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Initial clinical experience with ^{90}Y-FAPI-46 radioligand therapy for advanced stage solid tumors: a case series of nine patients

Running title: ^{90}Y-FAPI therapy for advanced cancer

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ABSTRACT

Introduction: Fibroblast activation protein (FAP) is overexpressed in several solid tumors and therefore represents an attractive target for radiotheranostic applications. Recent investigations demonstrated rapid and high uptake of small-molecule inhibitors of FAP (^{68}Ga-FAPI-46) for PET imaging. Here, we report our initial experience in terms of feasibility and safety of ^{90}Y-labelled FAPI-46 (^{90}Y-FAPI-46) for radioligand therapy (RLT) of extensively pretreated patients with solid tumors.

Methods: Patients were considered for ^{90}Y-FAPI-46 therapy in case of (a) exhaustion of all approved therapies based on multidisciplinary tumor board decision and (b) high FAP expression, defined as SUVmax ≥ 10 in more than 50% of all lesions. If tolerated, post-therapeutic ^{90}Y-FAPI-46 bremsstrahlung scintigraphy was performed to visually confirm systemic distribution and focal tumor uptake, and ^{90}Y-FAPI-46 PET scans at multiple time-points were performed to determine absorbed dose. Blood-based dosimetry was used to determine bone-marrow absorbed dose. Adverse Events were graded using CTCAE v.5.0.

Results: Nine patients with either metastatic soft tissue or bone sarcoma (N = 6) and pancreatic cancer (N = 3) were treated between June 2020 and March 2021. Patients received a median of 3.8 (IQR 3.25-5.40) GBq for the first cycle and three patients received subsequent cycles with a median of 7.4 (IQR 7.3-7-5) GBq. Post-therapy ^{90}Y-FAPI-46 bremsstrahlung scintigraphy demonstrated sufficient ^{90}Y-FAPI-46 uptake in tumor lesions in 7 of 9 patients (78%). Mean absorbed dose was 0.52 Gy/GBq (IQR 0.41-0.65) in kidney, 0.04 Gy/GBq (IQR 0.03-0.06) in bone marrow and below 0.26 Gy/GBq in the lung and liver. Measured tumor lesions received up to 2.28 Gy/GBq (median 1.28 Gy/GBq). Hematologic G3/G4 toxicities were noted in four patients (44%), of which

thrombocytopenia was most prevalent (N = 6; 67%), whereas other G3/G4 laboratory-based adverse events were N ≤ 2. No acute toxicities attributed to ^{90}Y-FAPI-46 were noted. Radiographic disease control was noted in three patients (33%).

Conclusion: FAP-targeted RLT with ^{90}Y-FAPI-46 was well tolerated with a low rate of attributable adverse events. Low radiation doses to organs at risk suggest feasibility of repeat cycles of ^{90}Y-FAPI-46. We observe signs of clinical activity, but further studies are warranted to determine efficacy and toxicity profile in a larger cohort.

INTRODUCTION

The fibroblast activation protein (FAP) is expressed by cancer associated fibroblasts as well as cancer cells such as sarcoma and mesothelioma (*1-3*). Therefore, FAP is an attractive target for both imaging and radionuclide therapy of solid tumors. Previously, several groups have described high tumor uptake for ^{68}Ga or ^{18}F labelled PET-compounds (*4-9*). We implemented imaging using the FAP-targeted inhibitor FAPI-46 for diagnostic work-up of cancer types such as pancreatic cancer and sarcoma (*10,11*).

Recently, FAP-targeted radioligand therapy has been described in few case reports (*12-14*), however feasibility has not been analyzed systematically yet. In this case series, ^{90}Y-labelled FAPI-46 (^{90}Y-FAPI-46) radioligand therapy (RLT) was offered to patients with advanced stage solid tumors who have exhausted all established lines of treatment. ^{90}Y features high branching-ratio β^-emission (99.99%) with an end-point energy of 2.280 MeV, allowing high dose deposition within defined tumor lesions. Its relatively short half-life of 64.1 h makes it appropriate for therapeutic combinations in which the biochemical vector exhibits short target retention time. Preclinical studies on FAPI-46 have demonstrated a decrease to 30% of tumor uptake from one hour to 24 hours p.i. (*14*). Post-therapy ^{90}Y-FAPI-46 scintigraphy is performed by measuring the β^-emission associated Bremsstrahlung radiation. ^{90}Y also decays by internal conversion (0.0032%), emitting a positron with a total kinetic energy of 0.760 MeV. Positron emission enables PET quantitative data for dosimetry (*15*).

We here report safety, dosimetry, and response for repeat ^{90}Y-FAPI-46 RLT in patients with advanced solid tumors.

MATERIALS AND METHODS

This is a monocentric, retrospective study of nine patients with progressive, advanced-stage solid tumors receiving ^{90}Y-FAPI-46 under compassionate access following clinical indication. Radionuclide treatment was decided for in a multidisciplinary tumor board. All patients have either previously progressed during established treatment options and were not eligible to receive other treatments. The institutional review board approved this study (Reference: 21-9842-BO). All patients gave written informed consent to undergo clinical RLT and for retrospective analysis of clinical data separately. All patients underwent PET imaging with ^{68}Ga-FAPI-46 prior to treatment to confirm FAP-positivity of tumor lesions, defined as SUVmax ≥ 10 in more than 50% of all lesions (Figure 1). Imaging procedures were described previously (*10*); in brief, patients received a median of 103 MBq ^{68}Ga-FAPI-46 (IQR 87-133.5) intravenously and were scanned after a median of 37 minutes (IQR 24.5-60) post injection. To be eligible for treatment, patients had to have adequate bone marrow function (i.e. leukocytes > 2,5 /nl, hemoglobin > 7,0 mg/dl, thrombocytes > 75 /nl) with exceptions for patients receiving regular transfusions. Renal scintigraphy with ^{99m}Tc-MAG3 was performed to rule out urinary tract obstruction prior to treatment.

^{90}Y-FAPI-46 Synthesis

The synthesis of ^{90}Y-FAPI-46 was performed with mean of Easyone synthesis module (Trasis, Ans, Belgium) connected to shielded ^{90}Y-YCl_3 solution, (Yttriga, Eckert and Ziegler, Berlin, Germany). Before the automated synthesis starts, the cassette is pre-loaded with FAPI-46 precursor (ABX, Radeberg, 8 µg/GBq), ascorbic acid/sodium acetate buffer saline vials. The synthesis was performed fully automated using a GMP-grade

reagent and controlled by a pre-programed sequence. The ^{90}Y-YCl_3 solution is transferred into the reactor followed by the precursor/buffer mixture. For radiolabeling the reaction mixture is heated to 90 °C for 20 min. Afterwards, the product is transferred into the bulk vial through a sterile filter and formulated with Pentetic acid (1mL, Ditripentat-Heyl), Ascorbic acid (ca. 40 mg/GBq, Vitamin C-Rotexmedica) and saline. The quality control procedures included RP-HPLC, ITLC, pH, endotoxine and sterility testing. The average yield has been 88±7%, HPLC radiochemical purity of 98±1%, a concentration of 883±70 MBq/ml and shelf life of 24 hours.

^{90}Y-FAPI-46 Administration

Patients underwent inpatient treatment to ensure radiation safety. Vital signs were monitored before and after administration of ^{90}Y-FAPI-46. Patient #1 and Patient 2# received a planned activity of 7.4 GBq ^{90}Y-FAPI-46 at first cycle. All other patients received a planned first activity (scout dose) of 3.8 GBq ^{90}Y-FAPI-46 with dosimetry. In case focal ^{90}Y-FAPI-46 uptake was noted in more than 50% of tumor lesions on post therapy ^{90}Y-FAPI-46 bremsstrahlung scintigraphy (Figure 1) and if clinically indicated, patients were eligible to receive further cycles with 2 x 3.8 GBq ^{90}Y-FAPI-46 (high dose), 4 hours apart. We chose fractionated applications to achieve optimal prolonged radiation delivery based on the observed short biological half-life during scout cycles, which appeared to be below 24 hours. Therapeutic solution was administered intravenously together with 500 ml of saline. Bremsstrahlung scintigraphy was performed about 24 hours or, if possible, 0.5 hours after therapy to visually confirm systemic distribution and focal tumor uptake. Whole body planar imaging was performed at a scan speed of 10 cm min^{-1}, with an energy

window of 90 -125 keV and using a medium energy collimator. All patients were discharged 48 h after therapy in accordance with radiation protection regulations.

Dosimetry

Patients underwent post-therapeutic dosimetry if tolerated. In case of severe pain, long acquisition ^{90}Y-FAPI-46 PET scans were not performed (N = 3 during cycle 1 and N = 1 during cycle 2) or patients who did not tolerate or refused repeated blood sampling (N = 4). Bone marrow dosimetry was measured using repeated blood samples (0.5, 1, 2, 4, 24, 36 and 48 hours p.i.) and estimated according to OLINDA/MIRD recommendations. Dose absorbed by tumor lesions and kidneys was estimated using PET acquisitions. PET images were acquired on multiple time-points (0.5, 3 and 18-24 hours p.i.) after ^{90}Y-FAPI-46 application and at least two time points were necessary to determine lesion dose. Tumor and organ dosimetry were assessed by analyzing the respective regions of interest in the PET images, from which the pharmacokinetic behavior was fitted to mono-exponential functions. Images were acquired in a SIEMENS mCT or Vision scanners, following an optimized protocol for quantification (*16*). PET quantification accuracy was validated in a NEMA phantom, being considered most favorable when scanned in a Si-PM PET/CT scanner. Maximum liver and lung dose were assessed individually based on minimum measurable ^{90}Y-FAPI-46 uptake in prior PET phantom studies. In this case we considered the number of disintegrations that would take place in the organ, assuming the minimum detectable activity concentration of 100 kBq/mL, the pharmacokinetics observed in blood dosimetry at the standard organ volumetry stated in the OLINDA.

Outcomes and Statistical Analysis

Toxicity was recorded as per Common Terminology Criteria for Adverse Events (CTCAE v 5.0). Clinical, laboratory and imaging follow-up was done as per clinical routine with laboratory and clinical visits every 2-4 weeks and imaging within 1-2 months. Imaging response was defined as per RECIST v1.1 for CT and PERCIST for FDG-PET/CT (*17,18*). Disease control was defined as complete (metabolic) response (CR/CMR), partial (metabolic) response (PR/PMR) or stable (metabolic) disease (SD/SMD). All patients have received baseline imaging with FDG-PET/CT to rule out sites of discordant disease. Post-therapeutic FDG-PET/CT were performed two weeks after first cycle treatment in seven (78%) patients (Supplement Figure 1-9). For overall response rate, response was defined as CR/CMR or PR/PMR. Descriptive statistics are used to present data; median and inter-quartile range (IQR) are used for continuous measures and absolute number and percentage for categorial data. No statistical tests were employed for this study. All statistical analysis was performed using R statistics (version 3.4.1, www.r-project.org).

RESULTS

Patient Characteristics

Nine patients with either metastatic soft tissue or bone sarcoma (N = 6) and pancreatic cancer (N = 3) were treated between June 2020 and March 2021 (Table 1). The median age was 57 years (IQR 55-62). At baseline, most patients have had a median of 6 (IQR 2-6.5) previous systemic treatment lines (Table 1) and were progressive during their last regimen. The Eastern Cooperative Oncology Group (ECOG) performance status of the majority of patients was ≥2 (N = 6; 67%) and only three patients had an ECOG of 1 at baseline (Table 1).

Treatment and Dosimetry

Patients received a median of 3.8 (IQR 3.25-5.40) GBq for the first cycle and 7.4 (IQR 7.3-7-5) GBq for any subsequent cycle. Patient #3 received three cycles of ^{90}Y-FAPI-46 in total with a cumulative activity of 18.3 GBq. Patients #8 and #9 have received two cycles of ^{90}Y-FAPI-46 for a total of 11.2 and 10.0 GBq, respectively. All other patients (N = 6) stopped treatment after the first cycle due to lack of focal ^{90}Y-FAPI-46 uptake based on post-therapy ^{90}Y-FAPI-46 scintigraphy in the tumor after the first cycle (N = 2), rapid deterioration or death prior to second cycle (N = 4).

Median renal absorbed dose was 0.52 Gy/GBq (IQR 0.41-0.65; N = 4) per cycle. A median marrow absorbed dose of 0.04 Gy/GBq (IQR 0.03-0.06; N = 5) was observed over all cycles. Liver and lung dosimetry were only considered for those patients in which bone marrow dosimetry was performed. The maximum observed dose in liver and lung was ≤ 0.26 Gy/GBq, based on the assumptions presented in the methodology.

Lesion dosimetry was available for nine lesions in six patients, exemplarily shown for patient #2 (Figure 2). Median tumor effective half-life was 8.7 h (range: 5.5 -18). Median dose absorbed by tumor lesions after the first cycle was 1.28 Gy/GBq (IQR 0.83-1.71) per cycle for target lesion and 0.95 Gy/GBq (IQR 0.74-1.32) for secondary lesions. The highest doses were observed in patients #6 (1.37 Gy/GBq), #3 (1.23 Gy/GBq) and #9 (2.28 Gy/GBq). For subsequent cycles in patient #3 and #9, a median lesion dose of 1.28 and 2.04 Gy/GBq per cycle was measured, respectively. Table 2 outlines dosimetry results.

Adverse Events and Follow-up

The median follow-up time was 44 days (IQR 36-83.5). Three patients are still under RLT and had received 3, 2 and 2 cycles, respectively. Five patients have died during follow up, all due to tumor progression and not deemed related to ^{90}Y-FAPI-46 (Table 1 and 3). In patients with progression, median time until progression or death was 18.5 days (IQR 14.8-38.5). There were no acute or allergic reactions observed immediately after infusion of ^{90}Y-FAPI-46. One patient, with advanced pulmonary metastasis and progressive intratumoral arteriovenous shunts, died due to acute respiratory failure attributed to tumor progression shortly after receiving his second cycle. Another patient developed fever shortly after her first cycle likely due to acute urinary tract infection and non-compliance to antibiotic medication. At baseline, five patients had one or more ongoing toxicities ≥ grade 3. These were anemia (N = 2), increase of alkaline phosphatase (N = 1) or gamma-glutamyltransferase (N = 3) (Table 3). During follow-up, four patients showed new grade 3/4 laboratory toxicity (Table 3, Figure 3). These were grade 3 thrombocytopenia (N = 4) possibly related to ^{90}Y-FAPI-46, all of which also in temporal relation to either tumor progression or initiation of concomitant other systemic therapy (Figure 3). One patient showed new grade 3 anemia and two patients had new increase of hepatic or pancreatobiliary serum markers ≥ grade 3 (Table 3). All were rated as disease progression given all three of these patients had pancreatic cancer (Figure 3). A detailed course of the relevant laboratory parameters is shown in the supplement (Supplement Figure 10).

Response Evaluation

Radiologic response as per RECIST v1.1 was available for eight patients. Median time between imaging and first cycle of ^{90}Y-FAPI-46 was 16 days (IQR 15-41). Disease control was noted in 4/8 patients (50%; all had stable disease). No responses were observed up until time of analysis. However, Patient #3 had marked regression of a target lesion (- 28%; Supplement Figure 3) after the first cycle with 3.5 GBq. Metabolic response as per PERCIST was available for 7 patients. Here, disease control was noted in 2/7 patients (29%) consisting of stable metabolic disease (SMD) in 1 patient (14%; Supplement Figure 3) and partial metabolic response (PMR) in another (14%; Supplement Figure 9). Radiologic responses are outlined in table 4.

DISCUSSION

We here report the first case series of patients with advanced stage solid tumors treated with ^{90}Y-FAPI-46 radioligand therapy. Repeated ^{90}Y-FAPI-46 application with individual dosimetry were employed to ensure the safety of each patient and maximum likelihood of treatment effect. Patients had to have high uptake on ^{68}Ga-FAPI-46 PET in majority of tumor lesions for treatment initiation and focal uptake on the first post-therapy ^{90}Y-FAPI-46 bremsstrahlung scintigraphy for continuation (see Figure 1; Supplement Figure 1-9). Patients had exhausted all available on-label or evidence-based treatment options and most prevalent ECOG score was 2 or higher. Treatment with ^{90}Y-FAPI-46 was offered under compassionate use with the intent to achieve anti-tumor effect with manageable toxicity. Based on biodistribution observed on ^{68}Ga-FAPI-46, RLT using ^{90}Y-FAPI-46 was expected to deliver therapeutic radiation doses to tumor while sparing

organs at risk (*4,11*). Indeed, acute toxicities or immediate (e.g. allergic) reactions to RLT were not observed. During follow up, new onset of adverse events was noted in almost all patients. However only a small proportion was attributed to ^{90}Y-FAPI-46, given most adverse events occurred after tumor progression or switch of systemic therapy (see Figure 3). Additionally, we noted that toxicity in one patient who had received multiple RLT cycles with cumulative activity of 18.3 GBq was limited to G1 thrombocytopenia. Ultimately, randomized trials on patients with symptomatic disease are needed for more detailed assessment of toxicity. Data from previous randomized trials evaluating ^{177}Lu-PSMA-617 or ^{177}Lu-DOTATATE identified hematotoxicity, especially thrombocytopenia, as relevant (i.e. frequently occurring as grade 3/4) side-effects (*19,20*). Based on our data, we expect a similar toxicity profile for ^{90}Y-FAPI-46. Therefore, repeated cycles of ^{90}Y-FAPI-46 RLT seem feasible, since dose absorbed by kidneys, bone marrow, liver and lung were low and comparable to that of other small-ligand ^{90}Y therapies (*21*). In our cohort, patients #3, #8 and #9 have received multiple cycles with cumulative activity up to 18.3 GBq.

When all other available therapeutic options failed, achieving disease control is the primary goal for a novel therapy. Previously, Kratochwil *et al.* reported on a patient with spindle cell soft tissue sarcoma who had a long period of stable disease under FAPI-46 RLT (*12*). While the follow up time is yet short, we observed radiographic disease control in half of the patients along with signs of tumor response. Patient #3 experienced meaningful benefit in form of stable disease over a period of 4 months with regression of a large pancreatic tumor mass. Patient #9 showed a partial metabolic response and achieved the highest lesion dose with 13.2 Gy during cycle two. Patients #3, #8 and #9 had additional cycles pending at time of analysis. Interestingly, three of the four patients with disease control are patients with soft tissue (N = 2) and bone (N = 1) sarcoma. The

fourth patient with pancreatic cancer received concomitant treatment with the tyrosine kinase inhibitor afatinib, which was well tolerated and therefore indicates potential feasibility of combination therapy. In the quest to provide the most efficacious therapy with acceptable toxicity, especially in non-responders, two future strategies should be considered; first, a more intense treatment regimen (i.e. short inter-cycle intervals or higher activities) and second, RLT drug combination therapy. FAP and cancer-associated fibroblasts are drivers of immune-escape (*22,23*), therefore immunotherapy might be a rationale companion for FAP-targeted radioligand therapy. Preclinical studies in several cancer types suggest a synergistic effect of FAP-targeting and immunotherapy (*24-27*). Recently, a case report showed good tolerance of ^{177}Lu-PSMA RLT in combination with pembrolizumab or sequentially after olaparib (*28*), which is currently investigated in ongoing prospective phase 1/2 trials (NCT03874884, NCT03805594).

^{90}Y has shorter half-life and higher energy per decay as compared to ^{177}Lu. Due to short retention time in the tumor described by Lindner *et al.* (*14*), ^{90}Y label seemed more suitable to achieve therapeutic radiation doses to the tumor. ^{90}Y PET based dosimetry has been successfully employed for hepatic radioembolization dosimetry, after administration of ^{90}Y-labelled spheres (*29*). Phantom studies suggest that recent developments in sensitivity and timing resolution for PET scanners could be advantageous for ^{90}Y accurate quantification (*16*) which could play a decisive role in the validation of ^{90}Y-labelled therapeutic drugs.

This study comes with limitations. The low number of patients and absence of a pre-defined imaging follow-up protocol does not allow for definitive conclusions regarding therapeutic efficacy and toxicity of ^{90}Y-FAPI-46. Further research is warranted to determine radiation dosimetry for ^{90}Y-FAPI-46, since quantification and subsequent

dosimetry is limited by the decay characteristics of ^{90}Y and relatively low activity concentration in tissues. Low activity concentration combined with detector limits impair accurate acquisition of the true lung and liver doses. However, the aim of this study was to report initial clinical experience and to demonstrate the feasibility of ^{90}Y-FAPI-46 RLT.

CONCLUSION

FAP-targeted RLT with ^{90}Y-FAPI-46 was well tolerated with a low rate of attributable adverse events, including thrombocytopenia. We find low radiation doses to kidney and bone marrow, which suggests feasibility of repeated cycles of ^{90}Y-FAPI-46. Although we observe first signs of clinical activity, larger trials are needed to determine efficacy and toxicity profile.

DISCLOSURE

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KEY POINTS

QUESTION: Is radionuclide therapy with ^{90}Y-FAPI-46 feasible for patients with advanced stage solid tumors and what are side-effects and absorbed doses?

PERTINENT FINDINGS: ^{90}Y-FAPI-46 leads to therapeutic irradiation of tumor lesions, and radiation exposure of critical organs is low. Further, we observe in a short follow-up a low rate of toxicities, including thrombocytopenia, attributed to ^{90}Y-FAPI-46 in patients with advanced and symptomatic disease.

IMPLICATIONS FOR PATIENT CARE: Radionuclide therapy with ^{90}Y-FAPI-46 seems to be well tolerated and repeated cycles are possible.

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Table 1: Patient characteristics

Pat No.	Age	Gender	Histology	Tumor sites (primary and metastatic)	ECOG	No of previous systemic therapies	Concomitant therapy	Subsequent therapy	^{68}Ga-FAPI-46 (SUVmax baseline)	Status	Follow-up (days)
1	22	male	Osteosarcoma	lung, heart, lymph nodes	2	7	-	-	12.1	Dead	24
2	66	male	Chordoma	bone, soft tissue, liver, lung, lymph nodes	3	2	-	Nivolumab	22.3	Dead	67
3	54	female	Fibrosarcoma	lung, lymph nodes, pancreas, bone	1	6	-	-	18.3	Follow-up	100
4	57	female	PDAC	liver, lung, lymph nodes, bone	3	2	-	Cisplatin	14.9	Dead	57
5	61	female	PDAC	pancreas, liver, lung, lymph nodes, bone	2	9	Trametinib	-	19.4	Dead	41
6	56	female	PDAC	pancreas, liver, lung, lymph nodes, kidney,	2	6		-	16.5	Dead	105
7	63	female	GNET	lung, liver, lymph nodes, bone, soft tissue	1	3	-	Nivolumab	16.1	Follow-up	44
8	61	male	Conventional chondrosarcoma	lung, lymph nodes, pancreas, bone	2	1	-	-	16.7	Follow-up	36
9	56	Male	Spindle cell sarcoma	Kidney, liver, lung pleura	1	6	-	-	28	Follow-up	36

Abbreviations: PDAC Pancreatic ductal adenocarcinoma, GNET Gastrointestinal neuroectodermal tumor, No Number

Table 2: ^{90}Y-FAPI-46 administered activity and absorbed doses per cycle

Pat No.	Cycle No.	Activity (GBq)	Radiation Dose (Gy/GBq)				
			Tumor lesion 1	Tumor lesion 2	Kidney	Liver and Lung[1)]	Bone marrow
1	1	7.1	0.74	0.63	-	-	-
2	1	7.0	-	-	-	-	-
3	1	3.5	1.23	1.23	0.75	< 0.18	0.06
3	2	7.3	1.28	0.95	0.41	< 0.19	0.04
3	3	7.5	1.47	1.35	0.61	< 0.15	0.04
4	1	3.8	-	-	-	-	-
5	1	3.8	-	-	-	< 0.16	0.06
6	1	3.0	1.37	-	-	-	-
7	1	3.5	0.91	0.84	0.52	< 0.16	0.03
8	1	3.8	0.49	-	0.11	< 0.26	0.08
8	2	7.4	-	-	-	-	0.08
9	1	2.6	2.28	-	0.65	< 0.21	0.04
9	2	7.4	1.79	-	0.45	< 0.25	0.02
Median			**1.28**	**0.95**	**0.52**	**< 0.19**	**0.04**
IQR			**0.83-1.71**	**0.74-1.32**	**0.41-0.65**	**< 0.16-0.24**	**0.04-0.07**

1) Estimation based on the maximum detectable activity concentration and blood tracer kinetic

Table 3: Adverse events after onset of treatment, related or unrelated.

Pat No.	General	laboratory-based adverse events																						
		Hematology								Kidney		Liver						Pancreatobiliary						new G3/G4 AE (laboratory)
		WBCs		ANC		Hb		Plts		sCR		T Bil		AST		ALT		GGT		ALP		Amylase		
		B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	B	**F**	
1	Acute respiratory distress tumor related (G5)	-	-	-	-	G3	G2	-	G3	-	-	-	-	-	-	-	-	G2	G1	G1	-	-	-	YES
2	Tumor pain (G2)	-	-	-	-	-	G1	-	G1	-	-	-	-	-	-	-	-	G1	G1	G1	G1	-	-	NO
3	none	-	-	-	-	-	-	-	G1	-	-	-	-	-	-	-	-	G1	G1	G1	G1	-	-	NO
4	Tumor prog, (G5)	G1	G2	-	G1	G3	G3	G1	G3	-	G2	-	G3	-	G1	-	-	G1	G3	G2	G2	-	-	YES
5	Tumor prog (G5)	-	-	-	-	G1	G2	G1	G3	-	G1	-	G2	G2	G4	G1	G4	G3	G4	G3	G3	-	-	YES
6	Pneumonia*, Tumor prog. (G5)	-	-	-	-	G1	G3	G1	G3	-	G2	-	G2	-	G2	-	-	G3	-	G1	G2	-	-	YES
7	Fever - urinary tract infection*	-	-	-	-	G1	G2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NO
8	none	-	-	-	-	G1	-	-	-	-	-	-	-	-	-	-	-	-	G1	G1	G1	-	-	NO
9	none	-	-	-	-	G1	G1	-	-	-	-	-	-	-	-	-	-	G3	G3	G2	G2	-	-	NO
	Any new AE (%)	**1 (11%)**		**1 (11%)**		**3 (33%)**		**6 (67%)**		**3 (33%)**		**3 (33%)**		**3 (33%)**		**1 (11%)**		**3 (33%)**		**1 (11%)**		-		
	Any new G3/G4 AE (%)	**-**		**-**		**1 (11%)**		**4 (44%)**		**-**		**1 (11%)**		**1 (11%)**		**1 (11%)**		**2 (22%)**		**-**		-		

*relation to ^{90}Y-FAPI-46 was ruled out
Abbreviations:
B baseline, F follow up, WBCs white blood cells, ANC Absolute neutrophil count, Hb Hemoglobin, PLTs Platelets (thrombocytes), AST Aspartate transaminase, ALT Alanine transaminase, GGT Gamma-glutamyltransferase, ALP Alkaline phosphatase, sCr serum creatinine, T Bil total Bilirubin, G grade as per CTCAE v5.0

Table 4: Radiologic and metabolic best overall response

Patient	CT target response	CT non target response	RECIST response	PET target response	PET non target response	PERCIST Response	SUVmax FDG baseline	SUVmax FDG Follow up
1	SD	SD	**SD**	PMR	SMD	**PMD**	14.8	21.8 (+47%)
2	PD	SD	**PD**	PMD	PMD	**PMD**	28.6	22.3 (-22%)
3	SD	SD	**SD**	SMD	SMD	**SMD**	6.5	4.9 (-25%)
4	PD	PD	**PD**	SMD	PMD	**PMD**	5.1	3.8 (-26%)
5	PD	PD	**PD**	SMD	PMD	**PMD**	18.9	17.2 (-9%)
6	SD	SD	**SD**	-	-	**-**	6.1	-
7	-	-	-	-	-	**-**	14.3	-
8	SD	PD	**PD**	PMD	SMD	**PMD**	12.5	13.3 (+6,4%)
9	SD	SD	**SD**	PMR	SMD	**PMR**	18	10.1 (-44%)
DCR (%)			**4/8 (50%)**			**2/7 (29%)**		
ORR (%)			**0/8 (0%)**			**1/7 (14%)**		

Abbreviations:
PD progressive disease, SD stable disease, PR partial response, PMR partial metabolic response, PMD progressive metabolic disease, SMD stable metabolic disease, DCR Disease Control Rate, ORR Overall Response Rate

Figure 1: Pre-therapeutic ^{68}Ga-FAPI-46 PET images and post-treatment ^{90}Y-FAPI-46 bremsstrahlung scintigraphies after first cycle of ^{90}Y-FAPI-46 radioligand therapy

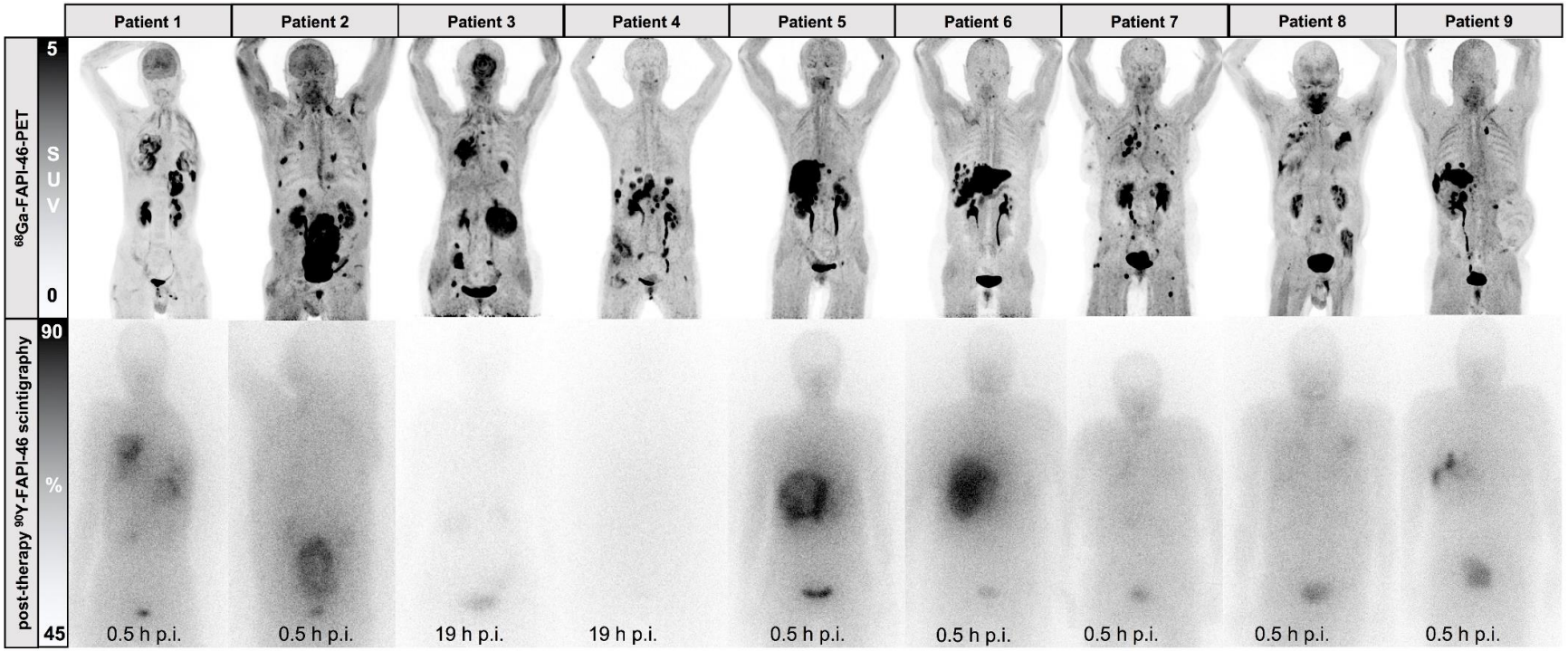


Figure 2: Post-therapy ^{90}Y-FAPI-46 PET images 4h p.i. with corresponding absorbed dose estimates for 4 lesions in patient #2

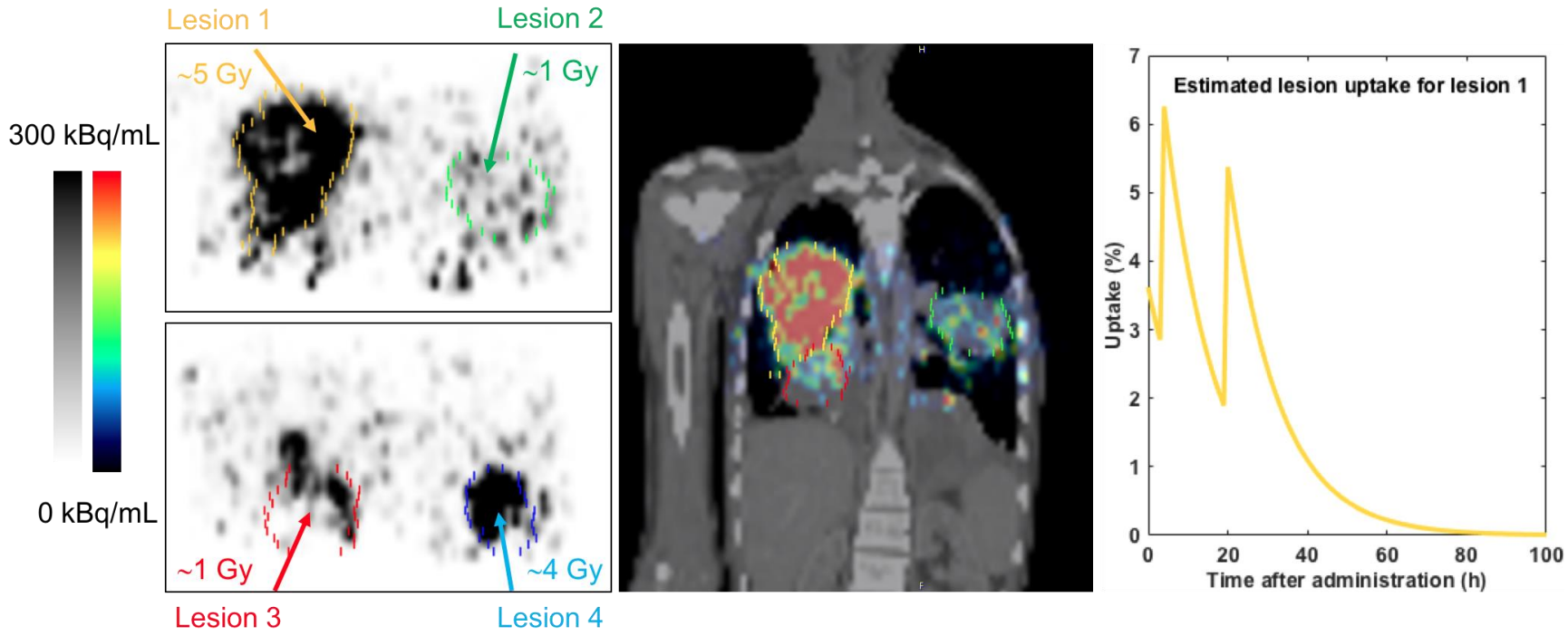
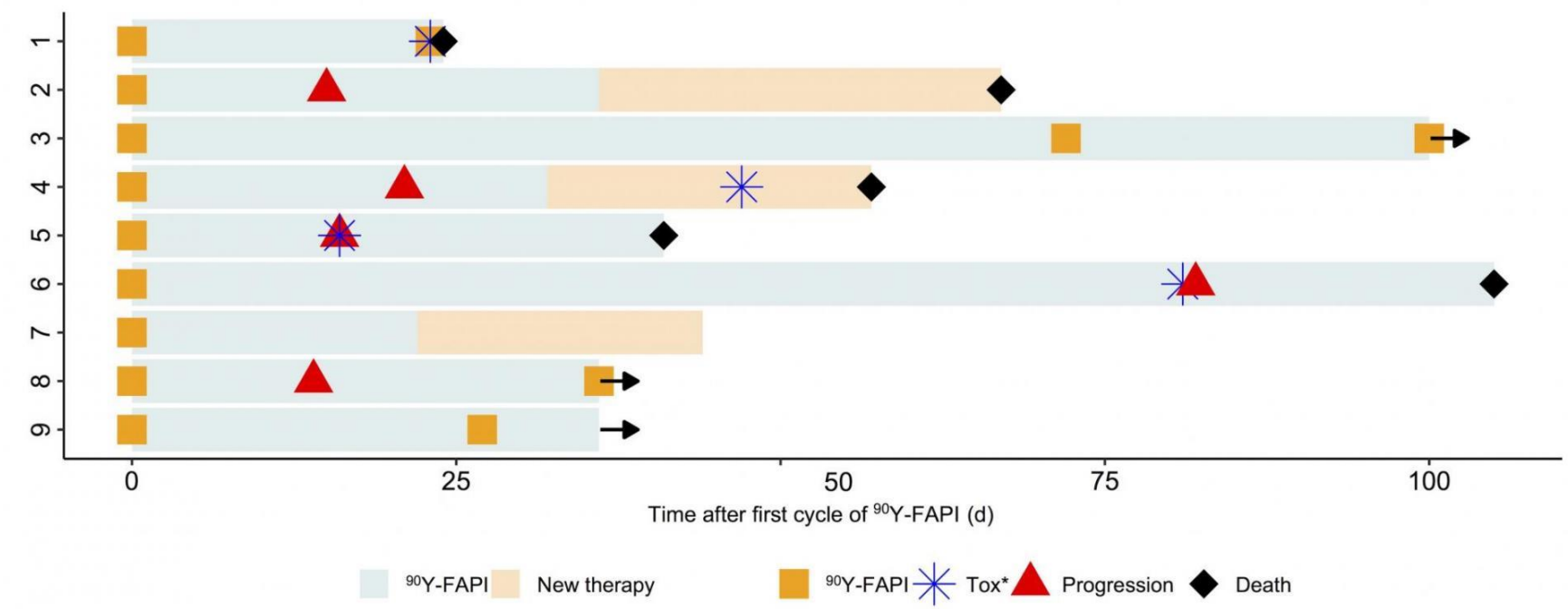
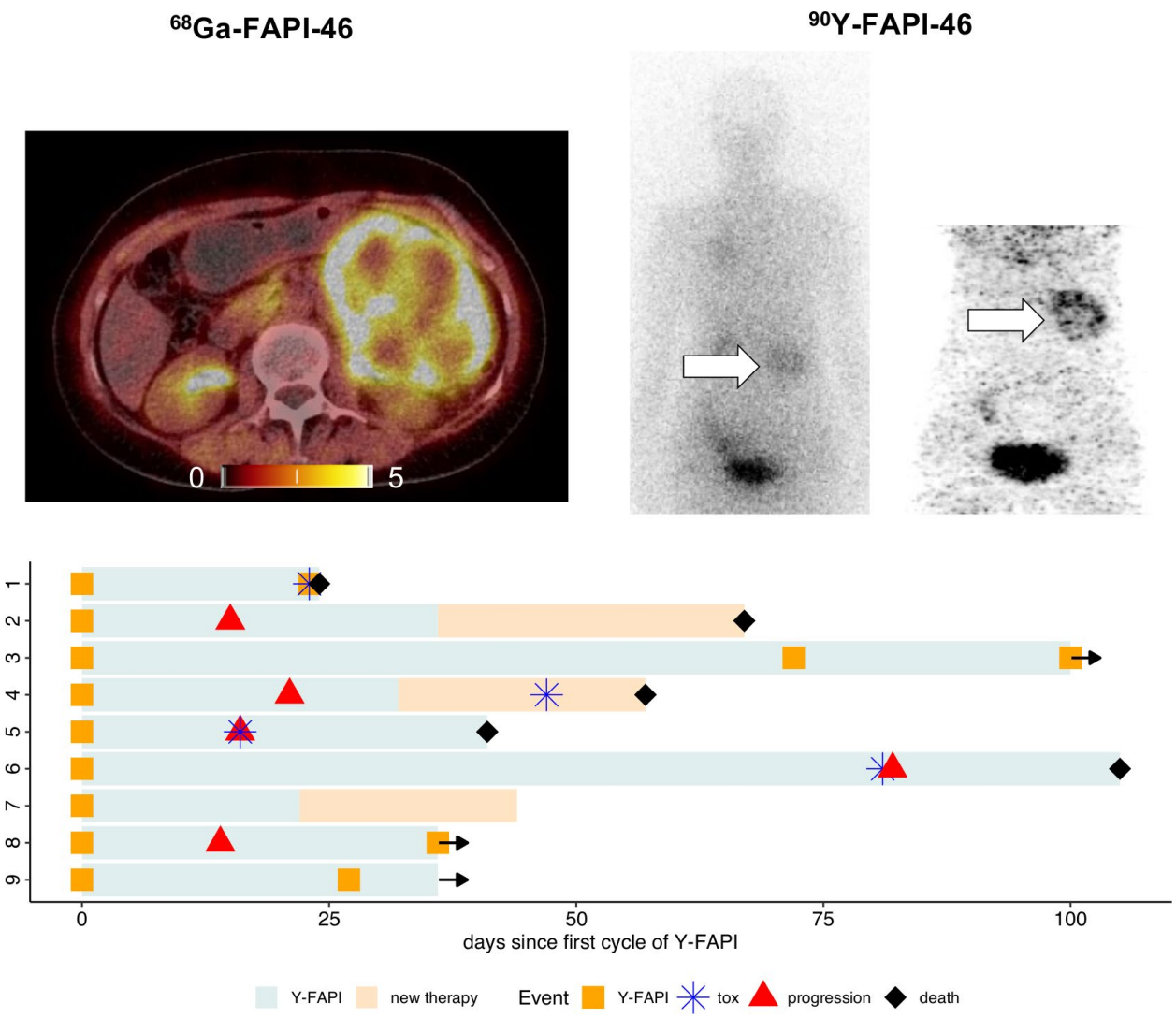


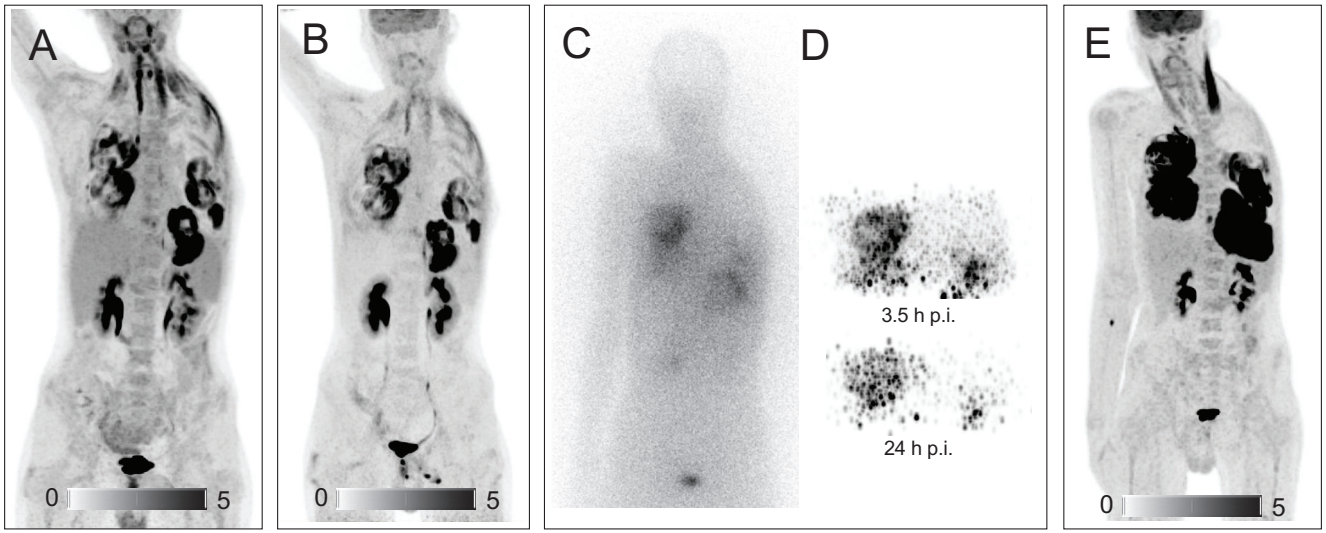
Figure 3: Swimmer plot of patients who received ^{90}Y-FAPI-46



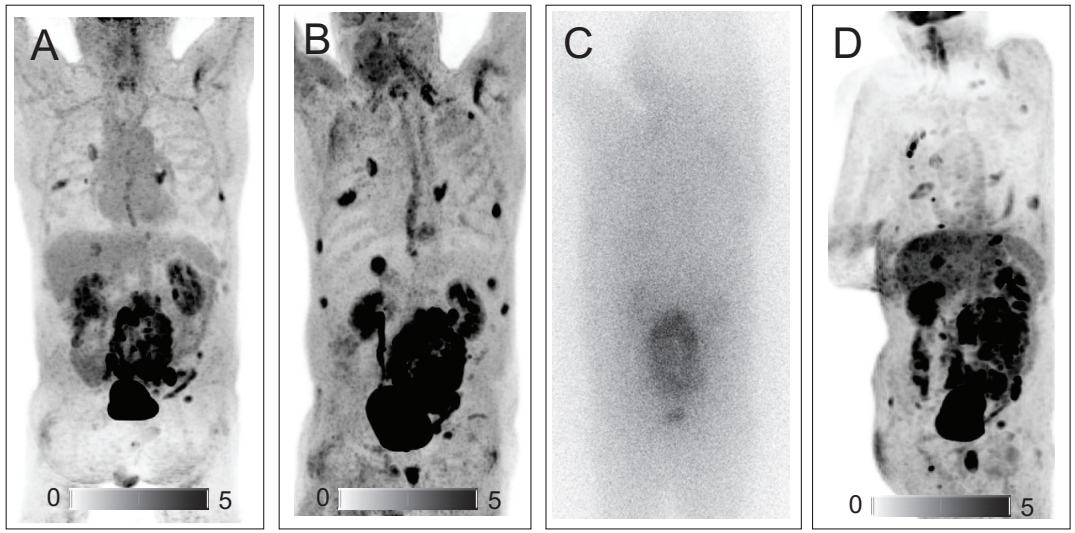
* Tox: Any new onset of toxicity greater or equal Grade 3 according to CTCAE. Arrows indicate patients who are continuing ^{90}Y-FAPI-46 radioligand therapy at time of analysis.

Graphical Abstract

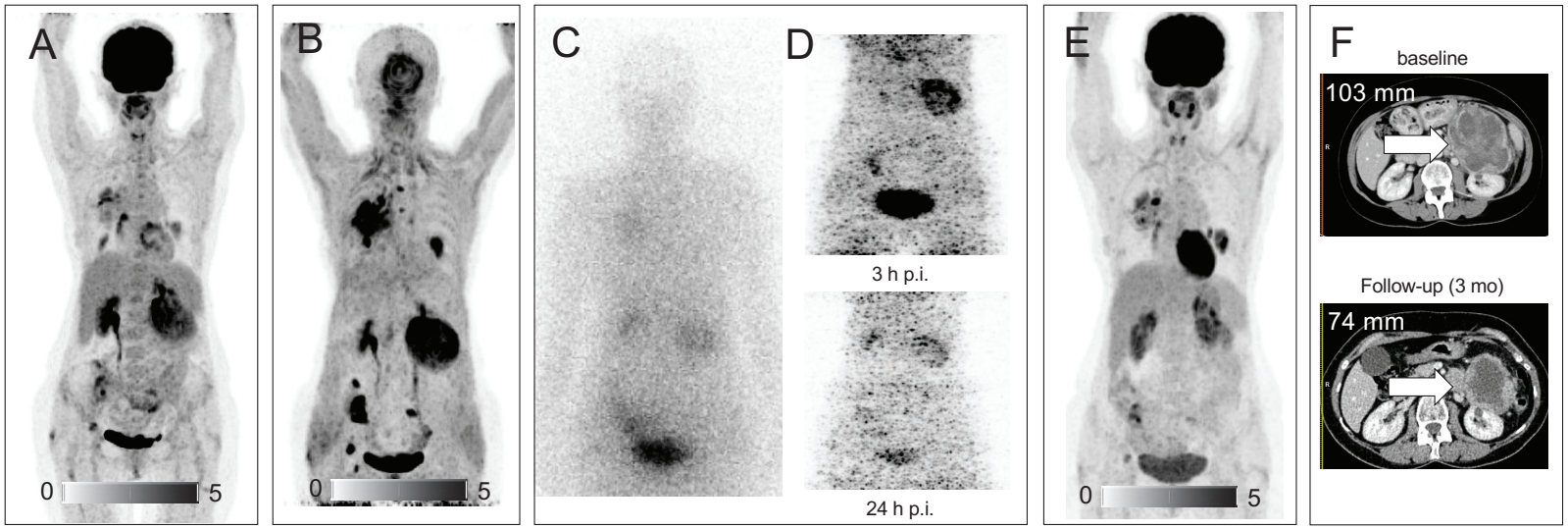




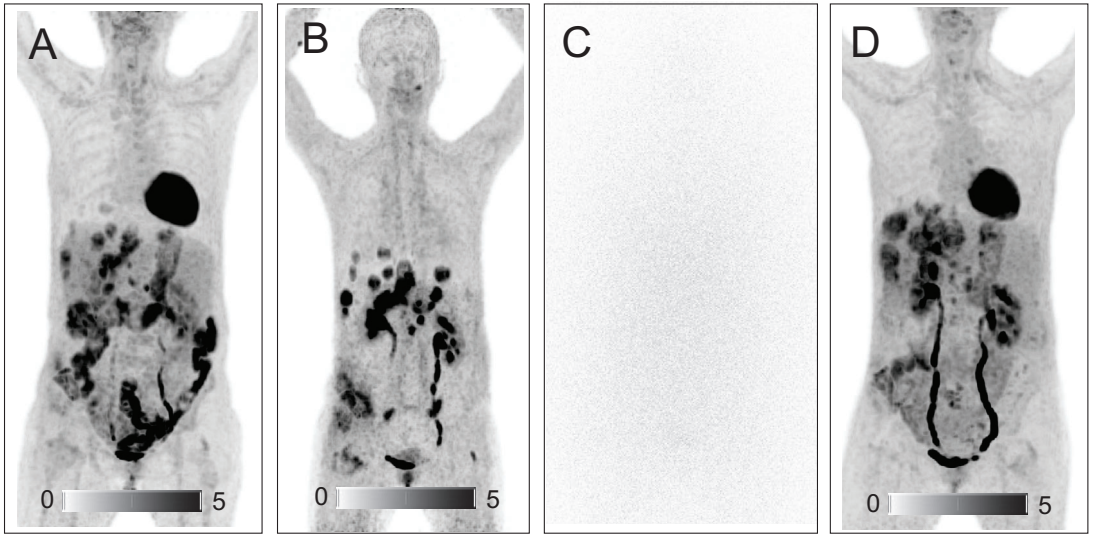
Supplement Figure 1 – Patient No 1: 22 year old male patient with metastasized osteosarcoma who has progressed in seven lines of chemotherapy. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, Bremstrahlungsscintigraphy 0.5 h p.i. (**C**) and post-treatment ^{90}Y-FAPI-46 PET 3.5 + 24 h p.i. (**D**) are displayed. **E** shows ^{18}FDG PET 14 days after RLT. Although, a progressive metabolic disease was observed, a second cycle was applied since RECIST showed stable disease and lack of other treatment options. The patient, with very advanced tumor disease, died shortly after second cycle due to tumor-related acute respiratory distress tumor, which was 24 days after the first cycle. A new thrombocytopenia grade 3 was observed.



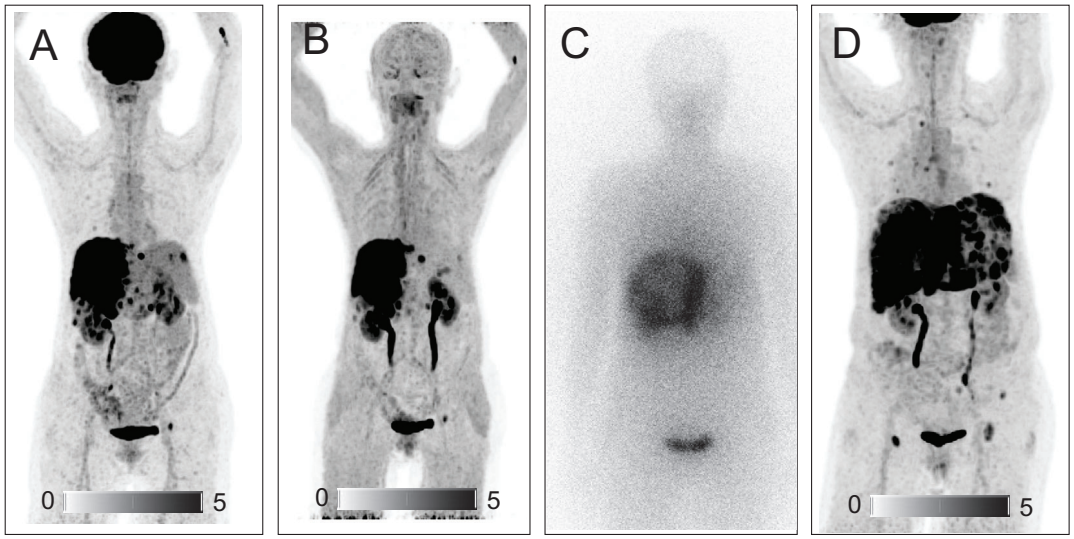
Supplement Figure 2 – Patient No 2: 66 year old male patient with locally relapsed and metastasized chordoma, suffering reduced performance status (ECOG 3) and severe tumor pain. He has progressed in two lines of therapy, without further evidence based therapy options. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 0.5 h p.i. (**C**). Post-treatment ^{90}Y-FAPI-46 PET could not be performed because of tumor pain. **E** shows ^{18}FDG PET 2 weeks after first cycle RLT with tumor progression. Therefore, a second cycle was not applied and a subsequent therapy with immune checkpoint inhibitor nivolumab as compassionate use was started. He did not show any G3/4 adverse events and died 67 days after first cycle RLT.



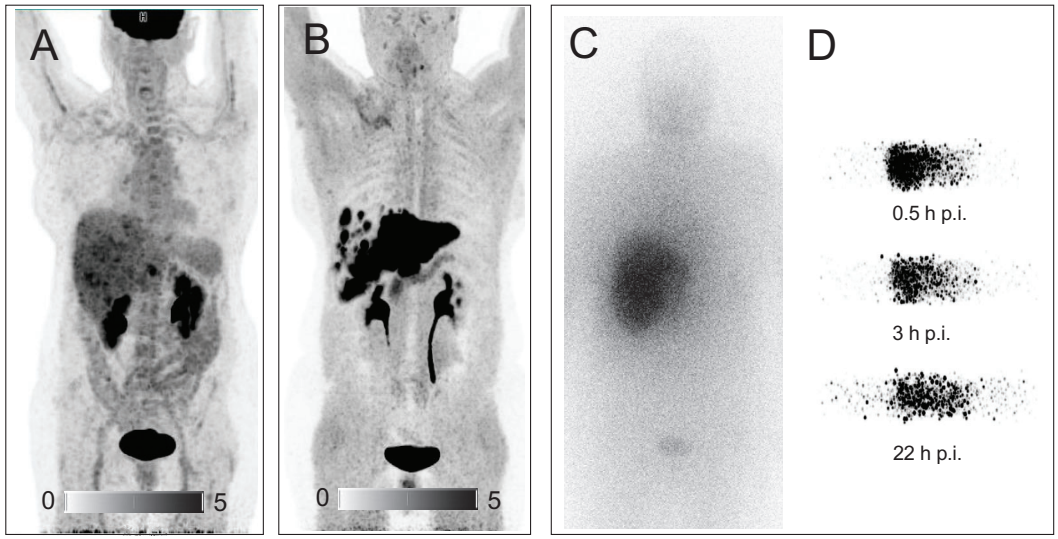
Supplement Figure 3 – Patient No 3: 54 year old female patient with metastasized fibrosarcoma who has progressed in six lines of chemotherapy. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 0.5 h p.i. (**C**) and post-treatment ^{90}Y-FAPI-46 PET 3 + 18 h p.i. (**D**) are displayed. **E** shows ^{18}FDG-PET 3 months after first cycle RLT. Showing stable disease, the patient received so far 3 cycles RLT. She did not show any G3/4 adverse events during follow-up time of 100 days. **F** Shows regression of a target lesion -28% following first cycle of ^{90}Y-FAPI-46



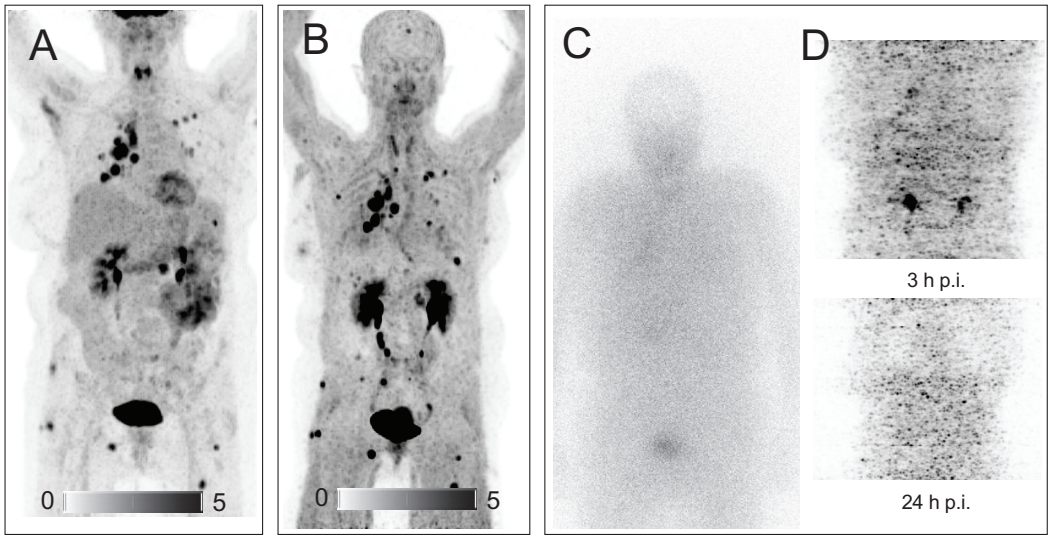
Supplement Figure 4 – Patient No 4: 57 year old female patient with metastasized pancreatic ductal adenocarcinoma, who had progressed in two lines of chemotherapy. She was not eligible for further chemotherapy, due to reduced performance status (ECOG 3), at time point of evaluation for RLT. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 19 h p.i. did not show focal uptake. (**C**). Post-treatment ^{90}Y-FAPI-46 PET could not be performed because of reduced performance status. **D** shows ^{18}FDG PET 2 weeks after first cycle RLT with tumor progression. Given missing uptake in post-treatment scan and rapid progression, a second cycle was not applied. Due to highly symptomatic tumor progression one cycle chemotherapy with cisplatin was applied as subsequent treatment. G3/4 adverse events occurred due to tumor progression and subsequent therapy. The patient died 57 days after first cycle of RLT.



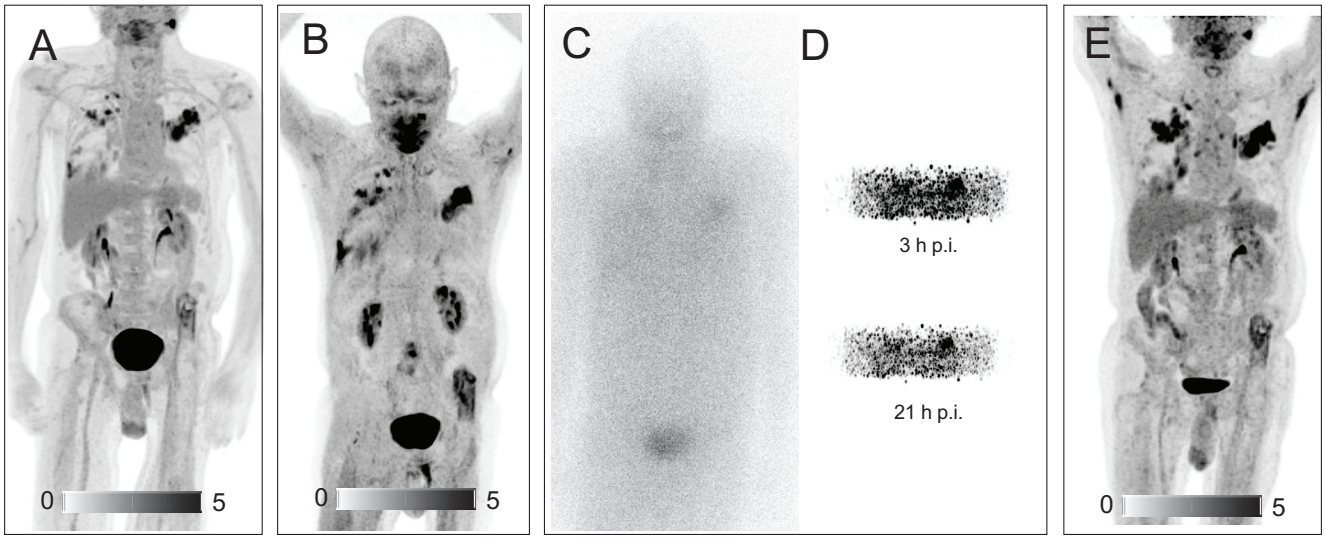
Supplement Figure 5 – Patient No 5: 54 year old female patient with metastasized pancreatic ductal adenocarcinoma who has progressed in nine lines of chemotherapy. Pretherapeutic MIP of FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 0.5 h p.i. (**C**) are displayed. Post-treatment ^{90}Y-FAPI-46 PET could not be performed because of reduced performance status. **(D)** shows ^{18}FDG-PET 2 weeks after first cycle RLT and concomitant treatment with the MEK inhibitor trametinib as compassionate use. Due to tumor progression, a second cycle was not applied. Trametinib was continued. G3/4 adverse events occurred later due to tumor progression. She died 41 days after first cycle RLT.



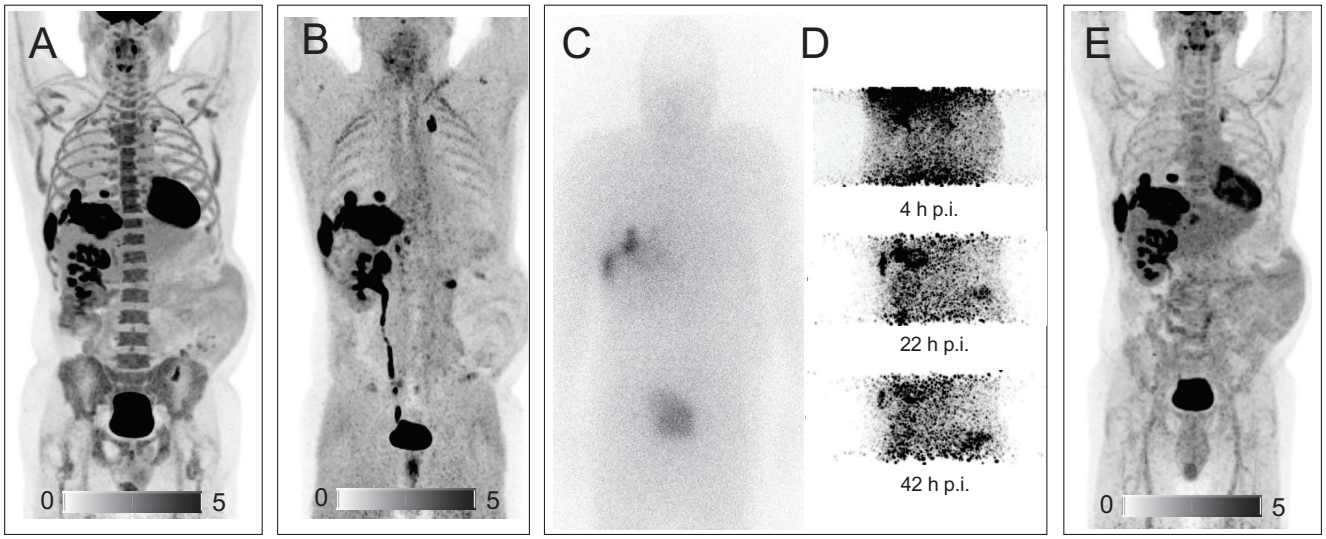
Supplement Figure 6 – Patient No 6: 56 year old female patient with metastasized pancreatic ductal adenocarcinoma, who has progressed in six lines of chemotherapy. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 0.5 h p.i. (**C**) and post-treatment ^{90}Y-FAPI-46 PET 0.5 + 3 + 22 h p.i. (**D**) are displayed. A FDG PET was not performed after RLT for this patient given low uptake in baseline scan. Concomitant treatment with the tyrosine kinase inhibitor afatinib was continued. CT scans displayed stable disease. G3/4 adverse event occurred later due to tumor progression. The patient died 105 days after first cycle of RLT.



Supplement Figure 7 – Patient No 7: 63 year old female patient with metastasized gastrointestinal neuroectodermal tumor (GNET) who has progressed in 3 lines of chemotherapy. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. The patient had insufficient retention of the radioligand as determined by bremstrahlungsscintigraphy 0.5 h p.i. (**C**) and post-treatment ^{90}Y-FAPI-46 PET 3 + 24 h p.i. (**D**). Therefore, no second cycle RLT was applied and no ^{18}FDG-PET was performed. A subsequent therapy with immune checkpoint inhibitor nivolumab as compassionate use was started. She did not show any G3/4 adverse events during follow-up time of 44 days after first cycle RLT.

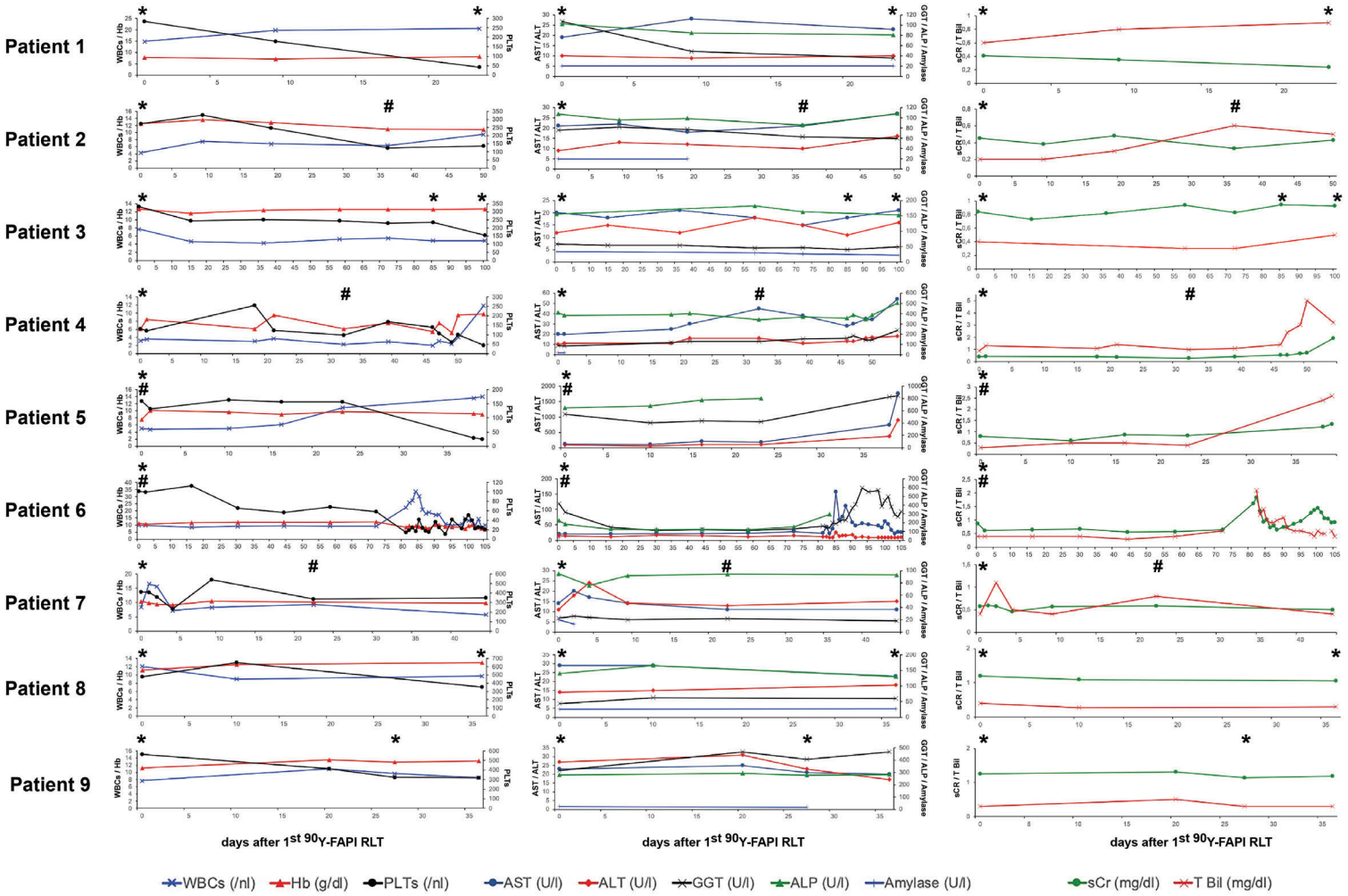


Supplement Figure 8 – Patient No 8: 61 year old male patient with metastasized conventional chondrosarcoma who has progressed in two lines of chemotherapy. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 0.5 h p.i. (**C**) and post-treatment ^{90}Y-FAPI-46 PET (**D**) are displayed. **E** shows ^{18}FDG-PET 2 weeks after first cycle RLT with tumor progression. Due to lack of further evidence base therapies and clinical benefit, a second cycle was applied and follow-up is pending. No G3/4 adverse events occurred during follow up of 36 days at time of submission.



Supplement Figure 9 – Patient No 9: 56 year old male patient with metastasized spindle cell sarcoma who has progressed in six lines of chemotherapy. Pretherapeutic MIP of ^{18}FDG-PET (**A**) and ^{68}Ga-FAPI-46 PET (**B**) scans are shown. Moreover, bremstrahlungsscintigraphy 0.5 h p.i. (**C**) and post-treatment ^{90}Y-FAPI-46 PET 4 + 22 + 42h p.i. (**D**) are displayed. **E** shows ^{18}FDG-PET 2 weeks after RLT with partial metabolic response. Therefore, a second cycle was applied. No G3/4 adverse events occurred during follow up of 36 days at time of submission.

Supplement Figure 10: Overview laboratory parameters with individual time scale for each patient



*** ^{90}Y-FAPI-46 RLT (Radioligandtherapy); # Concomitant / Subsequent therapy; WBCs white blood cells, Hb Hemoglobin, PLTs Platelets (thrombocytes), AST Aspartate transaminase, ALT Alanine transaminase, GGT Gamma-glutamyltransferase, ALP Alkaline phosphatase, sCr serum creatinine, T Bil total Bilirubin**