INTRODUCTION

- Pancreatic cancer represents 3% of all cancers and 7% of all cancer deaths in the USA, with a majority of cases diagnosed late and with limited treatment efficacy.
- Radiopharmaceutical Therapy (RPT) using antibodies (Abs) is emerging as a new approach for the treatment of solid cancers.
- Do to the long circulation time in blood, full-length antibodies bear concerns for hematological exposure to radioactivity.
- Antibody fragments with lower molecular weight like minibodies (Mb, 80 kDa) show rapid blood clearance, thus reducing off-target exposure, while maintaining the high target affinity typical of immunoglobulins.
- Integrin αvβ6 is mostly absent in healthy adult tissues but upregulated in a variety of carcinomas, including pancreatic cancer.

METHODS

- All animal studies were approved by ImaginAb Animal Care and Use Committee.
- In this preclinical proof of concept study, we evaluated a Mb targeting human αvβ6 (IAB56) as an RPT agent for the treatment of pancreatic cancer.
- To this end we first evaluated the β-emitter 177Lu-DOTAGA-IAB56 Mb in a dosimetry study in mice and extrapolated the organ exposures to humans.

- The IAB56 Mb was conjugated with DOTAGA and radio labeled with 177Lu. Doses of 1.48 MBq/animal were administered intravenously (iv) in non-tumor bearing mice and biodistributions collected at 0.5, 3, 6, 24, 48, 120 and 192 hours postinjection (p.i.) to quantify time course uptake at major organs.
- Then we tested its therapeutic efficacy in female NuJ (Jackson Laboratory, 002019) mice bearing the subcutaneous ductal adenocarcinoma xenograft CFPAC-1.
- Preclinical RPT studies were conducted in CFPAC-1 xenografts. A pancreatic carcinoma cell-line reported to have intermediate-to-low expression level of human αvβ6 (4-fold lower than BxPC3 pancreatic adenocarcinoma).
- When the tumor size reached 100-150 mm³ mice were randomized into three groups: vehicle, 18.5 MBq, and 11.1 MBq and 8.14 MBq treated groups versus vehicle **p<0.01; 18.5 MBq  and 11.1 MBq and 8.14 MBq treated groups versus vehicle **p<0.01; ***p<0.001; ****p<0.0001.

Binding Kinetics and FACS (CFPAC-1) to anti-αvβ6 Mb

- Mbs consist of two scFv antigen-binding domains fused to the CH3 domain of human IgG (Figure 1A).
- Minibody IAB56 binds to human αvβ6 with sub-nanomolar affinity and slow off-rates (Figure 1B).
- Flow cytometry analysis in CFPAC-1 cells shows strong binding to anti-αvβ6 (Figure 1C).
- To avoid the side effects observed in the clinic related to blocking integrin biological activity with αvβ6, IAB56 was engineered from a non-blocking antibody against any αvβ6 associated biological pathway (data not shown).