Introduction to FAP Program and PTRT Platform

October 2019
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Collaboration Overview

• Clovis Oncology has acquired rights to FAP-targeted radiopharmaceutical program from 3B Pharmaceuticals (3BP)
  – Includes U.S. and global rights, excluding Europe (inclusive of Russia, Turkey and Israel), where 3BP retains rights

• Clovis planning to file IND for FAP-targeted radiopharmaceutical therapy in 2H 2020

• FAP highly expressed in multiple tumor types; Clovis to pursue broad and accelerated clinical development program
  – FAP is highly expressed in many epithelial cancers, including more than 90 percent of breast, lung, colorectal and pancreatic carcinomas

• Clovis to acquire rights to discovery program for three additional targets for radionuclide therapy
  – Includes global rights

• Clovis to pay approximately $12 million in upfront payments to 3BP

Source: Rettig et al., 1993; Cancer Research
FAP = fibroblast activation protein alpha, IND = Investigational New Drug
Introduction to Peptide-Targeted Radionuclide Therapy

• Peptide-targeted radionuclide therapy (PTRT) involves a small amount of radioactive material (radionuclide) that is combined with a cell-targeting peptide for the treatment of cancer
  
  – PTRT is a form of radiopharmaceutical

• The targeting peptide is able to recognize and bind to specific features of tumors, such as antigens and cell receptors

• When injected into the patient’s bloodstream, the peptide attaches to cancer cells, delivering a high dose of radiation to the tumor while sparing normal tissues

• Examples of this therapeutic approach include:
  
  – LUTATHERA® a radiolabeled somatostatin analog approved for the treatment of midgut carcinoid tumors
  
  – $^{177}$Lu-PSMA-617, a radiolabeled prostate specific membrane antigen (PSMA) binding dipeptide in Phase 3 for metastatic castration-resistant prostate cancer (mCRPC)

Radionuclides for PTRT

- A number of different radionuclides can be used for PTRT, generally split between alpha (α) and electron (e⁻ or β⁻) emitters
  - Positron (e.g. ⁶⁸Ga) / gamma (e.g. ⁹⁹mTc) emitting radionuclides are employed for imaging (patient selection/monitoring)
- Radionuclides used for therapy emit ionizing radiation that cause DNA damage and cell death

Examples:
- Actinium-225 (²²⁵Ac)
  - Relatively large mass
  - Low penetration
  - Highly ionizing (destructive)
- Lutetium-177 (¹⁷⁷Lu)
  - Very small mass
  - Relatively higher penetration
  - Ionizing

Sources: Grzmil et al., 2019, Radiopharm
Ionizing Radiation Kills Cells by Causing DNA Damage

Un-repaired DNA damage leads to cell death

Potential to combine FAP-targeted radiotherapy with Rubraca
The Targeted Radiotherapy $^{177}$Lu-PSMA-617 has Emerged as a Potential Treatment for mCRPC

- $^{177}$Lu-PSMA-617 is comprised of a mCRPC targeting moiety - an anti-PSMA (Prostate Specific Membrane Antigen) peptide that specifically binds to prostate cancer cells, linker and the β-emitter radionuclide $^{177}$Lutetium ($^{177}$Lu)
- Prospective Phase 2 showed 57% >50% prostate specific antigen (PSA) decline, 82% PCWG2 RECIST 1.1 response after treatment with $^{177}$Lu-PSMA-617
- Phase 3 VISION trial on-going (NCT03511664)

3BP Peptides are Promising for Targeting Radionuclide Therapy in Solid Tumors

- Peptides are attractive targeting molecules due to their small size and ease of manufacture.
- For radiotherapy; the rapid systemic clearance, tissue distribution and tumor penetrance favor small peptides vs. other targeting moieties.

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<th>3BP Peptides</th>
<th>Monoclonal antibodies</th>
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<tr>
<td>Target Affinity</td>
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Fibroblast Activation Protein Alpha (FAP) is a Pan-tumor Target Expressed on Cancer-Associated Fibroblasts

- FAP is a transmembrane cell surface proteinase that degrades proteins of the extracellular matrix and is up-regulated in cancer

- FAP is highly expressed in cancer-associated fibroblasts (CAFs) which are found in the majority of cancer types, potentially making it a suitable target across a wide array of tumors
  - FAP has limited expression on normal fibroblasts reducing the potential for FAP-targeted agents having effects in normal tissue

Source: Linder et al., 2018, J. Nuclear Medicine
Small-molecule FAP-binding Imaging Agents Show Effective Tumor Targeting in Multiple Tumor Types

- University of Heidelberg (Germany) developed a series of specific PET imaging agents to evaluate FAP as a pan-tumor target
  - $^{68}$Ga-FAPI-04 selected as optimal
- Evaluated in 80 patients of 28 different tumor entities (54 primary tumors and 229 metastases)
- Strong FAP-mediated tumor uptake with low background in normal tissues and organs

3BP has Identified a FAP-binding Peptide for PTRT

- $10^{14}$ peptides were screened \textit{in vitro} against FAP using mRNA display selecting on affinity and stability to provide initial FAP-binding peptides
- Structure activity relationship (SAR) examined to increase affinity and stability further and sites for radionuclide attachment identified
- Peptide sequence optimized for \textit{in vivo} biodistribution
- Nominated preclinical lead and back-up; IND enabling work on-going

\begin{itemize}
  \item FAP-binding peptide
  \item Targets FAP expressing cancer-associated fibroblasts and tumor cells
\end{itemize}

* FAP binding peptide image added for illustrative purposes only. Does not represent actual sequence of FAP lead candidate

Sources: 3B Pharmaceuticals, Data on File; Park et al., 1999, \textit{J. of Biological Chemistry}
Biodistribution and Tumor Retention Time of FAP Lead Candidate is Supportive of Therapeutic Applications

- In FAP-positive tumor-bearing mouse studies, the tumor retention time (how long the radiopharmaceutical stays in the tumor) and biodistribution of 3BP lead candidate is supportive of therapeutic investigation.

Source: 3B Pharmaceuticals, Data on File
FAP-targeted Radiotherapy has Multiple Potential Modes of Anti-tumor Action

• Targeting tumors with a FAP-targeted radiotherapy has multiple modes of anti-tumor action primarily relying on radiation crossfire where tumor cells are irradiated by being in close proximity to CAFs
  – The depletion of CAFs impacts the growth of cancer cells and enhances anti-tumor immune responses

• Potential to combine FAP-targeted radiotherapy with PD-(L)1

Sources: Fischer et al., 2012, Clinical Cancer Research; Schuberth et al., 2013, J. Trans. Med.; Rettig et al., 1988, Immunology
FAP-Targeted Radionuclide Therapy Program Development Plan

• Initial development plan includes completion of pre-clinical studies and initial First-in-Human (FIH) studies:
  – IND enabling studies on-going
  – Planning to submit IND in 2H 2020 and initiate FIH study in solid tumors shortly thereafter
  – FIH study to determine the dose and tolerability of the FAP-targeting therapeutic and imaging agent
  – Once dose is established, expansion cohorts planned in multiple solid tumor types as part of a global clinical development program
  – Potential for accelerated approvals in multiple tumor types