Pan-Cancer Analysis of Fibroblast Activation Protein Alpha (FAP) Expression to Guide Tumor Selection for the Peptide-Targeted Radionuclide Therapy FAP-2286

Tanya T. Kwan,1 Minh Nguyen,1 Dirk Zboralski,2 Anne Schumann,2 Anne Breedenbeck,2 Matthias Paschke,2 Christian Haase,2 Aileen Hoehe,1 Ulrich Reineke,1 Christiane Smerling,1 Frank Osterkamp,2 Jim Xiao,1 Andrew D. Simmons,1 Thomas C. Harding,1 Kevin K. Lin1

1Clovis Oncology, Inc., Boulder, CO, USA; 2Bayer Healthcare, Leverkusen, Germany.

SUMMARY

- A pan-tumor immunohistochemistry (IHC) screen identified high FAP expression in multiple tumor types that correlated with in vitro FAP-2286 binding, suggesting that FAP is an attractive target for peptide-targeted radionuclide therapy.
- The phase 1 LuMIE trial (NCT04939510) is enrolling patients to evaluate FAP-2286 as a therapeutic (L6-Lu-FAP-2286) and imaging (Ga-FAP-2286) agent in multiple solid tumor types.

METHODS

- FAP IHC was performed by CellCarta on 360 formalin-fixed paraffin-embedded–preserved whole tumor tissue sections from 16 tumor types using the SP30 and Body (Spring Biosciences) on the Ventana Benchmark XT system.
- Overall FAP expression H-scores in the whole-tissue sections were calculated using the Visiopharm automated image analysis. FAP expression H-scores specific to the tumor and stroma compartments were calculated for a subset of samples using HALO (Indica Labs) automated image analysis.
- A trained pathologist validated the scoring results from both automated image analysis approaches.
- Autoradiography with 18F-FAP-2286 was performed on matched frozen tissue sections. Relative optical film density was determined using Visiopharm software (InterFocus) and correlated with a calibration curve.

RESULTS

- FAP expression in the TCGA Database revealed high FAP messenger RNA expression in a number of matched frozen tissue sections. Relative optical film density was calculated using the Visiopharm automated image analysis approaches.
- Autoradiography with 18F-FAP-2286 was performed on matched frozen tissue sections. Relative optical film density was determined using Visiopharm software (InterFocus) and correlated with a calibration curve.

REFERENCE

Aertgeerts et al.1

ACKNOWLEDGMENTS

This study was funded by Clovis Oncology, Inc. Medical writing was editorially supported by Clovis Oncology, Inc., and performed by Shery Liss and Stephen Sultz of ArfaMed Communications, an Arfa Health company.

INTRODUCTION

- FAP is a membrane-bound protease with limited expression in normal tissues but high expression on cancer-associated fibroblasts abundant in the stroma of most tumors.2
- FAP-M2286 is a potent and selective FAP-targeted peptide linked to the chelator DOTA that allows for attachment of radionuclides for therapeutic (eg, L6-Lu-FAP-2286) and imaging (eg, Ga-FAP-2286) applications (Figure 1).
- Assessing patterns of FAP expression in different tumor types can help guide tumor selection for L6-Lu-FAP-2286 therapy.

METHODS

- FAP IHC was performed by CellCarta on 360 formalin-fixed paraffin-embedded–preserved whole tumor tissue sections from 16 tumor types using the SP30 and Body (Spring Biosciences) on the Ventana Benchmark XT system.
- Overall FAP expression H-scores in the whole-tissue sections were calculated using the Visiopharm automated image analysis. FAP expression H-scores specific to the tumor and stroma compartments were calculated for a subset of samples using HALO (Indica Labs) automated image analysis.
- A trained pathologist validated the scoring results from both automated image analysis approaches.
- Autoradiography with 18F-FAP-2286 was performed on matched frozen tissue sections. Relative optical film density was determined using Visiopharm software (InterFocus) and correlated with a calibration curve.

RESULTS

FAP Expression in Publicly Available Data Sets

- Gene expression screening of multiple tumor types characterized by The Cancer Genome Atlas (TCGA) data set revealed high FAP messenger RNA expression in a number of tumor types (Figure 2).
- Autoradiography with 18F-FAP-2286 was performed on matched frozen tissue sections. Relative optical film density was determined using Visiopharm software (InterFocus) and correlated with a calibration curve.

Figure 1. Structure of FAP-2286

Figure 2. FAP mRNA Expression in Different Tumor Types

Figure 3. FAP Protein Expression Across Multiple Tumor Types

Figure 4. Representative Images for FAP Staining in Whole Tissue Sections

Figure 5. FAP Expression in Different Sarcoma Subtypes

Figure 6. FAP Expression in Different Mesothelioma Subtypes

Figure 7. Correlation Between FAP Expression by IHC and FAP-2286 Binding

Patterns of FAP Expression Across Tumor Types

- In most tumor types, FAP was predominantly localized to the stroma surrounding the tumor cells (Figure 4A).
- FAP expression in tumor cells was also observed.
- Tumor-cell FAP expression was rare in cancers of epithelial origin and, when present, appeared weaker than in the adjacent stroma (eg, esophagus: Figure 4B).
- Tumor-cell FAP expression was common, consistent, and strong in cancers of mesenchymal origin (eg, sarcoma and mesothelioma: Figure 4B).

Correlation Between FAP Expression by IHC and FAP-2286 Binding

- There was significant correlation between FAP expression observed by IHC and FAP-2286 binding as assessed by autoradiography in matched frozen tissues (Figure 7).