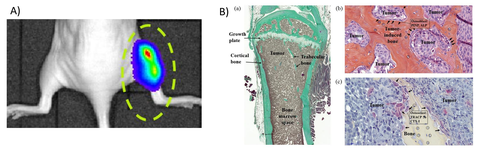

FIG 2: Analysis of bone metastasis growth. A) Bioluminescence imaging (BLI) can be used to assess tumor growth in vivo. B) Histological analysis reveals that bone marrow is filled with tumor cells that interact with bone-forming osteoblasts to form osteoblastic bone metastases, or with osteoclasts to induce rapid bone resorption and formation of osteolytic bone metastases. Images from Kähkönen et al., 2022.

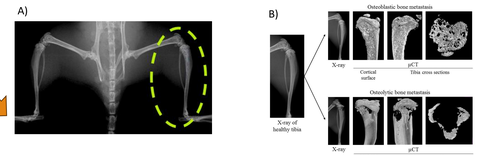

FIG 3: Analysis of cancer-induced bone changes. Imaging techniques such as A) X-ray and B) μ-computed tomography (μCT) can be used to assess tumor-induced bone growth in vivo. Cancer type -specific effects are observed in preclinical models and patients. In prostate cancer, typically observed bone metastases are osteoblastic, where bone marrow becomes filled with rapidly forming pathologic new bone, causing bone pain. In breast cancer, osteolytic bone metastases with rapid resorption of bone are typically observed, leading to increased risk of fractures. Images from Kähkönen et al., 2022.

Validation and clinical significance of The Platform

Table 3. Validation of the preclinical Bone Metastasis Technology Platform. Summary of preclinical findings in the platform in terms of drug efficacy and clinical outcome in current clinical practice or clinical development.

Drug	Preclinical findings	Clinical outcome
Bone-targeted treatments		
Xofigo, Radium-223 dichloride	Effectively decreases tumor burden and bone changes	Approved for the treatment of CRPC patients with bone metastases
Zometa, Zoledronic acid	Effectively prevents cancer-induced bone loss, no effect on tumor	Approved for the treatment of breast cancer patients with bone metastases
Immuno-oncology treatments		
Keytruda, pembrolizumab	No effects on bone metastases	4 phase III clinical trials failed in bone metastatic CRPC and TNBC
Epacadostat, IDO-inhibitor	No effects on bone metastases	No single agent activity on metastasis

Radium-223 dichloride

Preclinical results: Decreased tumor growth, as evaluated by decreased serum PSA values and osteoblastic bone growth (Suominen et al., 2017)

Clinical relevance: Approved for bone metastatic mCRPC, increases life expectancy of patients but does not cure the cancer.

Zoledronic acid

Preclinical results: Prevented cancer-induced bone loss but had no effect on tumor growth in a syngeneic breast cancer model (Kähkönen et al., 2019a)

Clinical relevance: Used in bone metastatic breast cancer patients to prevent cancer-induced bone loss.

Pembrolizumab

Preclinical results: No effects on prostate cancer bone metastases as evaluated by decreased serum PSA values and osteoblastic bone growth (Kähkönen et al., 2019b). No effect on growth of breast cancer bone metastases due to lack of tumor-infiltrating lymphocytes in the bone microenvironment (Kähkönen et al., 2018).

Clinical relevance: Failed to demonstrate efficacy in patients with prostate or breast cancer bone metastasis in phase III trials.

Epacadostat

Preclinical results: No effects on bone metastasis growth in a syngeneic breast cancer model (Kähkönen et al., 2019a).

Clinical relevance: No single agent activity in metastatic breast cancer patients.

Conclusions

Based on the database search we identified 20 therapies currently in clinical development for breast and prostate cancer with data available on bone metastasis. This is less than 1% of all drugs in active development, which is surprising, knowing that bone metastases are a major cause of death in breast and prostate cancer and highlights significant underestimation of the importance of targeting bone metastases in drug development.

When cancer cells metastasize, they change dramatically and become resistant to drugs designed to treat primary tumor. This is a problem especially in bone metastases due to effects of bone microenvironment. Preclinical efficacy for oncology drugs is usually confirmed only in subcutaneous models that are simplistic and do not recapitulate the complexity of metastatic disease. Relying solely on efficacy results obtained from subcutaneous models is one major reason for the current >95% failure rate of oncology drugs in clinical trials (Wong and Siah, 2019), which has led to $50 – 60 billion annual spending on failed oncology clinical trials (Jentzsch et al., 2023).

Clinical evaluation of the mechanism-of-action of therapies on bone metastases is limited because it is challenging to take tumor biopsies from bone metastases. Therefore, the biologically relevant and clinically predictive preclinical Bone Metastasis Technology Platform should be routinely used to study the mechanism-of-action and efficacy of therapies before entering clinical development in bone metastasizing cancers. The platform shows the same clinical features that are observed in bone metastatic patients in a cancer-type specific manner. Importantly, the results align with clinical findings of different therapies approved or evaluated for bone metastasis.

Summary

Tumor microenvironment in bone metastases has unique characteristics and is understudied as a potential primary cause of the lack of efficacy of many immunotherapies, especially in breast and prostate cancer. It is prime time to focus on bone metastases by increasing understanding of the immune landscape in the bone tumor microenvironment according to the OIO concept.

About OncoBone Ltd:
OncoBone Ltd a Virtual Contract Research Organization (CRO) with over 20 year of experience in preclinical CRO business

About OncoBone Ventures:
OncoBone Ventures is a biotech startup company developing novel therapies for cancer patients with bone metastases.
We are open for co-development and partnering.

About Bioseeker/1stOncology:

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