Trial space and market analysis for allogeneic cellular immunotherapy in primary bone tumours and bone metastatic disease

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Research Project (SURG0161)
Medical Innovation and enterprise BSc programme

Introduction

γδT cells engineered to express IL-15 and an anti-B7H3 opsonin are a candidate for allogeneic adoptive immunotherapy in bone cancer. The therapy could be administered in combination with zoledronic acid which has a high affinity for mineralised tissue (including bone), and could thus increase honing to the tumour site.[1] The premise is to develop a therapy that will maximise clinical benefit to as many people as possible. Therefore the purpose of this research is to investigate the patient population most suitable for an initial trial, considering the market size, clinical trial space and availability of patients.

Background

Primary bone cancers are rare malignant tumours originating in bone derived from primitive mesenchymal cells, accounting for 0.2% of all malignancies worldwide.[2,3] In the UK around 160 people are diagnosed with osteosarcoma each year.

Secondary bone cancer, also known as metastatic bone cancer, is cancer that has spread to the bones from another primary cancer site.

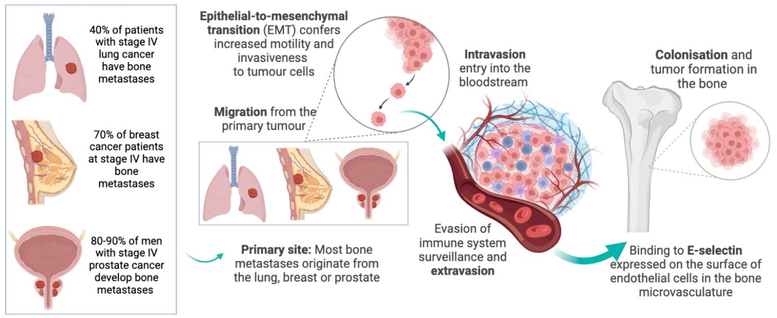

Figure 1: The process for bone metastasis, Figure generated in BioRender. Adapted from: Innovative Options for Bone Metastasis Treatment.[4] Data sources for bone metastases across cancers used in patient population analysis: lung,[5-7] breast,[7-9] and prostate.[7,10]

Most bone metastases originate from lung, breast and prostate cancers.[7] For patients who are initially diagnosed with these malignancies, the bulk of the tumour burden at the time of death is likely to reside in bone. In 2023 609,820 cancer deaths are projected to occur in the United States, 34% of which are either breast, lung or prostate cancer.[11] This means potentially 205,470 deaths in 2023 with bone metastases.

Methods

The study requires an assessment of patient populations and the clinical trial space:

Patient population

GlobalData Epidemiology Database | SEER registry | NHS admitted patient care statistics

Inclusion criteria:
Osteosarcoma (all stages)
Lung, breast and prostate cancer (Stage IV)

Analysis:
Recurrence rates and % of bone metastasis
Breakdown of diagnoses per UK hospital → number of available patients in UCL hospitals

Result (total patient N) vs Osteosarcoma

AGR% per indication → projected patient populations globally, US and UK

Age group per indication → pediatric and adult populations

Clinical Trial Space

GlobalData drugs database | Clinical trials database | Cancer Genome Atlas (Cbioportal)

Inclusion criteria: Preclinical Bone cancer, osteosarcoma, Ewing Sarcoma bone metastasis.
Exclusion discontinued and withdrawn studies

Analysis:
Studies by trial stage, indication, ATC classification, target and number of active/recruiting trials for each indication → analysis and comparison of targets

Result (total global studies for each indication)

Number of cell and gene therapies studies → analysis & comparison of targets to B7-H3

Necruiting/active trials Globally & UK → number of trial participants → available patients in UCL hospitals

Preliminary Results

Incidence of patients across 16MM countries with stage IV lung, breast and prostate cancer estimated to have bone metastasis equated to 331,690, vs 32,000 for all stages of osteosarcoma in 2022.[13] The UK the patient population equated to 52,000 vs 188 for Osteosarcoma. Stage IV lung cancer incidence figures for the UK had annual growth rate (AGR) of 4.7% between 2019-2022 vs 0.5% for Osteosarcoma. The AGR has been used to forecast patient populations for a potential trial.

NHS admitted patient care activity 2020-21 shows that primary bone tumours occur earlier in adolescence, and secondary tumours in an adult population.

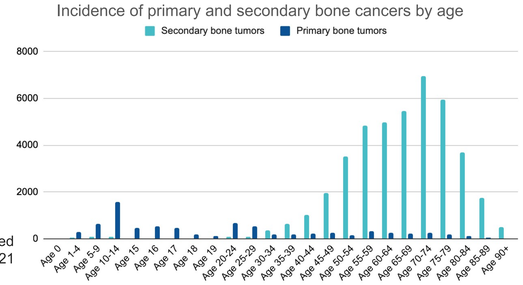

Figure 3: NHS Digital, Admitted Patient Care statistics, 2020-21

Trials in paediatric populations face challenges[15] which would result in a greater costs due to the need for specialised resources, additional regulations, and smaller patient populations. **Smaller patient numbers in osteosarcoma mean that fewer trials can be conducted within a given time.** Despite larger patient populations, only one active but not recruiting trial was found in the UK for treating metastases to the bone. There are currently 6 active trials in the UK for primary bone cancer, half of these trials include UCL hospitals as locations.[27] All are running trials in paediatric populations.

Primary Bone Cancer
UK: **6**
Global: **202**

Secondary Bone Cancer
UK: **1**
Global: **93**

Clinical trial landscape in bone cancer

Trials analysed[16] by development stage, indication, molecule type, and ATC classification

Total therapies in development: **285**
Primary bone cancer indications: **149**
Bone metastasis indications: **35**
Majority of trials at preclinical stage: **37.7%**
ATC classification: **Antineoplastic (Chemotherapy) agents**
Molecule type: **Small molecule (52.4%)**
Gene modified cell therapies: **15 Trials (5.5%)**

Cell and gene therapy trials for bone cancer by development stage and target

AXL and HER2 are the most investigated targets, each with three therapies in development.

AXL knockdown reduced progression of bone metastases in prostate and breast cancer cells. As a result, therapeutic Axl targeting may reduce tumour spread to the bones via neoplastic and host cell signalling axes.[17]

HER-2 was expressed in osteosarcoma but was not shown to have prognostic value.[18]

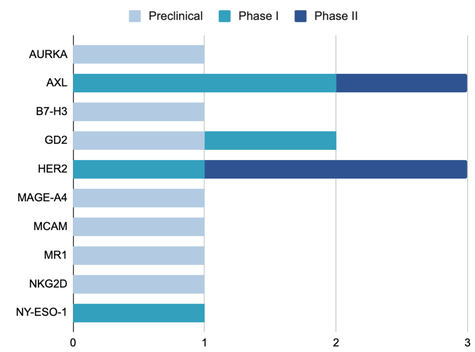

Figure 4: Cell and gene therapy trials in bone cancer by stage and target (15 CGT trials across 10 targets)

B7-H3 and metastasis

- The B7-H3 immunological checkpoint molecule is found to have a co-inhibitory role on T-cells, contributing to tumour cell immune evasion and thus a role in modulating cancer progression.[19]
- B7-H3 plays a tumour-promoting role, in processes such as proliferation, migration, and invasion; hypothesised to increase metastasis by activating the EMT process[20] and promote cancer stemness by lowering E-cadherin expression
- B7H3 knockdown inhibited cell migration and invasion.[21-24]

There is one cell and gene therapy trial found targeting B7-H3 in Preclinical stage.[25] One other trial outside of cell and gene therapies found targeting B7-H3 indicated for bone cancer is the Monoclonal antibody (enoblituzumab) in Phase I.[26]

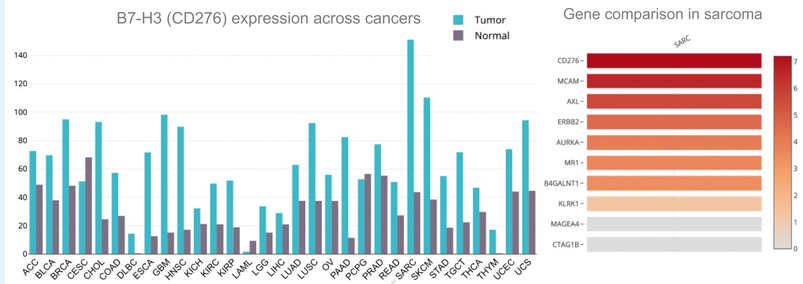

Figure 5: B7-H3 expression across cancers and multiple gene comparison for bone cancer cell and gene therapy targets in sarcoma. *Data Source: Cancer Genome Atlas Figures generated in: GEPIA*

An analysis of data from the cancer genome atlas shows B7-H3 expression is higher across cancers, and highest in sarcomas. Analysing the expression of CGT targets currently in development for bone cancers found B7-H3 (CD276) to have the highest expression in sarcomas.

Conclusion

- The estimated number of patients with bone metastasis from stage IV lung, breast and prostate cancers are far greater than all stages of Osteosarcoma.
- Fewer patients translates to fewer tumour samples available for study, hindering molecular characterization of the disease
- A trial in osteosarcoma will therefore face challenges associated both with recruiting from a smaller patient population and with conducting a clinical trial in a paediatric population.
- Despite the larger patient population affected by bone metastases, there are fewer preclinical trials focused on this indication compared to primary bone tumours.
- B7-H3 involvement in tumour progression and multiple gene comparison in sarcomas has been analysed. The target is found to be highly expressed in sarcoma and with greater novelty compared other targets such as AXL which have a larger number of preclinical studies.

The larger adult patient population, and unmet need reflected in the clinical trial landscape indicates that a secondary bone cancer would be a favourable patient population for an initial trial.

Patient group		Primary bone cancer	Secondary bone cancer
Patient Populations Incidence (N)	Global	32,049	331,690
	UK	188	51,357
AGR (2019-22)	Global	1.98%	7.17%
	UK	1.62%	7.52%
Projected patient population (2030)	Global	37,499	638,375
	UK	214	138,363
Preclinical studies per indication		132	32
Active/recruiting trials	Global	202	93
	UK	6	1
Median age group (NHS data)		10-14 years	40 years and above

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