Safety and Efficacy of ^{90}Y-FAPI-46 Radioligand Therapy in Patients with Advanced Sarcoma and Other Cancer Entities

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ABSTRACT

Purpose: We report efficacy and safety of ^{90}Y-labeled FAPI-46 (^{90}Y-FAPI-46-RLT) in patients with advanced sarcoma, pancreatic cancer, and other cancer entities.

Experimental Design: Up to four cycles of radioligand therapy (RLT) were offered to patients with (i) progressive metastatic malignancy, (ii) exhaustion of approved therapies, and (iii) high fibroblast activation protein (FAP) expression, defined as $SUV_{max} \geq 10$ in more than 50% of tumor. Primary endpoint was RECIST response after RLT. Secondary endpoints included PET response (PERCIST), overall survival (OS), dosimetry, and safety of FAP-RLT.

Results: Among 119 screened patients, 21 (18%) were found eligible [$n = 16/3/1/1$ sarcoma/pancreatic cancer/prostate/gastric cancer; 38% Eastern Cooperative Oncology Group (ECOG) ≥ 2] and received 47 ^{90}Y-FAPI-46-RLT cycles; 16 of 21 (76%) patients underwent repeat RLT. By RECIST, disease control was confirmed in 8 of 21 patients [38%; 8/16 (50%) of evaluable patients). There was one partial response (PR) and seven stable diseases after RLT. Disease control was associated with prolonged OS ($P = 0.013$). PERCIST response was noted in 8 of 21 patients [38%; 8/15 (53%) of evaluable patients]. Dosimetry was acquired in 19 (90%) patients. Mean absorbed dose was 0.53 Gy/GBq in kidney, 0.04 Gy/GBq in bone marrow, and <0.14 Gy/GBq in liver and lung. Treatment-related grade 3 or 4 adverse events were observed in 8 (38%) patients with thrombocytopenia ($n = 6$) and anemia ($n = 6$) being most prevalent.

Conclusions: ^{90}Y-FAPI-46-RLT was safe and led to RECIST PR in one case as well as stable disease in about one third of patients with initially progressive sarcomas, pancreatic cancer, and other cancers. Discontinuation after the first cycle and a low rate of PR requires future improvement of FAP-RLT.

Introduction

The fibroblast activation protein alpha (FAPα) is expressed at high levels on the cell surface of tumor-associated fibroblasts as well as on tumor cells for several entities including sarcoma (1–3). FAP was established as theranostic target through development and clinical translation of radioligands that enable imaging and therapy of malignant disease (4). Accuracy and clinical impact of FAP-directed PET was reported for several tumor entities, including sarcoma and adenocarcinoma of various origins (5–9). More recently, we reported feasibility of FAP-directed radioligand therapy (RLT) using ^{90}Y-labeled FAPI-46 (^{90}Y-FAPI-46) in a patient series of metastatic sarcoma and pancreatic cancer (10).

Despite a growing number of chemo-, targeted, or immune-based options, therapy resistance remains an enormous challenge in the treatment of metastatic cancer. Outcome is highly variable depending on the histologic subtype and stage. Systemic treatment of metastatic sarcoma leads to response in less than one third of patients (11) and very few patients with metastatic pancreatic cancer survive for more than 2 years (12). Efficacious therapy of metastatic disease through assessment of novel therapeutic classes is urgently needed. Targeted radionuclide therapy or RLT enables effective irradiation of systemic disease. RLT has led to high response rates along with prolonged survival in patients with eligible neuroendocrine tumors or prostate cancer (13, 14). FAP-directed RLT follows the same theranostic principle and has the potential to improve outcome of sarcoma, pancreatic cancer, and other FAP-expressing tumors (10).

Here we report efficacy, safety, and radiation dosimetry of ^{90}Y-FAPI-46 RLT in patients with metastatic sarcoma, pancreatic cancer, and other cancer entities.

Materials and Methods

Patients

This is a single-center, retrospective study. As reported previously (10), clinical ^{90}Y-FAPI-46 RLT was offered to patients meeting

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Translational Relevance

Several malignant solid tumors are characterized by high fibroblast activation protein (FAP) expression. FAPI-46 is a small theranostic ligand for FAP-directed PET imaging and subsequent radioligand therapy (RLT). ^{90}Y-labeled FAPI-46 (^{90}Y-FAPI-46 RLT) led to stable disease by CT/MRI in about one third of patients with initially progressive metastatic sarcoma, pancreatic cancer, and other cancer entities. Partial responses were noted in patients with sarcoma. Disease control was associated with prolonged overall survival. Organ radiation doses were below critical range and serious thrombocytopenia occurred in a few patients under RLT. Radionuclide therapy with ^{90}Y-FAPI-46 was safe and led to tumor control in a subgroup of patients. RLT should be further improved and assessed prospectively in patients with metastatic sarcoma.

all of the following conditions: (i) progressive metastatic solid tumor; (ii) exhaustion of approved therapies based on multidisciplinary tumor board decision; (iii) high FAP expression, defined as ^{68}Ga-FAPI-46 PET SUV_{max} ≥10 in more than 50% of tumor lesions; and (iv) adequate hematopoiesis (i.e., leukocytes >2.5/nL, hemoglobin >7.0 mg/dL, thrombocytes >75/nL) with exceptions for patients on stable transfusion. RLT was primarily offered for sarcoma and pancreatic cancer due to known high FAP expression level (7, 8). Renal scintigraphy with ^{99m}Tc-MAG3 was performed to exclude urinary tract obstruction. All patients underwent additional ^{18}F–2[18F]fluoro-2-deoxy-D-glucose (FDG) PET/CT at baseline to rule out sites of FAP-negative/FDG-positive discordant disease. In case of focal uptake on initial ^{90}Y-FAPI-46 bremsstrahlung scintigraphy after first RLT, patients were offered up to four cycle repeat RLT. RLT was decided for in a multidisciplinary tumor board.

Data were analyzed retrospectively. All patients gave written informed consent to undergo clinical RLT and for retrospective analysis of data. The institutional review board approved this study and consent for inclusion in this analysis was waived (reference: 22–10661-BO). The study was conducted in accordance with the Declaration of Helsinki. Preliminary findings in 9 patients were reported previously (10).

^{90}Y-FAPI-46 synthesis and administration

Radiosynthesis of ^{90}Y-FAPI-46 was reported previously (10). In brief, labeling was performed using an Easyone synthesis module (Trasis), FAPI-46 precursor (ABX, 8 μg/GBq), and ^{90}Y-YCl_3 solution (Yttriga, Eckert, and Ziegler) to achieve radiochemical purity of ≥95% and 24-hour shelf-life.

Patients underwent inpatient treatment on a nuclear medicine ward for 2 days. Three patients received approximately 7.4 GBq ^{90}Y-FAPI-46 at the first cycle. All other patients received a first activity of approximately 3.7 GBq ^{90}Y-FAPI-46 i.v. followed by dosimetry. Patients were eligible for repeat RLT in case focal ^{90}Y-FAPI-46 uptake was noted in tumor lesions on posttherapy ^{90}Y-FAPI-46 bremsstrahlung scintigraphy (Supplementary Fig. S1) and if clinically indicated. For all subsequent RLT cycles approximately 7.4 GBq ^{90}Y-FAPI-46 (high dose) was given through two infusions of 3.7 GBq, 4 hours apart. The time interval between cycles was 4 to 8 weeks.

Bremsstrahlung scintigraphy and dosimetry

Whole body planar bremsstrahlung scintigraphy was performed within 24 hours after RLT start to visually confirm systemic distribution and focal tumor uptake.

Bone marrow dosimetry was performed using the blood-method by drawing blood samples at fixed intervals [0.5, 1, 2, 4, 24, 36, and 48 hours postinjection (p.i.); ref. 15]. Doses absorbed by tumor lesions and kidneys were calculated using PET acquisitions as reported previously (10). In brief, PET images were acquired on multiple timepoints (0.5, 3, and 18–24 hours p.i.) after ^{90}Y-FAPI-46 application. At least two timepoints were necessary to determine lesion dose. Images were acquired on mCT or VISION scanner (Siemens Healthineers), following an optimized protocol for quantification (16). Tumor and organ absorbed doses were calculated by integration of a mono-exponential fit function over time. We assumed that the radionuclide content on liver and lung would be equal to the minimum quantifiable ^{90}Y-FAPI-46 uptake in PET phantom studies (17) and applied the blood pharmacokinetics for calculation of the absorbed doses.

Response and survival

Patients underwent repeated imaging by ^{18}F-FDG PET/CT or CT at 8- to 12-week intervals. For all patients combined, 118 imaging timepoints were reviewed. Morphologic and metabolic responses were assessed in accordance with RECIST1.1 and PERCIST1.0, respectively (18, 19). The primary endpoint was RECIST response after RLT.

RECIST or PERCIST objective response after RLT was defined by response category between baseline and restaging after RLT. Disease control after RLT was defined as either complete (metabolic) response (CR/CMR), partial (metabolic) response (PR/PMR), or stable (metabolic) disease (SD/SMD). Disease control rate (DCR) was reported as proportion of patients with disease control after RLT.

RECIST or PERCIST objective response under RLT (best response) was defined as most favorable response category between baseline and any interim timepoint during RLT including restaging after RLT.

Progression-free survival (PFS) was recorded from start of RLT until RECIST progression, death, or last follow-up. Overall survival (OS) was recorded from start of RLT until death or last follow-up conducted for all patients in March 2022.

Safety

Toxicity was recorded and categorized in accordance with Common Terminology Criteria for Adverse Events (CTCAE 5.0). Clinical and laboratory assessments were performed on inpatient admission and outpatient as per routine follow-up every 2 to 4 weeks. The investigators judged possible relation of events to either disease (progression) or to RLT.

Statistical analysis

Descriptive statistics include absolute number with proportion (%) or median with interquartile range (IQR). Kaplan–Meier plots were shown for OS. Difference in survival was assessed by log–rank test. Statistical analyses were performed using SPSS (version 20).

Data availability statement

The data generated in this study are available within the article and its supplementary data files. Further data generated in this study are not publicly available due to patient privacy but are available upon reasonable request from the corresponding author.

Results

Patient characteristics

Characteristics are summarized in **Table 1**. Individual patient data are listed in Supplementary Table S1. In total, 13 of 21 (62%) patients were female and 16 of 21 (76%) patients had metastatic sarcoma; other entities were pancreatic cancer (3/21, 14%), prostate cancer ($n = 1$), and gastric cancer ($n = 1$). Patients had received a median of three lines of local therapy and four lines of systemic therapy before admission. Three patients were on stable concomitant tumor treatment with afatinib, trametinib, and denosumab, respectively.

All patients were suffering from advanced-stage disease with involvement of multiple organs. Eastern Cooperative Oncology Group (ECOG) was 2 or higher in 8 of 21 (38%) patients. Tumor SUV_{max} in ^{68}Ga-FAPI-46 PET was higher than 10 in all patients and higher than 20 in 12 of 16 (75%) patients with sarcoma. Median SUV was highest for the sarcoma subgroup [maximum (max) 25.4, mean 14.3; Supplementary Table S2], particularly for patients with solitary fibrous tumor (max 29.1, mean 15.7). Very high FAP expression (SUV_{max} higher than 20) was noted in 9 of 9 (100%) patients with solitary fibrous tumor (Supplementary Fig. S1), 3 of 7 (43%) patients with other sarcoma, and none of the patients with pancreatic, prostate, or gastric cancer.

Table 1. Patient characteristics ($n = 21$).

Characteristics	Median	[IQR]	*n*	(%)
Gender				
Male			8	(38)
Female			13	(62)
Age	61	[56–66]		
Race				
White or White European			21	(100)
Tumor entity				
Sarcoma			16	(76)
Pancreatic cancer			3	(14)
Prostate cancer			1	(5)
Gastric cancer			1	(5)
Disease sites on screening PET				
Lung			17	(81)
Lymph nodes			11	(52)
Bone			10	(48)
Liver			9	(43)
Soft tissue			9	(43)
Pleura			5	(24)
Pancreas			5	(24)
Peritoneum			4	(19)
Brain			1	(5)
Thyroid			1	(5)
Heart			1	(5)
Adrenal gland			1	(5)
Kidney			1	(5)
Stomach			1	(5)
Spleen			1	(5)
Prostate			1	(5)
ECOG performance status				
0–1			13	(62)
2			6	(29)
3			2	(10)
Time from initial diagnosis (years)	3	[2–5]		
Previous lines of local therapy	3	[1–6]		
Previous lines of systemic therapy	4	[3–6]		

Treatment characteristics

Flow chart diagram of patients is shown in **Fig. 1**. In total, 47 RLT cycles were applied in 21 patients. Four of 21 (19%) patients did not continue after the first cycle due to insufficient tumor radiation by dosimetry ($n = 3$) or switch to breast cancer therapy ($n = 1$). Two of 21 (10%) patients were under active RLT at the time of analysis. Of the remaining 15 patients, 6 of 15 (40%) underwent all four RLT cycles and 9 of 15 (60%) received less than the four planned cycles. Clinical reasons for discontinuation were tumor progression (5/15, 33%), rapid deterioration (2/15, 13%), or thrombocytopenia (2/15, 13%; Supplementary Table S3). Representative images of baseline ^{68}Ga-FAPI-46 PET, post-RLT ^{90}Y Bremsstrahlung scintigraphy, and PET are shown in Supplementary Fig. S1.

Tumor response

Tumor response by RECIST or PERCIST is summarized in **Table 2**. RECIST disease control after RLT was achieved in 8 of 21 patients (38%), specifically 8 of 16 (50%) evaluable patients (1/16, 6% partial response; 7/16, 44% stable disease; primary endpoint: RECIST after RLT in **Table 2**). RECIST evaluation was not performed in 5 of 21 patients (24%), as 3 patients had not yet reached re-staging at the time of analysis and 2 patients died before re-staging CT/MRI.

PERCIST disease control after RLT was achieved through stable metabolic disease in 8 of 21 (38%) patients, specifically 8 of 15 (53%) evaluable patients. Disease control after RLT was noted in 7 of 12 (58%) patients with sarcoma versus 1 of 4 (25%) patients with other solid tumor (Supplementary Table S4).

Best RECIST response under RLT (any imaging timepoint from start until restaging after RLT) was achieved in 11 of 17 (65%) evaluable patients (3/17, 18% partial response; 8/17, 47% stable disease; secondary endpoint; **Table 2**). By PERCIST, 3 of 15 (20%) evaluable patients demonstrated partial metabolic response and 7 of 15 (47%) stable metabolic disease at any timepoint under RLT.

Survival

PFS and OS are shown in **Fig. 2**. Eleven of 21 (52%) patients had more than 6 months of follow-up after start of RLT. Median PFS [95% confidence interval (CI)] was 3.4 (1.1–5.7) months (**Fig. 2A**). Within the observation period, 11 of 21 (52%) patients died. Median OS (95% CI) was 10.0 (4.4–15.5) months (**Fig. 2B**). Median OS was significantly longer for RECIST responders (log-rank $P = 0.013^{*}$), stratified by response category: partial response (not reached), stable disease (14.4 months), progressive disease (6.6 months), nonavailable response status (2.2 months; **Fig. 2C**).

Dosimetry

In total, 32 dosimetry timepoints were evaluated in 19 of 21 (90%) patients. Eight of 19 (42%) patients had more than one dosimetry timepoint. Dosimetry results are summarized in **Table 3**.

Mean (Standard Deviation; StdDev) radiation dose was 0.53 (0.04), 0.04 (0.01), 2.81 (1.25), and 2.15 (0.67) Gy/Gbq for kidney, bone marrow, tumor lesion with highest radioligand uptake, and lesion with second highest uptake in each patient, respectively. None of the patients reached critical radiation dose limit for the assessed organs.

Safety

Adverse events are listed in **Table 4**. Within all recorded adverse events ($n = 51$), 6 (12%) were based on clinical symptoms and

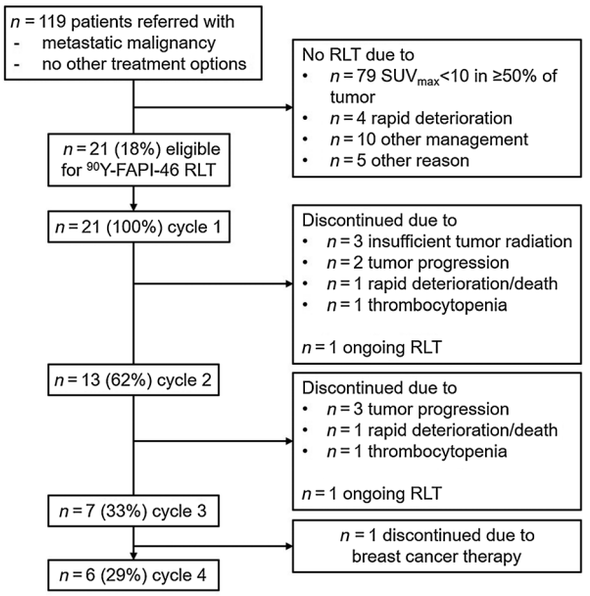

Figure 1.
Patient flow diagram.

45 (88%) on laboratory findings. In total, 8 of 21 (38%) patients experienced any adverse event grade 3 or 4.

Grade 3 or 4 anemia and thrombocytopenia were noted in 6 of 21 (29%) and 6 of 21 (29%) patients, respectively. Other grade 3 or 4 events occurred in single patients. By the investigators' judgment, severe thrombocytopenia was deemed related to RLT in 1 male patient (grade 3 after one cycle) and 3 female patients (grades 3, 4, and 4 after one, one, and two RLT cycles, respectively). In 2 female patients, thrombocytopenia led to discontinuation of RLT with subsequent recovery of thrombocyte count in one and lost follow-up in the other patient. In the other 2 patients with thrombocytopenia RLT was discontinued due to other cause (insufficient tumor radiation dose and disease progression, respectively).

Discussion

Feasibility and safety of repeat ^{90}Y-FAPI-46 RLT was reported in a subgroup of the presented patients previously (10). Here we summarize an extended cohort with longer follow-up including objective tumor response, safety, and dosimetry assessments for 47 ^{90}Y-FAPI-46 RLT cycles in 21 patients suffering from sarcoma, pancreatic cancer, or other solid tumors. Majority of patients had more than 6 months follow-up after treatment initiation and median OS was reached. At baseline, all RLT candidates had high uptake on ^{68}Ga-FAPI-46 PET. After the first RLT, focal uptake on posttherapy ^{90}Y-FAPI-46 bremsstrahlung scintigraphy was noted for more than 80% of patients. From baseline to re-assessment after RLT about half of evaluable patients and more than one third of the entire cohort demonstrated disease control by RECIST. Assessment of imaging timepoints under or after RLT showed RECIST partial response in 3 patients. Dosimetry did not reveal critical organ dose under repeat RLT and safety was favorable with potentially related thrombocytopenia in 4 patients (19%) and RLT discontinuation in 2 (10%).

Few clinical cohort studies were published on FAP-directed RLT. These report responder and nonresponder cases along with select safety and dosimetry data for various tumor entities ranging from pancreatic, breast, ovarian, gastroenteric, and thyroid origin among others to sarcoma (20–22). However, comparison is limited by lack of systematic response assessment and short follow-up time for previous cohort studies. Mature survival data under FAP-RLT have not been analyzed thus far.

In line with our findings, serious adverse events were observed in only few cases previously: 1 of 21 (20), 3 of 11 (22), and 0 of 15 (21) patients, respectively. In our cohort, occurrence of grade 3 thrombocytopenia was noted in 2 patients. Grade 4 thrombocytopenia occurred in 2 patients with concomitant kinase inhibitor therapy, which may have contributed to hematotoxicity. Overall, RLT was discontinued in 2 patients due to thrombocytopenia, which mandates monitoring of blood counts for patients undergoing FAP-RLT. Other hematologic and nonhematologic adverse events were noted in close temporal association with tumor progression and were judged unrelated. Possible unrelated events were noted for anemia, elevated liver enzymes, and respiratory distress in patients with rapid deterioration due to progressive disease. Acute toxicity or immediate (e.g., allergic) reactions to RLT were not observed. In our small cohort, the rate of thrombocytopenia was higher than previously observed for other

Table 2. Tumor response by RECIST (CT or MRI) or PERCIST (^{18}F-FDG PET).

Best response under RLT	RECIST (CT, MRI, $n = 17$[a])	(%)	PERCIST (PET, $n = 15$[a])	(%)
CR	0	(0)	0	(0)
PR	3	(18)	3	(20)
SD	8	(47)	7	(47)
PD	6	(35)	5	(33)
Response after RLT	**RECIST[b] (CT, MRI, $n = 16$[a])**	**(%)**	**PERCIST (PET, $n = 15$[a])**	**(%)**
CR	0	(0)	0	(0)
PR	1	(6)	0	(0)
SD	7	(44)	8	(53)
PD	8	(50)	6	(40)
DCR	8	(50)	8	(53)

Note: Response was determined on imaging under RLT (any imaging timepoint from start, best response) and after completion of RLT.
Abbreviations: CR, complete response; DCR, disease control rate after RLT; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Number of evaluable patients.
[b]Primary endpoint

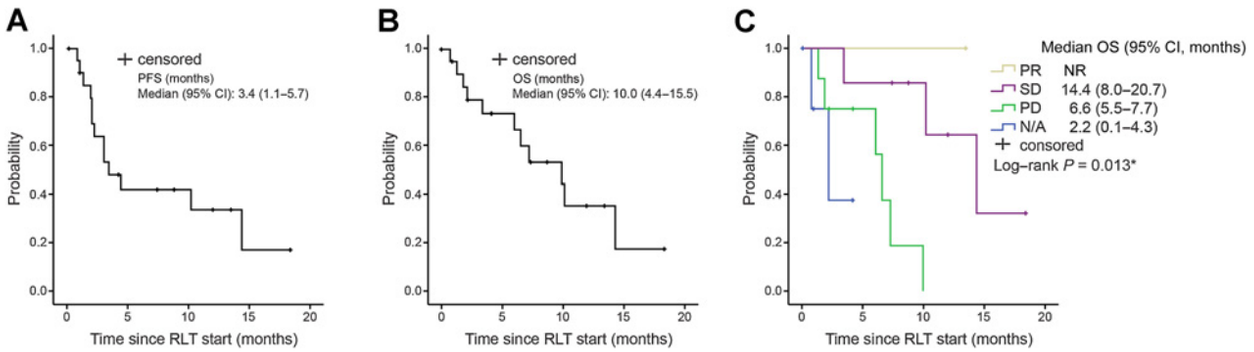

Figure 2.

Survival after start of RLT. PFS (**A**) and OS (**B**) for all 21 patients stratified by the primary endpoint RECIST response after RLT (**C**). *$P < 0.05$. NA, not applicable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.

RLT (13, 14, 23). However, thrombocytopenia was manageable and the overall rate of FAP-RLT related grade ≥3 hematotoxicity was low. In randomized trials on ^{177}Lu-PSMA-617 or ^{177}Lu-DOTATATE RLT, grade ≥3 events that led to discontinuation or modification of RLT were observed in less than 10% of patients (13, 14). Furthermore, the randomized TheraP trial demonstrated favorable safety of ^{177}Lu-PSMA-617 when compared with cabazitaxel in patients with metastatic prostate cancer (23). Dosimetry, in line with previous FAP-, prostate-specific membrane antigen- (24), or somatostatin receptor-directed RLT (25) dose assessments, demonstrates low levels of radiation to organs which underlines favorable risk/benefit ratio for FAP-RLT in those patients with intense FAP positivity. In our screening cohort, the proportion of FAP-RLT candidates (18%), with SUV_{max} ≥10 in more than 50% of tumor, was lower when compared with prostate-specific membrane antigen or somatostatin receptor RLT screening. This underlines heterogeneity of FAP expression and the importance of FAP imaging to identify suitable patients at baseline.

We present the largest dosimetry cohort for FAP-RLT thus far. Average radiation dose of ^{90}Y-FAPI-46 for kidney and bone marrow were comparable with previously reported values for ^{177}Lu-FAP-2286 (22) and ^{177}Lu-FAPI-46 (20). Liver and lung radiation dose were outside critical range. In line with previous studies, critical organ radiation dose after up to four cycles of ^{90}Y-FAPI-46 RLT was not reached in any patient. Thus, repeat ^{90}Y-FAPI-46 RLT for up to four cycles is feasible. However, as reported previously ^{90}Y-FAPI-46 retention time in tumor tissue was considerably shorter than retention observed for ^{177}Lu-FAP-2286 (22) or current PSMA/SSTR directed radioligands (26, 27). Short retention in tumor tissue contributes to suboptimal tumor-to-organ radiation, limits the use of therapeutic radionuclides with long half-life, including ^{177}Lu, ^{131}I, or ^{225}Ac and calls for future improvement of radioligand design. ^{90}Y has shorter half-life and higher energy per decay as compared with ^{177}Lu and thus seemed more suitable for labeling FAP ligands with short tumor retention time, such as FAPI-46.

Tumor control and survival under FAP-RLT have not been assessed systematically yet. Here we report for the first time RECIST/PERCIST response as well as up to 18 months survival follow-up after RLT. All patients had progressive disease at baseline. Partial response and stable disease according to RECIST were noted in 18% and 47% evaluable patients under RLT, and in 6% and 44% evaluable patients after completion of RLT, respectively. Partial response and stable disease were almost exclusively noted in patients with sarcoma. Sarcomas often express high levels of FAP in both tumor and stroma compartments (3), whereas in other tumor entities FAP almost exclusively resides on stromal fibroblasts (28). Sarcoma presents high target concentration throughout the tumor, which likely supports high ^{68}Ga-FAPI-46 PET SUV and improved radiation delivery. Therefore, ^{68}Ga-FAPI-46 uptake and FAP expression in sarcoma are under investigation in an ongoing prospective investigator-initiated trial at our site (NCT05160051).

By the end of the observation period, more than half of patients had died. Median OS of 10 months was within range previously reported for outcome of metastatic sarcoma or pancreatic cancer in advanced therapy lines (29, 30). RECIST response after completion of RLT was significantly associated with OS. Data indicate that disease control may

Table 3. Tumor and critical organ radiation dose under ^{90}Y-FAPI-46 RLT (n = 21 patients, n = 32 dosimetry timepoints).

Cycle *n*	**1**		**2**		**3**		**4**		**Overall**	
Dosimetry timepoints (*n*)	**14**		**8**		**6**		**4**		**32**	
	Mean	**(StdDev)**	**Mean**	**(StdDev)**	**Mean**	**(StdDev)**	**Mean**	**(StdDev)**		
^{90}Y-FAPI-46 activity [GBq]	**4.2**	**(1.5)**	**7.1**	**(2.0)**	**7.7**	**(0.7)**	**7.2**	**(0.2)**	**Mean**	**(StdDev)**
Radiation dose [Gy/GBq]										
Tumor lesion 1	4.10	(5.26)	3.52	(3.93)	2.33	(2.27)	1.29	(0.29)	2.81	(1.25)
Tumor lesion 2	2.63	(5.72)	2.82	(3.44)	1.54	(0.55)	1.62	(1.00)	2.15	(0.67)
Kidney	0.48	(0.17)	0.51	(0.15)	0.56	(0.08)	0.55	(0.06)	0.53	(0.04)
Liver and lung	0.18	(0.05)	0.17	(0.15)	0.13	(0.03)	0.10	(0.03)	0.14	(0.04)
Bone marrow	0.04	(0.02)	0.04	(0.02)	0.03	(0.01)	0.03	(0.01)	0.04	(0.01)

Table 4. Safety in 21 patients.

Event category		All grades (*n*)	Grade ≥ 3 (*n*)	(%)	RLT related[a] grade ≥ 3 (*n*)	(%)
Hematology						
	White blood cell decreased	5	0	(0)	0	(0)
	Anemia	11	6	(29)	0	(0)
	Platelet count decreased	11	6	(29)	4	(19)
	Neutrophil count decreased	1	0	(0)	0	(0)
Renal/electrolytes						
	Hypernatremia	1	0	(0)	0	(0)
	Hyperkalemia	1	0	(0)	0	(0)
	Creatinine increased	3	0	(0)	0	(0)
Liver						
	Blood bilirubin increased	1	0	(0)	0	(0)
	Aspartate aminotransferase increased	2	1	(5)	0	(0)
	Alanine aminotransferase increased	2	1	(5)	0	(0)
	GGT increased	3	1	(5)	0	(0)
	Hypoalbuminemia	4	0	(0)	0	(0)
Clinical						
	Acute respiratory distress	1	1	(5)	0	(0)
	Tumor pain	1	0	(0)	0	(0)
	Fever	1	0	(0)	0	(0)
	Back pain	1	0	(0)	0	(0)
	Abdominal pain	1	1	(5)	0	(0)

Note: Safety was assessed in accordance with CTCAE 5.0.
Abbreviation: GGT, gamma-glutamyl transferase.
[a]Safety events judged likely related to RLT.

translate into prolonged survival and is therefore a relevant oncologic endpoint in our patient cohort. Patients who did not undergo response assessment after RLT, had died early or present with short or censored follow-up.

We observed disease control in more than half of patients with progressive metastatic sarcoma at the advanced stage thus more than one third of patients presented with ECOG 2 or higher. RLT was offered after exhaustion of the evidence-based treatment options, with a median of three prior lines of local therapy and four lines of systemic therapy. Only 2 patients, one with conventional chondrosarcoma and one with solitary fibrous tumor, had received ≤1 systemic therapy. For both diseases, only limited evidence-based data on systemic therapy are available and 1 patient (no. 8, 83 years old) refused chemotherapy.

Advanced disease and extensive pretreatment likely contributed to a high rate of treatment discontinuation (60%) in candidates for repeat RLT by dosimetry. In patients with progressive and extensive metastatic disease, tumor control to prevent further deterioration and death is the primary goal of therapy. In patients with sarcoma, limited options exist beyond the first line for the treatment of advanced stage (11, 30, 31). High target expression on tumor and stroma together with responses seen in our cohort underline that FAP-directed therapy is a promising new approach in patients with metastatic sarcoma. Given the low toxicity profile, FAP-RLT should also be explored in combination with other treatment modalities to investigate potential synergistic effects.

This study comes with limitations. Flow of patients including baseline assessment, activity scheme, dosimetry, and follow-up staging were predefined in our clinical protocols. However, management may have deviated depending on individual patients' condition. Retrospective assessment may have introduced selection bias and misclassification or information bias. Definitive conclusions regarding therapeutic efficacy and toxicity of ^{90}Y-FAPI-46 should therefore be based on future prospective evidence.

Conclusion

FAP-directed RLT using ^{90}Y-FAPI-46 was tolerated well and revealed organ radiation doses below critical range. ^{90}Y-FAPI-46 RLT led to RECIST stable disease in about one third of patients with initially progressive sarcomas, pancreatic cancer, and other cancers. Partial response was noted in 1 patient with sarcoma after RLT. Response was positively associated with OS. FAP-RLT needs further improvement and prospective assessment in patients with metastatic sarcoma.

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W.P. Fendler: Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **K.M. Pabst:** Resources, data curation, formal analysis, investigation, visualization, methodology, writing–review and editing. **L. Kessler:** Resources, data curation, formal analysis, investigation, methodology, writing–review and editing. **P. Fragoso Costa:** Resources, data curation, investigation, writing–review and editing. **J. Ferdinandus:** Resources, data curation, writing–review and editing. **M. Weber:** Resources, writing–review and editing. **M. Lippert:** Resources, data curation, investigation, methodology. **K. Lueckerath:** Writing–review and editing. **L. Umutlu:** Resources, writing–review and editing. **K. Kostbade:** Resources, writing–review and editing. **I.A. Mavroeidi:** Resources, data curation, investigation, writing–review and editing. **M. Schuler:** Resources, writing–review and editing. **M. Ahrens:** Writing–review and editing. **C. Rischpler:** Resources, investigation, writing–review and editing. **S. Bauer:** Resources, writing–review and editing. **K. Herrmann:** Resources, supervision, writing–review and editing. **J.T. Siveke:** Resources, writing–review and editing. **R. Hamacher:** Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, visualization, writing–review and editing.

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Note

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