Current status of FAP therapy in solid tumors

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FAP-ligands as novel cancer radiopharmaceuticals in nuclear medicine have been recently translated successfully into the clinical space. Particularly small molecules (i.e. FAPI-46, FAPI-74) and peptides (i.e. FAP-2286, DOTAGA.SA.FAPi) seem to be some of the most promising molecular probes for imaging and therapy. Back in 2019, there have been slight reservations about adopting this new imaging probe, after the decades of the solidly established role of FDG PET/CT in oncological imaging. At that time, it was expected that these novel ligands might challenge Onco-PET as new cornerstones in the individualized tumor staging and even beyond. However, FAP-targeted imaging is today not intended to replace FDG PET/CT, but rather to complement cancer imaging and therapy, where cancer subtypes exhibit low glucose metabolism which often leads to moderate or very insufficient FDG uptake. Recently, numerous FAP-imaging studies -ranging from single-case reports to larger patient cohorts and even prospective trials have reinforced the empirical understanding of FAP-imaging as a potentially "disruptive" modality compared to FDG PET/CT. The broader application of FAPI PET/CT has gained momentum, shaping a new narrative in oncological imaging and beyond. FAPI PET/CT is now increasingly recognized as a novel imaging agent that does not aim to replace FDG PET/CT, but rather supports it by enhancing diagnostic accuracy in specific sub-cohort of tumor entities, where FDG PET/CT tends to underperform. Several FAP-derivates- such as FAPI-04, FAPI-46, FAPI-74 for PET imaging as well as FAPI-34 for SPECT imaging were rapidly introduced into clinical practice. To date, FAP-imaging agents have steadily paved their way into clinical practice, particularly in tumor entities such as pancreatic ductal adenocarcinoma, gastroesophageal cancers, and hepatocellular carcinoma. Even in lung cancer, where FDG PET/CT has long held a well-established and clinically robust role, FAPI PET/CT has quickly emerged as a strong competitor, especially in case of lung adenocarcinoma. FAPI PET/CT has been gaining increasing acceptance beyond academic and scientific field as a tool for improved oncological imaging, while FAP theranostics is still in the elaboration and early translation. In contrast to imaging probes, FAP-derivates for therapy require a rather long residence (>48 h) time following successful target-binding at the cancer-associated fibroblast or FAP-positive tumor cells to enable the radiotoxic effect (beta- and alpha-emitter) and deliver enough LET to the cancer microenvironment. Meanwhile, FAP-based imaging probes are advancing into the clinical application, with Phase-II/III clinical trials expected as early as Q4/2025 (NCT07217704 & NCT07217717). In contrast, FAP-targeted therapeutics remain in the Phase-I or proof-of-concept stage but brings hope for patients with systemic disease who are left out and urgently need additional innovation drives beyond the standard care. This review article will give insight into the most recent developments in the FAP-Therapeutic applications of

Abbreviations: ATC, Anaplastic thyroid cancer; CAF, Cancer-associates fibroblasts; DTC, Differentiated thyroid cancer; FAP, Fibroblast activation protein; FAPI, Fibroblast activation protein inhibitor; MTC, Medullary thyroid cancer; n.a., Not available; RLT, Radioligand therapy; PD, Progressive disease; PR, Partial response; SD, Stable disease; TC, Thyroid Cancer

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cancer treatments using several different promising FAP-derivates to improve FAP-theranostic in oncology.
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Introduction

During the preceding three decades, radioligand therapy (RLT) has evolved from a niche modality into a mainstream component within the field of oncology.[1] The regulatory approvals of [^{177}Lu]Lu-DOTATATE for somatostatin receptor−positive neuroendocrine tumors and [^{177}Lu]Lu-PSMA-617 for metastatic castration-resistant prostate cancer have firmly established RLT as an effective, systemic treatment.[2-4] These advances underscore a fundamental principle: once a suitable molecular target has been identified, the theranostic approach - employing the same target molecule for diagnostic imaging and therapeutic radionuclide delivery - can be expanded to encompass additional tumor entities.[5]

In the context, there has been an increasing focus on the tumor microenvironment as a potential therapeutic target.[6] It is important to note that malignant tumors are not composed solely of cancer cells, but rather of a complex ecosystem comprising stromal fibroblasts, extracellular matrix, immune cells, vasculature, and signaling molecules.[7] One of the most prominent stromal cell populations is the cancer-associated fibroblast (CAF), which plays a pivotal role in tumor initiation, growth, invasiveness, and resistance to treatment.[6] A molecular target of particular interest expressed by CAFs is the f**ibroblast activation protein (FAP)**, a membrane-bound serine protease with both dipeptidyl peptidase and endopeptidase activity.[8-10] The creation of a tumor-promoting milieu is facilitated by FAP-positive CAFs through enzymatic and non-enzymatic interactions.[11] Clinically, high stromal FAP expression has been shown to be consistently associated with a poor prognosis across a range of tumor types.[12,13] FAP is expressed at low level in most normal adult tissues, but is strongly induced in sites of tissue remodeling, fibrosis, wound healing, and within the stromal compartment of the vast majority of epithelial tumors.[14-16] High FAP expression has been documented in various tumor entities including breast, pancreatic, colorectal, lung, head and neck, and cholangiocarcinoma.[17,18] In a significant proportion of these cancers, immunohistochemical analysis reveals the presence of FAP overexpression observed in over 80 % of tumor samples.[19,20]

The targeting of CAFs with pharmacological agents has yielded only limited benefits in the past, due to the genetic stability and non-malignant nature of fibroblasts.[21,22] However, RLT offers a solution to this challenge: the labeling of FAP targeting ligands with a therapeutic radionuclide, e.g. ^{177}Lu, enables the selective delivery of radiation to FAP-expressing stromal cells. By enabling a crossfire effect, the radiation is deposited in stromal cells and extends to adjacent malignant cells, creating a potent antitumor effect despite indirect targeting.[21]

Radiochemistry and development of [^{177}Lu]Lu-FAPI agents

The first FAP-targeted tracers suitable for imaging were **quinoline-based molecules**, which were optimized for high affinity to the enzymatic pocket of FAP and rapid clearance from non-target tissues.[23,24] ^{68}Ga-labeled FAPI-02 and FAPI-04 were among the first-generation ligands evaluated clinically and were optimized for imaging with short tumor retention times and high tumor uptake, properties ideal for PET but inadequate for therapy.[25,26] Subsequent [^{68}Ga]Ga-FAPI-46 (Fig. 1) and [^{18}F]FAPI-74 analogues offered improved pharmacokinetics and better synthetic accessibility, especially with [^{18}F]FAPI-74 due to ^{18}F-labeling. This led to widespread adoption in clinical PET/CT imaging.[27-30]

While these properties are well-suited for PET, they fall short of the requirements for therapy. The therapeutic efficacy of the treatment is contingent upon the prolonged tumor residence to deliver meaningful absorbed doses.[21,31] Three major strategies have been identified as key to improving their suitability for therapeutic applications:

Dimerization defined as the linkage of two FAPI moieties via a flexible spacer, has been demonstrated in the context of quinoline moieties, as exemplified by DOTAGA.(SA.FAPI)\$_2$. This has been demonstrated to enhance avidity towards the target, thereby slowing dissociation rates and increasing tumor absorbed doses.[32]

a) Another line of development introduced albumin-binding motifs into the quinoline scaffold, such as EB-FAPI (LNC1004).[33,34] The incorporation of small lipophilic or charged groups with affinity for serum albumin, has been demonstrated to extend the circulation half-life of the ligand. This, in turn, has been shown to enhance tumor delivery, but also marrow exposure.[35-37]

b) A parallel development path led to peptidic scaffolds such as FAP-2286, which is built on a cyclic peptide that is linked to DOTA. FAP-2286 has been observed

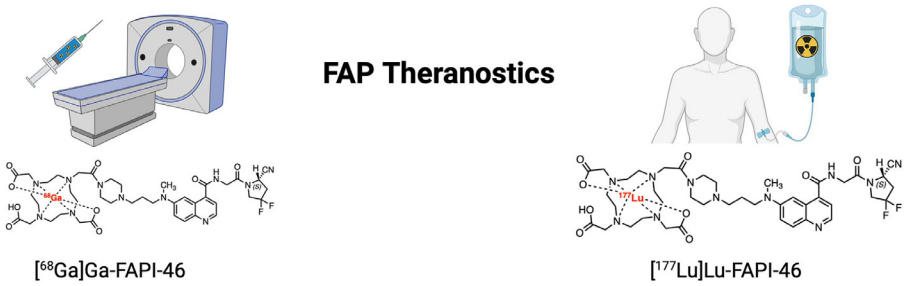

Fig. 1 FAP Theranostics. Created in BioRender. Kunte, S. (2026) https://BioRender.com/2piwn3g.

to demonstrate a slower dissociation rate and a prolonged tumor retention time.[38]

The field of chelation chemistry has historically placed considerable reliance on DOTA, a strategy that has been demonstrated to ensure optimal *in vivo* stability of ^{177}Lu conjugates.[39] For FAPI dimers, DOTAGA has been shown to be particularly useful because it allows conjugation to two targeting moieties simultaneously.[32]

The labeling process is uncomplicated, ^{177}Lu routinely achieves >95% radiochemical purity, and is compatible with GMP production. These robust chemical foundations have facilitated the rapid expansion of FAPI ligands from bench to bedside.[40-42]

^{177}Lu is well suited for FAP-targeted therapy due to its emission profile (Fig. 1). It decays with a physical half-life of 6.65 days by emitting β^- particles with a maximum energy of 497 keV (mean energy ≈ 134 keV).[43,44] These particles have the capacity to penetrate up to 2 mm, thereby most likely delivering effective crossfire from CAFs to adjacent tumor cells while sparing distant normal tissue.[45,46]

The γ-emissions at 113 keV (6.2% abundance) and 208 keV (10.4% abundance) of ^{177}Lu permit SPECT/CT, thereby enabling personalized dosimetry and adaptive treatment planning - features not available with pure β^-- emitters.[43-45] Practical advantages include established isotope supply, well-documented clinical safety from PSMA and DOTATATE programs, and manageable radiation protection requirements.[47,48]

Patient selection and imaging with FAPI PET/CT

FAPI PET/CT is pivotal in the selection of patients. It confirms target expression, provides lesion-level uptake data, and guides therapy planning.[49] In practice, the selection of patients for [^{177}Lu]Lu-FAP therapy mirrors the approach taken with PSMA PET/CT for prostate cancer.[4,50] However, due to the fact that FAP expression is not confined to a specific tumor entity but is instead prevalent across a wide spectrum of solid tumors, the diagnostic landscape is more extensive.[51] This raises both opportunities and challenges: while many patients may qualify, tracer uptake patterns can vary both inter- and intraindividually for the same tumor entity.[52-54]

A range of PET tracers is now available for diagnostic imaging, each representing a different stage of ligand development. The most widely used tracers are [^{68}Ga]Ga-FAPI-04 and [^{68}Ga]Ga.FAPI-46, while [^{18}F]FAPI-74 offers logistical advantages through centralized production and distribution.[25,29]

The heterogeneity of uptake remains a formidable challenge. In such cases, complementary FDG PET/CT helps to identify FAPI-negative but biologically aggressive lesions, thus preventing undertreatment.[55,56] Clinical studies have demonstrated the intense uptake in a wide range of cancers including breast, pancreatic, gastric, cholangiocarcinoma, head and neck, and sarcomas.[51] Several head-to-head studies have compared FAPI with FDG. FAPI often provides superior lesions detectability in gastric cancers, cholangiocarcinoma, pancreatic cancers, and certain sarcomas. FDG remains more sensitive in some hematologic malignancies and highly glycolytic tumors with low stromal content.[55-57] The two modalities are complementary rather than interchangeable.

Unlike [^{18}F]FDG, where SUV thresholds have been extensively validated, standardized interpretation criteria for FAPI PET are still evolving.[58,59] Most early therapeutic protocols categorize a lesion as "positive" if uptake clearly exceeds background levels in organs such as the liver and muscle.[54,60]

Although FAP expression is minimal in most normal tissues, there are several situations that can lead to physiological or false-positive uptake. For instance, FAP is upregulated in tissue repair as well as in fibrotic processes or inflammation. Understanding these pitfalls is crucial when interpreting scans for therapy eligibility.[61] Recently, a standardized reporting system entitled FAP-Reporting and Data System (RADS) has been proposed, which defines the likelihood of lesion being malignant based on a 5-point scale (with 1, certainly benign and 5, malignancy definitely present; Fig. 2).[62] This system may then further assist in identifying patients eligible for therapy in a theranostic setting.

FAPI PET/CT also provides a tool for **post-therapy follow-up**. Changes in uptake intensity and tumor-to-background ratios can be monitored across treatment cycles. A decrease in SUV_{max} may correlate with response, although standardized criteria (analogous to PERCIST for FDG PET) have not yet been validated for FAPI.[63,64]

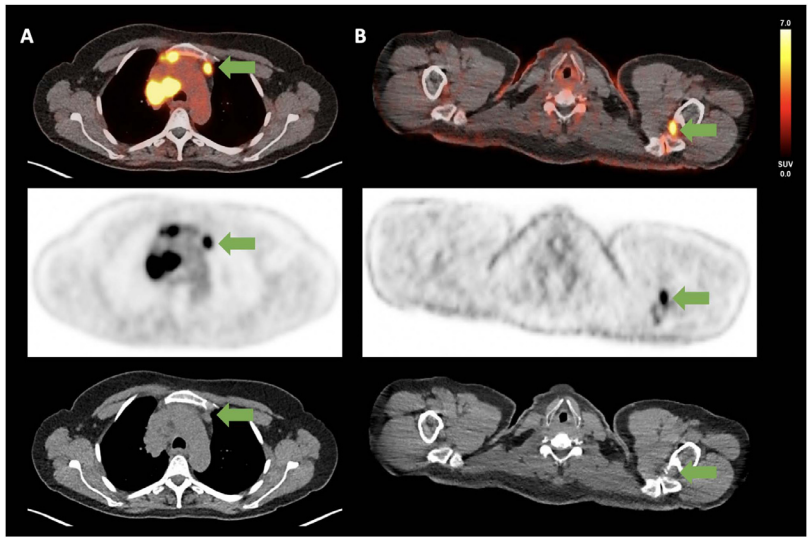

Fig. 2 Examples of FAP-RADS lesions. (A) The green arrow point to an enlarged mediastinal lymph node with intense FAPI uptake (SUVmax 9.33) in a lung cancer patient (FAP-RADS 5). (B) The green arrow points to an intra-articular FAPI uptake (SUVmax 10.02), which is attributed to degenerative changes (FAP-RADS 1).

Clinical dosing schemas and logistics of FAP therapy

Before each treatment cycle, laboratory tests including blood counts, renal and hepatic function are obtained. Dosing schemes for [^{177}Lu]Lu-FAPI are informed by prior experience with PSMA and DOTATATE therapies but require adjustment based on ligand pharmacokinetics.[2,4] Typically, each cycle comprises 3−9 GBq of activity administered intravenously over one to two minutes followed by a saline flush. The cycles are repeated every 4 to 6 weeks for a maximum of 4−6 administrations, although modifications depend on tumor histopathology (e.g. Ki67 rate) and disease status.[36,65]

In the multicenter LuMIERE trial phase 1 in advanced solid tumors, [^{177}Lu]Lu-FAP-2286 was administered to escalating cohorts from 3.7 to 9.25 GBq every six weeks for up to six cycles. Dose-limiting toxicities were not observed at the lower dose levels. At 9.25 GBq, hematologic toxicity (mainly grade 3−4 thrombocytopenia and leukopenia) was seen in a subset but was overall manageable.[65,66]

In a first-in-human escalation using EB-FAPI ([^{177}Lu]Lu-LNC1004), cohorts received 2.22, 3.33, or 4.99 GBq every 6−8 weeks. The tumor absorbed doses were markedly higher than with monomeric FAPI ligands, thus achieving disease control rates up to 70−80%. However, marrow toxicity was dose-limiting above 3.3 GBq per cycle. Hematologic toxicity became the dose-limiting factor at the highest activity (4.99 GBq). The optimal therapeutic dose appears to be 3.33 GBq per cycle.[36]

Investigational studies with dimeric ligands typically used cumulative doses in the range of 6.3 − 55.5 GBq over 1-6 cycles.[67,68] Clinical experience is more limited than with FAP-2286 or EB-FAPI, but early results suggest that dimerization improves tumor uptake and retention sufficiently to support therapeutic dosing at conventional activity levels.[68]

Typically, response assessment is typically performed after each cycle using SPECT/CT or after 2−3 cycles using FAPI-directed PET or cross-sectional imaging.[66,69] In investigational protocols, post-therapy SPECT/CT is acquired for dosimetry, which helps adapt future dosing and contributes to research on dose−response relationships.[66,67,70] To conduct FAP-directed therapy a stepwise procedure as proposed in Fig. 3 might be helpful.

Biodistribution and dosimetry of FAP therapy

As ^{177}Lu emits γ-photons, post-therapy SPECT/CT can be performed at multiple time points, thus enabling direct measurement of time−activity curves in organs and lesions.[43-45] Consequently, ^{177}Lu is considered an excellent isotope for translational dosimetry studies. Across ligands, a common feature is high uptake in FAP-expressing tumor stroma with relatively low background uptake in most normal tissues.[10]

The absorbed doses to tumors reported vary considerably depending on the type of FAP ligand employed. Monomeric FAPI compounds generally yield tumor doses of <2 Gy/GBq to tumors, a level that is insufficient to achieve robust tumor control. Dimers achieve up to 4 Gy/GBq, which, when multiplied by the number of cycles delivered, results in a therapeutically meaningful exposure. Albumin-binding compounds, such as EB-FAPI, have been shown to achieve up to 8 Gy/GBq. Peptidic ligands such as FAP-2286 fall into an intermediate range of 2−5 Gy/GBq, thereby demonstrating sufficient retention to support therapeutic efficacy. This is comparable to the absorbed doses observed in approved ^{177}Lu therapies.[71-75]

Excretion occurs primarily via the kidneys, with variable amounts of hepatobiliary clearance.[21,76] Organs at risk thus

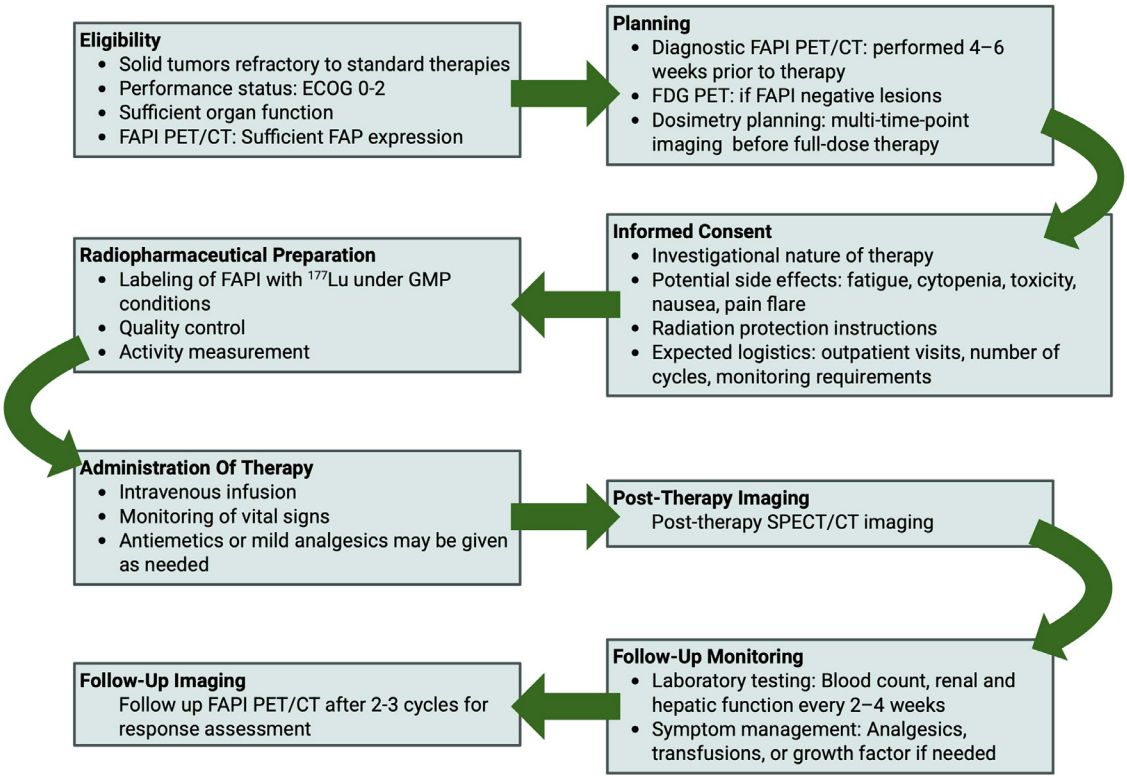

Fig. 3 Flowchart FAP-directed Therapy. Created in BioRender. Kunte, S. (2026) https://BioRender.com/yk6xblm.

include the kidneys, which receive 0.5−1.5 Gy/GBq depending on the scaffold, and red marrow with 0.1−0.2 Gy/GBq. For ligands with longer circulation times, e.g. albumin-binding compounds, red marrow becomes the limiting organ. Gastrointestinal and hepatic exposure is generally mild.[71-74]

The available safety data indicate good acute tolerability, with most patients experiencing only transient fatigue or nausea. Hematologic toxicity is the primary concern, manifesting predominantly as mild cytopenia (grade 1-2) and infrequently as grade 3 with dimers, and, at higher doses as myelotoxicity (grade 3−4) with EB-FAPI.[36,68,77] As [^{177}Lu]Lu-FAP therapy is still in early clinical development, long-term safety data are limited. Monitoring for cumulative marrow suppression, renal dysfunction, or secondary malignancies remains essential. Furthermore, heterogenous tumor and organ doses have been observed to vary between patients and between lesions. This emphasized the importance of personalized dosimetry whenever feasible, particularly in early-phase trials or when using novel ligands.[71,74]

Efficacy across solid tumor entities

Despite the initial focus of the earliest studies of [^{177}Lu]Lu-FAPI on the evaluation of safety and dosimetry, encouraging results of efficacy have already been observed. Across several small and heterogeneous cohorts, including basket trials and compassionate-use programs, patients with advanced solid tumors refractory to standard treatments have achieved disease stabilization and, in some cases, objective responses. Whilst the present findings are limited in scope, they do provide the first clinical evidence that FAP-directed radioligand therapy can exert meaningful antitumor effects in heavily pretreated populations (Table 1).[21]

Head and neck cancer

Fu et al. treated a patient with nasopharyngeal cancer and metastases within the liver, pancreas and bones with 3.7 GBq of [^{177}Lu]Lu-FAPI-46. The patient exhibited progressive disease at the subsequent follow up.[78]

Thyroid gland

Several basket studies have included patients with thyroid cancer. Assadi et al. administered a single cycle of [^{177}Lu]Lu-FAPI-46 (3.7 GBq) to a patient with osseous and nodal metastasized anaplastic thyroid cancer and observed stable disease according to RECIST 1.1 at the follow-up.[79] Ballal et al. investigated the response to [^{177}Lu]Lu-DOTAGA-(SA-FAPi)$_2$ (mean cumulative dose 8.2 GBq) in 15 patients with differentiated thyroid cancer and progression during thyrosin kinase inhibition treatment. In a total of seven patients, PET-based response evaluation was successfully conducted, yielding either a partial response (four patients) or stable disease (three patients).[80] In addition, a patient suffering from medullary carcinoma was administered a single dose of 1.65 GBq [^{177}Lu]Lu-DOTAGA-(SA-FAPi)$_2$, which resulted in partial

Table 1 Overview of studies.

Entity	No. Of Patients	Dose (GBq)	Cycles	Response (RECIST 1.1)	Safety	Reference
Nasopharynx	1	3.7	1	PD	No G3/G4 toxicity	[78]
ATC	1	3.7	1	SD	No G3/G4 toxicity	[79]
DTC	15	5.5	45 (total)	PR 4/7; SD 3/7	No G3/G4 toxicity	[80]
MTC	1	1.65	1	PR	No G3/G4 toxicity	[67]
FTC	73	5.5	1-9	PD 19/73; death 20/73	Grade 3 thrombo cytopenia and anemia	[82]
TC	12 (1 MTC, 11 DTC)	2.22; dose escalating by 50 %	1-2	PR 3/12; SD 7/12; PD 2/12	Myelotoxicity Grade 3-4 in 3/12	[36]
Breast	5	1.85-3.8	1-4	SD 3/5; PD 2/5	No G3/G4 toxicity	[79]
Breast	4	5.8 (cumulative)	1-3	SD 2/4; PD 2/4	No G3/G4 toxicity	[74]
Breast	19	19 (cumulative)	2-6	PR 4/16; PD 6/16	No G3/G4 toxicity	[83]
Lung	1	13.7 (cumulative	4	SD	No G3/G4 toxicity	[79]
Lung	1	7.4	1	PR	No G3/G4 toxicity	[85]
Lung	1	7	1	PR	No G3/G4 toxicity	[86]
Pancreas	2	3.7	1-2	PD	No G3/G4 toxicity	[79]
Pancreas	1	1.85	1	n.a.	No G3/G4 toxicity	[87]
Pancreas	5	5.8 (cumualtive)	2	PD	No G3/G4 toxicity	[74]
Colorectal	3	3.7	1-2	SD	No G3/G4 toxicity	[79]
Colorectal	1	5.8 (cumualtive)	1	PD	No G3/G4 toxicity	[74]
Prostate	1	1.85	1	SD	No G3/G4 toxicity	[79]
Bladder	1	7.4	1	PR	No G3/G4 toxicity	[89]
Ovary	2	3.7-10 (cumulative)	1-3	SD	No G3/G4 toxicity	[79]
Ovary	1	5.8 (cumulative)	2	PD	No G3/G4 toxicity	[74]
Cervix	1	6.66 (cumulative)	2	PD	No G3/G4 toxicity	[79]
Sarcoma	1	8.5 (cumulative)	4	PD	Grade 3 anemia	[79]
Leiomyosarcoma	1	23 (cumulative)	4	PD	No G3/G4 toxicity	[91]
Sarcoma	5	6.7-7.4	4	PR 4/5; PD 1/5	No G3/G4 toxicity	[49]
Solitary fibrous tumor	1	14.8 (cumulative)	2	PR	No G3/G4 toxicity	[92]

ATC: anaplastic thyroid cancer; DTC: differentiated thyroid cancer; MTC: medullary thyroid cancer; n.a.: not available; PD: progressive disease; PR: partial response; SD: stable disease; TC: thyroid cancer.

response at the subsequent follow-up (Fig. 4).[81] No severe side effects were reported in either study. They further provided [^{177}Lu]Lu-DOTAGA-(SA-FAPi)$_2$ monotherapy to 65 patients with FTC (median activity 5.5 GBq per cycle) and [^{177}Lu]Lu/[^{225}Ac]Ac-DOTAGA.FAPi dimer tandem therapy to eight patients. 20/73 patients died (16/20 due to the thyroid cancer) and 19/73 showed disease progression. 3/73 presented with grade 3 thrombocytopenia.[82] Fu et al. further conducted a dose-escalating study using 2.22 GBq [^{177}Lu]Lu-EB-FAPI ([^{177}Lu]Lu-LNC1004) and subsequently increasing the activity by 50% in 12 patients with radioiodine-refractory thyroid cancer (1/12 medullary, 11/12 differentiated thyroid cancer). 10/12 patients exhibited disease control as defined by RECIST 1.1. Three patients demonstrated signs of Grade 3-4 myelotoxicity.[36]

Breast cancer

Several studies have reported on the experience of treating heavily pretreated, metastasized breast cancer with FAP-directed therapy, including a total of 30 patients. Assadi et al. included five patients who were treated with up to three cycles of [^{177}Lu]Lu-FAPI-46. Subsequent imaging revealed stable disease in 3/5 and progressive disease in 2/5 patients.[79] Baum *at al.* administered two cycles of [^{177}Lu]Lu-FAP-2286 (cumulative dose 5.8 GBq) to four patients. Two patients exhibited progressive disease, while two patients demonstrated stable disease, respectively.[74] In the study conducted by Yadav et al., a total of 19 patients were treated with up to six cycles of [^{177}Lu]Lu-FAP-2286 (cumulative dose 19 GBq). Follow-up PET/CT scans were available for 16 patients: of these, four exhibited partial response, while six demonstrated progressive disease.[83] Zhang recently treated 14 patients with radiolabeled 3BP-3940 with ^{177}Lu, ^{90}Y, or ^{225}Ac - used alone or in combination, who showed good tolerability.[84] The full publication is expected. In neither of the studies were any side effects observed that were classified as CTCAE grade 4 or higher.

Lung cancer

For patients diagnosed with lung cancer, case reports are the only available source of information regarding the use of FAP-directed radioligand therapy. Assadi et al. reported on a

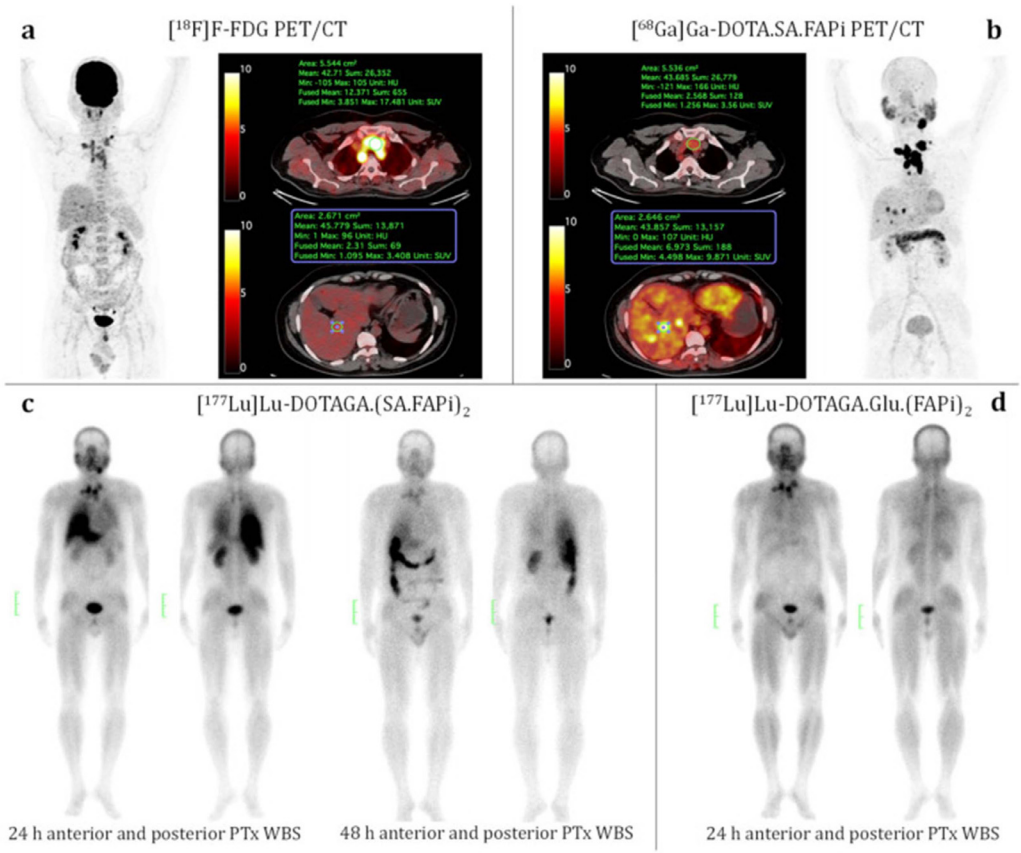

Fig. 4 The intra-individual [18F]FDG PET/CT and [68Ga]Ga-DOTA.SA.FAPi PET/CT scans of a 40-year-old patient with medullary thyroid carcinoma showed advanced metastases in the neck and liver regions. Following [177Lu]Lu-DOTAGA.(SA.FAPi)2 therapy (c), the patient showed a significant therapy response demonstrated on whole-body planary images [adapted from 81].

patient with metastasized adenocarcinoma of the lung and stable disease following treatment with four cycles of [^{177}Lu]Lu-FAPI-46 (cumulative dose 13.7 GBq).[79] Another patient with metastasized adenocarcinoma was treated by Yang et al. with 7.4 GBq of [^{177}Lu]Lu-FAPI-2286 and exhibited partial response according to the follow up imaging.[85] Rao et al. administered 7 GBq of [^{177}Lu]Lu-FAP-2286 to a patient with metastasized squamous lung cancer and observed a partial response.[86] No relevant adverse effects or toxicities were reported in both studies.

Pancreatic cancer

Strong desmoplastic reaction within tumor stroma has been associated with superior diagnostic performance with FAP-targeted ligands and offers a promising avenue for FAP-targeted application (Fig. 5). To date, three studies have reported on FAP-directed therapy in pancreatic cancer patients. Assadi et al. included two patients with metastatic disease following systemic therapy undergoing [^{177}Lu]Lu-FAPI-46 therapy. One subject underwent two cycles (cumulative dose 5.5 GBq), while the other subject underwent a single cycle (3.7 GBq). As demonstrated in the subsequent imaging, both cases exhibited progressive disease.[79] Kaghazchi et al. published a case report on a patient with end-stage metastasized pancreatic cancer who underwent one cycle (1.85 GBq) of [^{177}Lu]Lu-FAPI-46 therapy. Due to the advanced stage of the illness, the patient passed away after a period of 6.5 weeks, prior to the assessment of response.[87] Baum et al. included a heterogenous cohort of five patients, of whom three presented with metastasized disease and two were therapy-naïve. Patients were administered two cycles of [^{177}Lu]Lu-FAP-2286 therapy (cumulative dose 5.8 GBq). The response assessment revealed progressive disease in the complete cohort.[74] Perrone et al. recently treated 15 patients with [^{225}Ac]Ac-3BP-3940 resulting in PD in 11/15 and PR in 4 /15 patients.[88] The full publication is expected. In neither study was there a report of adverse events.

Colorectal cancer

Assadi et al. reported on three patients with advanced colorectal cancers who underwent [^{177}Lu]Lu-FAPI-46 following extensive pretreatment. One subject received two cycles, while two subjects received one cycle (3.7 GBq/cycle). All three patients showed stable disease at the follow-up.[79] Baum et al. treated one patient with metastasized disease with one cycle of [^{177}Lu]Lu-FAP-2286 therapy. He subsequently demonstrated progressive disease.[74] No adverse events of grade 3 or higher were observed.

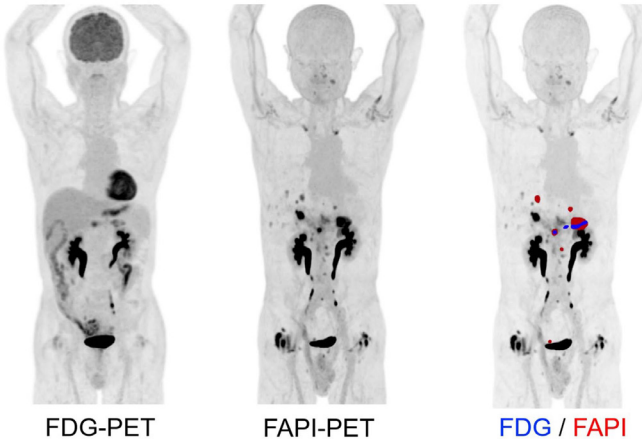

Fig. 5 This intra-individual comparison of FAPI and FDG imaging in a patient with disseminated pancreatic cancer revealed superior diagnostic performance of FAPI imaging in terms of lesion-based detection rate (published with courtesy of Watabe et al.).

Genitourinary cancer

Two case reports are available which report on the administration of FAP-directed therapy in patients with genitourinary cancer. Assadi et al. included one patient with prostate cancer, who presented with stable disease following one cycle of [^{177}Lu]Lu-FAPI-46 (1.85 GBq).[79] Li et al. administered one cycle of [^{177}Lu]Lu-FAP-2286 (7.4 GBq) to a patient with urothelial carcinoma of the bladder, who exhibited a partial response three months post-treatment.[89] Wirtz et al. reported about No adverse effects were reported.

Ovarian cancer

A total of three case reports are available, detailing the experience of women suffering from ovarian cancer who are undergoing FAP-directed therapy. Assadi et al. treated two patients with [^{177}Lu]Lu-FAPI-46 (one with one cycle and 3.7 GBq and one with three cycles and 10 GBq cumulative dose). Both of the showed stable disease at the follow-up.[79] Another patient underwent two cycles of [^{177}Lu]Lu-FAP-2286 therapy (cumulative dose 5.8 GBq) and subsequently exhibited progressive disease afterwards.[74] Lapi et al. reported about a case of tandem [^{177}Lu]Lu/[^{225}Ac]Ac-3BP-3940 treatment resulting with complete response.[90] No adverse effects were observed.

Cervical cancer

A single case report has been published on the use of [^{177}Lu]Lu-FAPI-46 in a woman with cervical cancer who received two cycles (cumulative dose 6.66 GBq). The subject presented with progressive disease on post-treatment imaging, with no reported side effects.[79]

Sarcoma and solitary fibrous tumors

A total of five studies is available on the use of FAP-directed therapy in patients diagnosed with mesenchymal malignancies. Assadi et al. reported on a pediatric patient suffering from metastasized sarcoma who was treated with four cycles of [^{177}Lu]Lu-FAPI-46 (cumulative dose 8.5 GBq). The subject showed progressive disease as well as grade 3 anemia.[79] Banihashemian et al. published a case report about a patient with metastasized leiomyosarcoma who underwent four cycles of [^{177}Lu]Lu-FAPI-2286 (cumulative dose 23 GBq). The patient also presented with progressive disease at the follow-up.[91] A further study included five patients with different sarcomas (leiomyosarcoma, thyroid sarcoma, alveolar soft sarcoma, pleomorphic cell sarcoma, neurofibrosarcoma) who received four cycles of [^{177}Lu]Lu-FAPI-2286. Partial responses were observed in four of the patients, while the patient with the pleomorphic cell sarcoma exhibited progressive disease.[49] In a further case report of Luthra et al. presented two cycles of [^{177}Lu]Lu-FAPI therapy (cumulative dose 14.8 GBq) in a patient with metastasized solitary fibrous tumor, who showed partial response at the follow-up.[92] Lanzafame et al. reported about three patients treated with [90Y]Y-FAPI-46 following FAPα immunohistochemistry staining, who presented with disease control. With the exception of the case reported by Assadi et al. no adverse events were observed.

Palliative benefits

Beyond objective tumor shrinkage, [^{177}Lu]Lu-FAPI therapy has demonstrated significant palliative effects, particularly in terms of pain relief, as evidenced by numerous studies. Furthermore, some patients reported about an improved quality of life, including increased appetite, weight and strength gain, reflecting symptomatic benefit even without radiologic partial response.[67,74,78,87,89,93] These outcomes underscore the potential supportive role of [^{177}Lu]Lu-FAPI in patients with advanced disease, even in cases where tumor shrinkage is minimal. It is evident that a multitude of factors appear to influence the efficacy of [^{177}Lu]Lu-FAPI therapy. This highlights the multifactorial determinants of therapeutic success and emphasize the importance of patient selection, ligand optimization, and adequate treatment delivery.

Combination strategies with [^{177}Lu]Lu-FAPI therapy

A further question is whether FAPI therapy is most effective as a stand-alone treatment or as part of a broader multimodal regimen. It is suggested by preclinical data and early clinical experience that [^{177}Lu]Lu-FAPI may achieve its greatest impact when combined with other therapies that exploit synergistic mechanisms.

CAFs have been demonstrated to contribute to an immunosuppressive microenvironment by secretion of interleukins and chemokines.[6] The depletion of CAFs induced by radiation has been demonstrated to result in a reduction of stromal barriers, an enhancement of immune cell infiltration, and an upregulation of antigen presentation.[94] This creates an opportunity to combine [^{177}Lu]Lu-FAPI with immune checkpoint inhibitors.[95] In mouse models, CAF irradiation via FAPI-based radionuclides has been shown to increase $CD8^+$ T cell infiltration and improve responses to PD-1 blockade.[94-96]

Dense desmoplasia in tumors like colorectal adenocarcinoma has been shown to impede the efficacy of systemic chemotherapy. By irradiating and partially ablating CAFs, [^{177}Lu]Lu-FAPI has been hypothesized to remodel the extracellular matrix, thereby enhancing the delivery of chemotherapy drugs. As indicated by preclinical models, there is an increased propensity for chemosensitivity subsequent to the depletion of CAFs.[97] Banihashemian et al. administered chemotherapy in combination with [^{177}Lu]Lu-FAP-2286 to a patient suffering from metastasized breast cancer. The patient underwent six cycles of Docetaxel, Carboplatin, Trastuzumab and Pertuzumab in combination with four cycles of FAP-directed therapy at 6.6 GBq. A complete response was revealed at the follow-up as per PET/CT imaging, with no adverse events being observed.[98] Subsequent phase 2 studies are planned, for example in patients with non-small cell lung cancer or pancreatic cancer.[66]

Tyrosine kinase inhibitors and anti-angiogenic drugs have been demonstrated to modulate the tumor microenvironment. Adding [^{177}Lu]Lu-FAPI has the potential to facilitate complementary stromal targeting, thereby circumventing resistance pathways, as evidenced in xenograft mice with sarcoma.[99] Raeisi et al. administered a combination therapy of sorafenib and four cycles of [^{177}Lu]Lu-FAP-2286 to a patient with medullary thyroid carcinoma. No follow-up imaging was conducted, however, clinical symptoms improved and serum calcitonin levels decreased.[100]

Despite the potential of multimodal strategies, there are several challenges that still need to be addressed. A significant concern pertains the issue of overlapping toxicity, as the combination of radionuclide therapy with myelosuppressive chemotherapy has the potential to amplify marrow suppression, necessitating meticulous scheduling and dose adjustments. The optimal timing and sequencing of treatments remains to be resolved. For instance, there is a need to determine whether FAPI therapy should be used as a priming strategy before immunotherapy or administered concurrently.

Limitations

Whilst [^{177}Lu]Lu-FAPI therapy has demonstrated encouraging safety and early efficacy signals, it is imperative to acknowledge several significant limitations.

CAF heterogeneity and FAP biology

CAFs do not constitute a uniform population.[101] Distinct subsets of cells have been identified, including myofibroblastic CAFs, inflammatory CAFs, and antigen-presenting CAFs.[102-104] It is important to note that not all CAFs express FAP to the same degree.[105] Consequently, FAPI PET uptake and the ensuing therapeutic response may be subject to variation depending on the composition of the CAFs within the tumor.[51] Furthermore, FAP expression may undergo alterations over time, in response to therapeutic interventions, or in conjunction with disease progression.[106] For instance, the administration of immune therapy has been observed to result in a transient upregulation of stromal FAP expression, a phenomenon that has the potential to modify the efficacy of FAPI therapy.[107] As FAP is also expressed in wound healing and fibrotic conditions, there is a risk of off target binding in benign tissues, especially following radiation therapy.[6,108,109]

Tumor heterogeneity of uptake

In a given patient, metastases may exhibit intense FAPI uptake while others may demonstrate a negative response. In the treatment of such heterogeneous disease there is a risk of undertreatment of non-avid lesions. Uptake intensity and retention differ furthermore significantly between patients, even within the same histological subtype. This variability poses a significant challenge to the standardization of therapy protocols. The heterogeneous uptake reduces the likelihood of uniform tumor control. Dual-tracer imaging using FAPI and FDG PET/CT may facilitate the identification of patients at risk of progression in FAPI-negative sites.[54,59,110]

Current state of clinical evidence

Most published data originate from phase I trials, compassionate-use reports, or small basket cohorts. However, robust phase II/III efficacy data are lacking. To date, no trial has been conducted that has directly compared [^{177}Lu]Lu-FAPI with standard systemic therapies in any tumor type. In the absence of such data, the true added value of FAPI therapy remains uncertain. Due to limited follow up data, long-term safety and durability of responses remain to be established.

Whilst [^{177}Lu]Lu-FAPI represents an exciting frontier in the field of radioligand therapy, its biological and clinical limitations must temper expectations. Future progress will depend on refining ligand design, stratifying patients more precisely using companion imaging, and generating robust randomized evidence. Addressing these limitations is imperative for the transition of [^{177}Lu]Lu-FAPI from experimental use into mainstream oncology practice.

Uncertainty also surrounds dosing and scheduling. The optimal number of cycles, cumulative activity, and inter-

cycle interval remain to be identified, and questions persist regarding re-treatment at relapse or cumulative marrow tolerance. The efficacy of adaptive strategies guided by interim imaging and dosimetry are promising but is yet to be validated. Establishing dose-response relationships and linking imaging biomarkers such as maximum SUV or retention to outcomes are key research needs.

Emerging directions in FAPI theranostics

The story of ^{177}Lu is still being written. The rapid progress of [^{177}Lu]Lu-FAPI therapy from preclinical concept to multicenter human studies within only a few years highlights the adaptability of the theranostic model. Innovations in ligand design continue, including trimeric and tetrameric constructs, refined albumin binders, and hybrid tracers with intraoperative fluorescence. Alternative radionuclides such as ^{225}Ac and ^{161}Tb are under investigation. A series of preliminary studies involving [^{225}Ac]Ac-FAPI have shown feasibility but also highlight risks of marrow toxicity.[111-113] Preclinical studies showed promising results in mice with pancreatic cancer by applying [^{64}Cu]Cu-FAPI-04 and [^{225}Ac]Ac-FAPI-04.[114,114] ^{161}Tb is a β-emitter similar to ^{177}Lu but with additional Auger electrons, potentially delivering higher local dose to small clusters of cells. Terbium isotopes are still in early development but could represent a future alternative.[115,116] Additionally, a phase I/IIa study using [^{203}Pb]Pb-PSV359 and [^{212}Pb]Pb-PSV359 (NCT06710756) in patients with solid tumors has just launched. Concepts such as sequential [^{177}Lu]Lu-/[^{225}Ac]Ac-FAPI therapy are being explored, leveraging the crossfire of β-particles with the potency of α-particles for selected lesions. The FDA recently approved a phase I study using CAM-FAP-Ac-225.[117] Eli Lilly and Company also announced a phase Ia/Ib study providing LY4337713 (FiREBOLT) to patients with FAP positive cancers (NCT07213791). Future studies using ^{211}At are expected.[118]

Advances in imaging standardization, AI-driven dosimetry, and adaptive treatment planning will further refine personalization.

Recent developments have introduced a new generation of covalently binding FAP ligands. These tracers exhibit enhanced tumor retention and improved tumor-to-background ratios, thereby increasing both diagnostic contrast and therapeutic efficacy.[119] The first clinical imaging experiences and early treatment cases further confirm the translational potential of these ligands.[120]

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Google-Assisted AI for language editing and research. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing interest

RAW has received speaker honoraria from Novartis/AAA and PentixaPharm and reports advisory board work for Novartis/AAA and Bayer. FLG has a patent application for quinolone-based FAP-targeting agents for imaging and therapy in nuclear medicine and shares a consultancy group for iTheranostics. FLG is also an advisor at ABX, Telix, Alpha Fusion and SOFIE Biosciences. All other authors declare that there is no conflict of interest.

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Sophie C. Siegmund: Data curation, Formal analysis, Software, Writing – original draft. **Emil Novruzov:** Project administration, Resources. **Eduards Mamlins:** Resources, Validation, Visualization. **Yuriko Mori:** Data curation, Software. **Sven Otto:** Data curation, Methodology. **Martin Canis:** Formal analysis. **Tadashi Watabe:** Writing – review & editing. **Richard P. Baum:** Supervision, Writing – review & editing. **Rudolf A. Werner:** Conceptualization, Project administration, Writing – review & editing. **Frederik L. Giesel:** Conceptualization, Resources, Supervision, Visualization, Writing – review & editing.

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