EDUCATIONAL SEMINAR

Humanized Mouse Models in Pre-Clinical Efficacy Studies in Oncology

BIOCOM CRO Event
January 23, 2018

Agenda

8.00 – 8.30
Registration and networking

8.30 – 8.45
Introduction, by Jussi Halleen, CEO, Pharmatest

8.45 – 9.15
Humanized mouse models for drug discovery in the immuno-oncology era
by H. Toni Jun, Director Scientific Engagement, CrownBio

9.15 – 9.45
Novel bone metastasis models in humanized mice
by Mari Suominen, Research Director, Pharmatest

9.45 – 10.00
Q&A

The problem in oncology drug development

A massive amount of oncology drug candidates fail in clinical trials due to poor efficacy

Roughly 1 in 50 promising cancer drug candidates makes it to the market

The failure rates are higher in oncology than in any other indication area

Why the high failure rates?

- Traditionally, the majority of preclinical efficacy testing has been performed using models where cancer cell lines are injected to mice subcutaneously
- These models are cheap, fast, and easy to perform
- However, their clinical predictivity is poor because the tumor cells have different properties and behavior than in their natural (orthotopic and metastatic) tumor microenvironment
- Patient-derived xenografts (PDX) provide an improvement because they include well-defined tumor pathology

How to reduce the high failure rates?

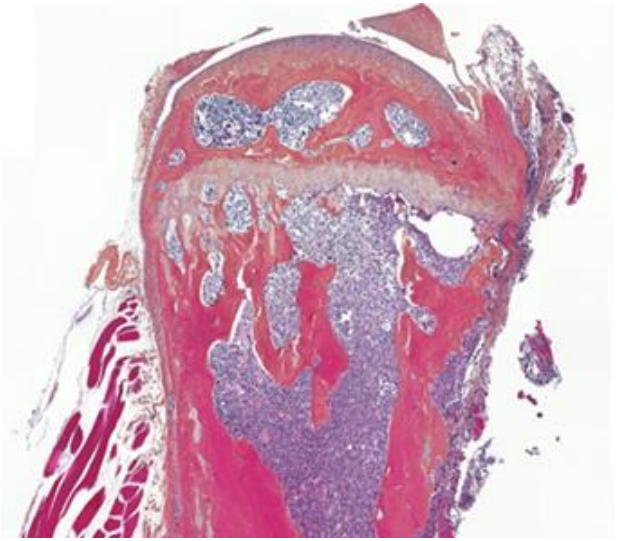
- An optimal cancer therapy should affect tumor cells in the primary tumor AND in metastatic sites
- Targeting metastases is extremely important because:
  - Metastatic microenvironment may dramatically change tumor properties and induce drug resistance
  - It is the metastases that eventually kill the patients
- Contrary to subcutaneous models, metastasis models are difficult to perform and require special expertise
- Large screenings could be performed in subcutaneous models, but efficacy should be confirmed in relevant metastasis models before entering clinical trials

The value of correct microenvironment

- Example case: Angiogenesis inhibitors (Kerbel RS, 2015)
- Good efficacy in subcutaneous models, but no effects in early clinical trials
- Retrospective testing in orthotopic and metastasis models showed no efficacy
- Tumor growth in lungs or many other sites, except sc, co-opts the existing vasculature, and does not need angiogenesis

Pharmatest Services

- Founded in 1998 (20 year anniversary in June 2018)
  - First US sales office in Boston area in February 2013
  - Second US sales office in San Diego in July 2016
  - Pharmatest USA established in June, 2017
- Privately owned CRO with special expertise in bone biology
- Offers preclinical efficacy services in oncology and skeletal diseases
- Leading experts in bone metastasis models since 2007
- 40% of the staff have a Ph.D.



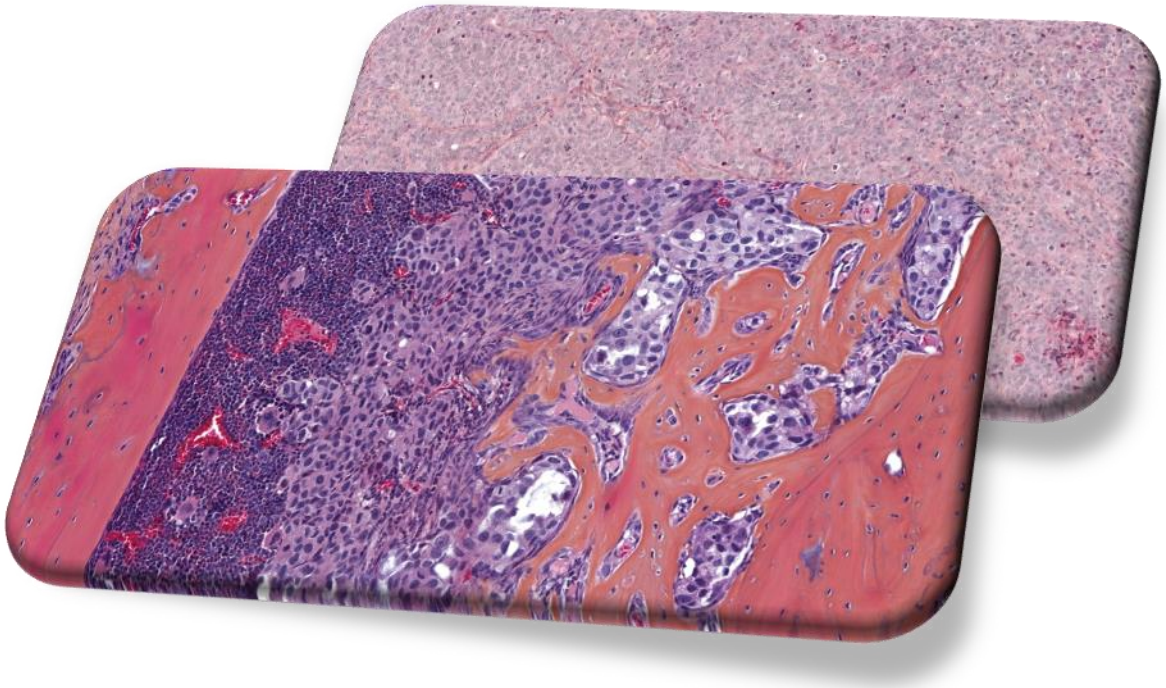
Bone metastases

- In advanced stages, 70% of breast, 85% of prostate, and 30% of lung cancer patients develop bone metastases
- Despite the recent progress in cancer drug development, bone metastases are incurable and dramatically increase mortality
- Novel precision medicines, including immunotherapies, hold the potential to more effectively treat metastatic tumors

The problem with bone metastases

- Bone microenvironment changes tumor properties and induces drug resistance
- Efficacy of most drug candidates is currently tested only in preclinical models where the tumor cells are not in the bone microenvironment
- The outcome is that in cancers that develop bone metastases, a massive amount of drugs will fail in clinical trials due to poor efficacy

Bone microenvironment changes tumor properties



- Figure on the back demonstrates subcutaneous tumor mass
- Figure in the front shows the same tumor cells in bone, demonstrating organized structures and interactions with the bone microenvironment

Our message

1. To emphasize the importance of confirming compound efficacy in relevant preclinical metastasis models before entering clinical trials

2. To urge all service providers to start developing and offering preclinical metastasis models

3. To convince all pharma industry developing oncology drugs to start using preclinical metastasis models

The outcomes would be

- Dramatically decreased failure rates in clinical trials
- Massive cost savings for the pharma industry
- Significantly faster entrance of truly efficacious new oncology drugs to the markets
- Increased life expectancy and improved quality of life of cancer patients with metastases

Agenda

8.00 – 8.30
Registration and networking

8.30 – 8.45
Introduction, by Jussi Halleen, CEO, Pharmatest

8.45 – 9.15
Humanized mouse models for drug discovery in the immuno-oncology era
by H. Toni Jun, Director Scientific Engagement, CrownBio

9.15 – 9.45
Novel bone metastasis models in humanized mice
by Mari Suominen, Research Director, Pharmatest

9.45 – 10.00
Q&A