Poster #**671P**

✉ Prof Jonathan McConathy | jmcconathy@uabmc.edu

LuMIERE: A phase 1/2 study evaluating safety, dosimetry, and preliminary activity of [^{177}Lu]Lu-FAP-2286 in patients with advanced solid tumors

Jonathan McConathy,[1] Yusuf Menda,[2] Jordi Rodon,[3] Ajit H Goenka,[4] Ryan H Moy,[5] Sophie Morse,[6] Arnaud Demange,[7] Paola Aimone,[8] Thomas A Hope[9]

[1]Department of Radiology, The University of Alabama at Birmingham, AL, USA; [2]University of Iowa Health Care, IA, USA; [3]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, TX, USA ; [4]Mayo Clinic in Rochester, MN, USA ; [5]Columbia University Irving Medical Center, NY, USA; [6]Novartis Pharmaceuticals Corp., East Hanover, NJ, USA; [7]Advanced Accelerator Applications, a Novartis Company, Geneva, Switzerland; [8]Novartis Pharma AG, Basel, Switzerland; [9]University of California San Francisco, CA, USA

KEY FINDINGS & CONCLUSIONS

- PET imaging with [^{68}Ga]Ga-FAP-2286 identified lesions in patients with a range of solid tumors.
- [^{177}Lu]Lu-FAP-2286 was well tolerated in heavily pretreated patients with solid tumors, with a low incidence of DLTs and Grade ≥3 AEs observed.
- For all radioactive dose levels of [^{177}Lu]Lu-FAP-2286 investigated (3.70–9.25 GBq), the absorbed doses in normal organs did not raise any concerns and were within accepted tolerance limits.
- Overall, the safety profile for [^{177}Lu]Lu-FAP-2286 supported its continued development in the phase 2 part of the study investigating [^{177}Lu]Lu-FAP-2286 as monotherapy and in combination with chemotherapy.

Scan to obtain poster

https://bit.ly/Jonathan671P

This study is sponsored by Advanced Accelerator Applications, A Novartis company.
Poster presented at ESMO 2024, 13–17 September 2024.

INTRODUCTION

- Fibroblast activation protein (FAP) is a transmembrane protein that is highly expressed on the surface of cancer-associated fibroblasts present in the tumor microenvironment of most epithelial cancers.[1–3]
- FAP expression is very low in normal tissue, but is readily observable at sites of wound repair or fibrosis.[4]
- Preclinical models demonstrated rapid uptake of [^{68}Ga]Ga-FAP-2286 and [^{177}Lu]Lu-FAP-2286 in FAP-positive tumors, supporting their development for imaging and therapeutic use, respectively.[2]
- LuMIERE (NCT04939610) is a phase 1/2 open-label study evaluating [^{177}Lu]Lu-FAP-2286 in patients with advanced FAP-expressing solid tumors.[5]
- The data reported here are from the phase 1 part of the study.

METHODS

- **Patients eligible for [^{177}Lu]Lu-FAP-2286 in phase 1:**
  - Were aged ≥18 years
  - Had advanced/metastatic solid tumors that were refractory to or that had progressed following prior therapy
  - Had [^{68}Ga]Ga-FAP-2286 uptake in tumoral lesions (PET imaging).
- The phase 1 dose escalation was based on a Bayesian optimal interval design and included four dose levels of [^{177}Lu]Lu-FAP-2286: 3.70 GBq (n=3), 5.55 GBq (n=6), 7.40 GBq (n=7), and 9.25 GBq (n=11).
- Patients received ≤6 cycles every 6 weeks.
- Dosimetry, clinical, and safety evaluations were performed after each dose.
- **Primary endpoints for phase 1:**
  - Dose-limiting toxicities (DLTs; assessed during cycle 1)
  - Adverse events (AEs)
  - Serious adverse events
  - Clinical laboratory abnormalities.
- Secondary endpoints for phase 1 included absorbed dose estimated in organs and tumor lesions and investigator-assessed objective response by Response Evaluation Criteria in Solid Tumors v 1.1.
- Data analyses reported in this poster used a data cut-off of 31 January 2024, except for the preliminary dosimetry data (cut-off: 27 June 2024).

RESULTS

- Across six US sites, 35 patients were enrolled and imaged and 27 were treated; reasons for not receiving treatment were laboratory parameters out of treatment range (n=3), decline in Eastern Cooperative Oncology Group performance status (n=2), high [^{68}Ga]Ga-FAP-2286 uptake in the lung due to lung fibrosis (n=1), inadequate [^{68}Ga]Ga-FAP-2286 uptake in tumor lesions (n=1), and lost to follow-up (n=1).
- Among the 27 patients treated, the median age was 60 years and 51.9% were male. The most common tumors were pancreatic (n=9), colorectal (n=4), and head and neck (n=3).

Safety

Adverse events – [^{68}Ga]Ga-FAP-2286 safety set

- One patient experienced a Grade ≥3 AE (small intestinal obstruction; not considered treatment related) following imaging with [^{68}Ga]Ga-FAP-2286.

Dose-limiting toxicities – [^{177}Lu]Lu-FAP-2286 DLT evaluable set

- Grade 4 lymphopenia at dose level 2 (5.55 GBq) was reported on Day 22 in a 68-year-old male patient, after their first dose of [^{177}Lu]Lu-FAP-2286. The patient presented with Grade 2 lymphopenia at screening and had received five prior lines of therapy plus palliative radiation.
- Grade 3 hemoptysis at dose level 4 (9.25 GBq) was observed in a 72-year-old female patient with uterine leiomyosarcoma. At screening, the patient was receiving anticoagulants for atrial fibrillation, and imaging showed lung metastases containing pseudoaneurysms. The patient had received seven prior lines of therapy plus palliative radiation.

Adverse events – [^{177}Lu]Lu-FAP-2286 safety set

- Overall, 14 patients (51.9%) experienced treatment-related AEs, two of whom had Grade ≥3 events (n=1 lymphopenia; n=1 hemoptysis) (**Table 1**).

Serious adverse events – [^{177}Lu]Lu-FAP-2286 safety set

- A total of eight patients (29.6%) experienced serious AEs, with one (hemoptysis) being determined to be treatment related.

Clinical laboratory abnormalities – [^{177}Lu]Lu-FAP-2286 safety set

- There were no Grade ≥3 decreases in neutrophil, hemoglobin, or platelet levels over time, across all dose levels up to 9.25 GBq (**Figure 1**).

Preliminary dosimetry – [^{177}Lu]Lu-FAP-2286 dosimetry set

- In patients evaluable for dosimetry at the preliminary analysis (n=23), across all cohorts, the overall mean (standard deviation) observed absorbed dose following first administration in cycle 1 was 0.41 (0.17) Gy/GBq in the kidneys and 0.037 (0.011) Gy/GBq in the red marrow.

Preliminary efficacy – [^{177}Lu]Lu-FAP-2286 efficacy set

- Best response included partial response in one patient and stable disease in nine patients (six confirmed, three unconfirmed; **Figure 2**).

Recommended phase 2 dose of [^{177}Lu]Lu-FAP-2286

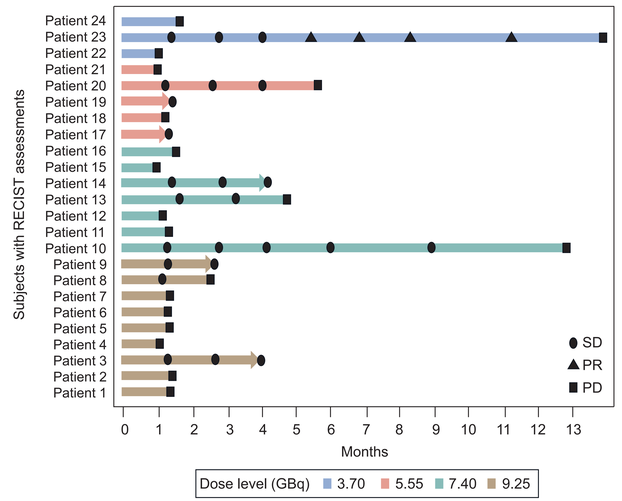
- The recommended phase 2 dose for [^{177}Lu]Lu-FAP-2286 monotherapy was 9.25 GBq; this will be administered every 4 weeks in phase 2.

Table 1. Treatment-emergent adverse events – [^{177}Lu]Lu-FAP-2286

	All grades		Grade ≥3	
Preferred term, n (%)	All causality	Treatment-related	All causality	Treatment-related
Patients with ≥1 TEAE	27 (100.0)	14 (51.9)	11 (40.7)	2 (7.4)
Fatigue	7 (25.9)	3 (11.1)	0	0
Abdominal pain	6 (22.2)	1 (3.7)	2 (7.4)	0
Anemia	6 (22.2)	4 (14.8)	0	0
Arthralgia	5 (18.5)	1 (3.7)	0	0
Diarrhea	5 (18.5)	2 (7.4)	0	0
Dyspnea	5 (18.5)	0	1 (3.7)	0
Blood bilirubin increased	4 (14.8)	0	1 (3.7)	0
Weight decreased	4 (14.8)	0	0	0
Abdominal distension	3 (11.1)	0	1 (3.7)	0
Ascites	3 (11.1)	0	2 (7.4)	0
Back pain	3 (11.1)	0	1 (3.7)	0
Cholangitis	3 (11.1)	0	3 (11.1)	0
Constipation	3 (11.1)	0	0	0
Nausea	3 (11.1)	1 (3.7)	0	0
Cancer pain	2 (7.4)	0	1 (3.7)	0
Hyponatremia	2 (7.4)	0	1 (3.7)	0
Lymphopenia	2 (7.4)	1 (3.7)	1 (3.7)	1 (3.7)
Asthenia	1 (3.7)	0	1 (3.7)	0
Device occlusion	1 (3.7)	0	1 (3.7)	0
Hemoptysis	1 (3.7)	1 (3.7)	1 (3.7)	1 (3.7)
Pulmonary embolism	1 (3.7)	0	1 (3.7)	0
Renal infarction	1 (3.7)	0	1 (3.7)	0
Spinal compression fracture	1 (3.7)	0	1 (3.7)	0
Spontaneous bacterial peritonitis	1 (3.7)	0	1 (3.7)	0

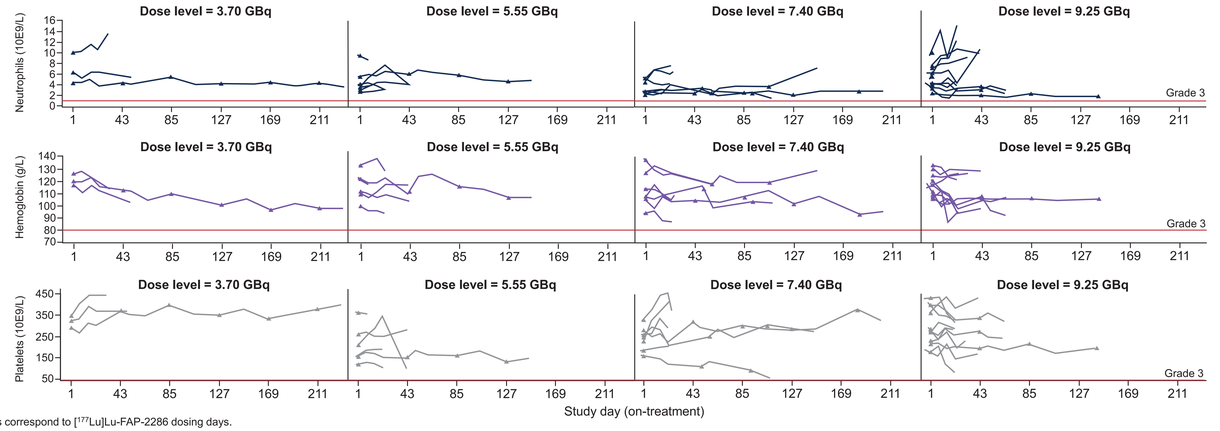
TEAE, treatment-emergent adverse event. TEAEs occurring in ≥3 patients (all grades) or ≥1 patient (Grade ≥3). N=27.

Figure 2. RECIST assessments over time – [^{177}Lu]Lu-FAP-2286 (efficacy set)



PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Figure 1. Hematology parameters over time by dose – [^{177}Lu]Lu-FAP-2286 safety set



Triangles correspond to [^{177}Lu]Lu-FAP-2286 dosing days.

References

1. Fitzgerald AA & Weiner LM. Cancer Metastasis Rev 2020;39:783–803.
2. Zboralski D, et al. Eur J Nucl Med Mol Imaging 2022;49:3651–67.
3. Mona CE, et al. J Nucl Med 2022;63:1021–6.
4. Puré E & Blomberg R. Oncogene 2018;37:4343–57.
5. ClinicalTrials.gov. Available at https://clinicaltrials.gov/study/NCT04939610. Accessed July 2024.

Acknowledgments

We thank all the patients and their families, and all staff involved in the study. Medical writing support was provided by Ryan Riley, PhD, at Aspire Scientific Ltd (Bollington, UK), and funded by Advanced Accelerator Applications, a Novartis Company.

Disclosures

Prof Jonathan McConathy declares consulting for Blue Earth Diagnostics, ImaginAb, Novartis, and Telix; consulting and research support from GE Healthcare and Eli Lilly/Avid; and research support from Cytosite Biopharma. The corresponding abstract for this poster presentation includes full disclosure information for all authors.