

# [<sup>68</sup>Ga]Ga-FAPI-46 PET accuracy for cancer imaging with histopathology validation: a single-centre, single-arm, interventional, phase 2 trial



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## Summary

**Background** The fibroblast activation protein  $\alpha$  (FAP)-directed radiotracer [<sup>68</sup>Ga]Ga-FAPI-46 for PET–CT has shown promising diagnostic accuracy in cancer staging in retrospective studies. We aim to investigate the positive predictive value (PPV) of [<sup>68</sup>Ga]Ga-FAPI-46 PET for detecting FAP-expressing tumours and the potential association between PET radiotracer uptake intensity and immunohistochemical FAP expression.

**Methods** This single-centre, single-arm, interventional, phase 2 trial was conducted at the University Hospital Essen, Essen, Germany. Adults aged 18 years or older undergoing initial staging or restaging were eligible if they had at least one measurable tumour lesion (>1 cm) and a confirmed or suspected diagnosis of breast cancer, colorectal cancer, endometrial cancer, oesophageal cancer, head and neck cancer, ovarian cancer, pancreatic ductal adenocarcinoma (PDAC), prostate cancer, thyroid cancer, glioma, hepatocellular carcinoma, lymphoma, multiple myeloma, non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), sarcoma, seminoma, cancer of unknown primary origin, or other tumour types; had a planned or recent surgery or biopsy within 8 weeks before or after enrolment; and an ECOG performance status of 2 or less. Key exclusion criteria were previous external beam radiotherapy to the target lesion and receiving systemic cancer therapy within 1 month before enrolment. PET–CT images were acquired at a median of 11 min (IQR 10–14) after an intravenous injection of a median of 145 Megabecquerel (MBq; 124–154) of [<sup>68</sup>Ga]Ga-FAPI-46 and analysed by three independent, masked readers. The study concluded on day 30 of follow-up if histopathological confirmation and archived tumour tissue were already available, or on the day of biopsy or surgery within 8 weeks of receiving [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT. Immunohistochemical FAP expression (score 0–3) was evaluated by an independent masked pathologist. The primary endpoint was the PPV of [<sup>68</sup>Ga]Ga-FAPI-46 PET for detecting immunohistochemical FAP-positive tumours (histopathologically confirmed) on a per-patient and per-region basis, with a predefined threshold of PPV of at least 75%, analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, NCT05160051, and is complete.

**Findings** Between Dec 1, 2021, and Feb 6, 2024, 158 eligible participants were enrolled and three were excluded. 98 (63%) of 155 participants who received [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT were male and 57 (37%) were female. One (1%) participant was African, two (1%) were Asian, and 152 (98%) were White. The median age of participants was 62 years (IQR 55–70). The median follow-up was 29 days (29–30). The patient-based PPV of [<sup>68</sup>Ga]Ga-FAPI-46 PET for detecting FAP-positive tumours based on immunohistochemical FAP staining was 90% (95% CI 84–95) and region-based PPV was 92% (85–96) in 127 (88%) of 144 participants with histopathological validation. Five (6%) of 90 adverse events were classified as possibly related to [<sup>68</sup>Ga]Ga-FAPI-46. Seven (8%) adverse events were serious, none related to [<sup>68</sup>Ga]Ga-FAPI-46. One participant died due to disease progression.

**Interpretation** These results confirm the safety and potential of [<sup>68</sup>Ga]Ga-FAPI-46 PET as an imaging biomarker for the detection of FAP-expressing tumours. Further studies are warranted to refine the specificity and define the role of [<sup>68</sup>Ga]Ga-FAPI-46 PET in clinical practice.

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## Introduction

Fibroblast activation protein  $\alpha$  (FAP) is expressed by sarcomas and cancer-associated fibroblasts in the

stroma of more than 90% of epithelial tumours.<sup>1</sup> In tumours with a desmoplastic reaction (such as breast, colon, or pancreatic cancers), the stroma can comprise

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## Research in context

### Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed studies published in English since the first publications on FAP-directed PET-CT from April 6, 2018, to Jan 10, 2025 (the final analysis), using the terms “FAP”, “PET/CT”, “immunohistochemistry”, and “biomarker”. We found one interim analysis of a prospective translational exploratory study evaluating the correlation of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET uptake intensity with immunohistochemical FAP expression in 15 patients with solid tumours, which support further exploration of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET as a pan-cancer imaging biomarker. Further retrospective studies, mainly with inhomogeneous and small cohorts, show promising accuracy for [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET.

### Added value of this study

To our knowledge, the FAPI PET trial is the first prospective phase 2 clinical trial to assess the positive predictive value (PPV) of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET for the detection of

immunohistochemical FAP-positive tumours and its role as an imaging biomarker. We validated a high PPV and a low positive association between [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET uptake intensity and immunohistochemical FAP expression. Furthermore, we observed a diagnostic accuracy similar to that of [ $^{18}\text{F}$ ]FDG PET, with indications of higher inter-reader reproducibility and a favourable safety profile.

### Implications of all the available evidence

Our findings confirm [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET as an imaging biomarker for FAP-expressing tumours, showing high PPV and detection rates. The use of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET-CT demonstrates no relevant risks while providing consistent and standardisable results, supporting its suitability for broader clinical use and research. Further studies are needed to evaluate the specificity. Building on these results, the Department of Nuclear Medicine at University Hospital Essen will investigate a gastrointestinal cancer-specific cohort of patients with more restricted inclusion criteria (EUCT 2023-506030-70-00).

more than 90% of the tumour mass. Notably, aside from tumours, FAP expression in adult tissues is largely restricted to fibrotic processes and wound healing.<sup>2</sup>

Since its emergence in 2018, FAP-directed PET-CT has become increasingly important in oncological imaging, offering a novel pathway for targeting the tumour microenvironment. However, the full scope of clinical application of this imaging modality is still being investigated.<sup>3,4</sup> Among the available radiotracers, the quinoline-based agent [ $^{68}\text{Ga}$ ]Ga-FAPI-46 has shown promising accuracy (80–100%) for tumour detection and staging in several retrospective studies.<sup>5–7</sup>

In a preliminary analysis within a prospective exploratory imaging trial, Mona and colleagues reported an association between [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET uptake intensity and immunohistochemical FAP expression in a small cohort of 15 patients.<sup>8</sup> Although these findings provide initial biological validation, prospective phase 2 studies with larger cohorts and systematic histopathological validation have not yet been published.<sup>3</sup> This absence of robust, prospective evidence represents a crucial gap in knowledge, particularly regarding the validation of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET as an imaging biomarker capable of reliably reflecting tissue-level FAP expression, which is a prerequisite for use in tumour staging, patient selection, and therapy monitoring in the context of FAP-targeted treatments.<sup>3</sup>

In this trial, we aimed to investigate the positive predictive value (PPV) of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET for detecting FAP-expressing tumours and examine the potential association between PET radiotracer uptake intensity and immunohistochemical FAP expression. Furthermore, we compare detection rates and inter-reader reproducibility with [ $^{18}\text{F}$ ]FDG PET.

## Methods

### Study design and participants

This single-centre, single-arm, interventional, phase 2 trial was conducted at the University Hospital Essen, Essen, Germany. Adults aged 18 years or older undergoing initial staging or restaging were eligible if they had at least one measurable tumour lesion (>1 cm) and a confirmed or suspected diagnosis of breast cancer, colorectal cancer, endometrial cancer, oesophageal cancer, head and neck cancer, ovarian cancer, pancreatic ductal adenocarcinoma (PDAC), prostate cancer, thyroid cancer, glioma, hepatocellular carcinoma, lymphoma, multiple myeloma, non-small-cell lung cancer (NSCLC), renal cell carcinoma (RCC), sarcoma, seminoma, cancer of unknown primary origin, or other tumour types; had a planned or recent surgery or biopsy within 8 weeks before or after enrolment; and an ECOG performance status of 2 or less. Key exclusion criteria were previous external beam radiotherapy to the target lesion, systemic cancer therapy (chemotherapy, immunotherapy, biologics, or targeted agents) within 1 month before enrolment, pregnancy or breastfeeding, prolonged QTcF interval (>470 ms in females or >450 ms in males) on a screening electrocardiogram (ECG), congenital long QT syndrome, or any condition that (as judged by the investigators) compromises study participation. Information on age, sex, and race was self-reported by participants.

Written informed consent was obtained from all participants. The study was approved by the local institutional ethics committee at the University Hospital Essen (21–9909-AF). This study is registered with ClinicalTrials.gov, NCT05160051 (completed).

### Randomisation and masking

[<sup>68</sup>Ga]Ga-FAPI-46 and clinical [<sup>18</sup>F]FDG PET scans were each analysed by three independent, experienced nuclear medicine physicians and radiologists, affiliated with the Department of Radiology (n=1; LK) or Nuclear Medicine (n=5; MMW, CL, ATK, KMP, and PS) at the University Hospital Essen. Department of Nuclear Medicine readers varied in experience (1–7 years) and location at the time of reading scans (Essen n=3, Duisburg n=1, and Bonn n=1).

Imaging data were anonymised before interpretation. Readers were provided with attenuation-corrected PET images and corresponding anatomical cross-sectional datasets. Apart from basic clinical information (patient age, uptake time, and tumour disease), readers were masked to the study details. Immunohistochemical FAP expression (score 0–3) was evaluated by an independent pathologist (ME) at the University Hospital Erlangen, Erlangen, Germany, who was masked to all study data except for tumour diagnosis and the biopsied or resected region.

### Procedures

A delegated member of the research team supervised [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT and the follow-up procedures. Study data on eligibility criteria, patient demographics, tumour diagnosis, concomitant medication, medical history, study procedures, protocol-mandated laboratory tests, adverse events, imaging readouts, preimaging and post-imaging physician surveys, surgical or biopsy findings, and lesion validation were collected and managed using a central REDCap database (version 15.5.3).

[<sup>68</sup>Ga]Ga-FAPI-46 PET–CT was performed on day 0 within 1 h after completion of the screening procedures, which included measurement of heart rate, blood pressure, ECG, and physical examination.

[<sup>68</sup>Ga]Ga-FAPI-46 was synthesised at the local radiopharmacy using FAPI-46 precursor obtained from SOFIE (Dulles, VA, USA), as reported previously.<sup>9</sup> 155 participants received a median activity of 145 Megabecquerel (MBq; IQR 124–154 MBq) [<sup>68</sup>Ga]Ga-FAPI-46 intravenously, in line with the study protocol (150 plus or minus 50 MBq; protocol-defined range) and current guidelines.<sup>3</sup> PET–CT images were acquired at a median of 11 min (10–14) post-injection, within the predefined 15 min (plus or minus 5 min) window. Whole-body PET scans (base of skull to the proximal thigh) were weight-adjusted (2 min per bed position for those weighing <80 kg, 3 min per bed position for those weighing 80–90 kg, and 4 min per bed position for those weighing >90 kg) and combined with low-dose CT for attenuation correction. Additional scans of the extremities were acquired when clinically indicated, such as for participants with a confirmed diagnosis of sarcoma of the lower limb. Imaging was performed on PET–CT systems (Biograph mCT or Biograph Vision, Siemens Healthineers,

Erlangen, Germany), with analysis focused on the PET component.

[<sup>68</sup>Ga]Ga-FAPI-46 PET–CT scans were analysed by three independent, masked readers. All readers completed training sets and guidelines, including recognition of common pitfalls. Lesions were classified as FAP-positive if showing focal uptake higher than the surrounding background. Four regions were analysed separately (primary tumour, lymph nodes, visceral organs, and bones). A region was classified as positive if at least one lesion in this region was visually positive. To evaluate the region-based uptake of suspicious lesions, standardised uptake value (SUV)<sub>peak</sub> was assessed for the lesion with highest uptake in the respective region. Discrepancies among readers were resolved by a majority vote (at least two of three readers).

For safety analysis of [<sup>68</sup>Ga]Ga-FAPI-46 administration, participants were monitored for adverse events during and within 2 h after injection. To assess delayed adverse events, an additional on-site visit at 7 days plus or minus 1 day and a telephone follow-up at 30 days plus or minus 3 days after [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT were conducted. Heart rate, blood pressure, ECG, and physical examination were assessed during the on-site visit.

The study concluded on day 30 of follow-up if histopathological confirmation and archived tumour tissue were already available, or on the day of biopsy or surgery within 8 weeks of receiving [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT. Participants could be withdrawn at any time based on patient request (eg, participant decision or inability to comply with study procedures) or investigator discretion (eg, if the participant did not meet the inclusion criteria). Any participant receiving [<sup>68</sup>Ga]Ga-FAPI-46 who was subsequently withdrawn remained under medical supervision until discharge was deemed appropriate.

To assess the impact on treatment management (not reported here), treating physicians completed pre-imaging and post-imaging questionnaires. Participants could additionally consent to be included in a different prospective observational study (NCT04571086) for confirmation of management changes and outcome analysis, including overall survival.

FAP immunohistochemistry was performed on formalin-fixed paraffin-embedded human tissue samples obtained from clinical biopsies or surgeries, following standard laboratory procedures (appendix pp 1–3).<sup>10</sup>

An additional, clinical [<sup>18</sup>F]FDG PET–CT scan was performed as previous standard imaging (imaging protocols are provided in the appendix p 1). [<sup>18</sup>F]FDG PET–CT images were also analysed by three masked readers with the same criteria as [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT imaging.

A region-based lesion validation of positive findings on [<sup>68</sup>Ga]Ga-FAPI-46 or [<sup>18</sup>F]FDG PET was based on histopathology (biopsy or surgery) performed within 8 weeks before or after [<sup>68</sup>Ga]Ga-FAPI-46 PET–CT.

For the REDCap database see <https://project-redcap.org/>

See Online for appendix

Validation was performed by unmasked local investigators after reviewing images and reports (appendix p 4).

### Outcomes

The primary endpoint was the PPV of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET for detecting immunohistochemical FAP-positive tumours (histopathologically confirmed) on a per-patient and per-region basis, with a predefined threshold of PPV of at least 75%. Secondary endpoints included the association between [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET uptake intensity and immunohistochemical FAP expression, sensitivity and specificity for detecting immunohistochemical FAP-positive tumours on a per-patient and per-region basis (confirmed by histopathology); detection rates compared with previous standard imaging ([ $^{18}\text{F}$ ]FDG PET; confirmed by histopathology); inter-reader reproducibility; and safety. Specificity was a prespecified secondary outcome but could not be reliably assessed due to the low number of false positives and true negatives.<sup>11</sup> Further secondary endpoints, including detection rate compared with previous standard imaging on a per-patient and per-region basis (confirmed by combined histopathology, biopsy, follow-up imaging, or clinical follow-up) and impact on clinical management and staging or prognostic group assignment will be reported separately in a registry study (NCT04571086) to allow for a longer follow-up period.

### Statistical analysis

For the primary endpoint the null hypothesis assumed that [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET has a PPV of no more than 50% for detecting immunohistochemical FAP-positive tumour lesions. The alternative hypothesis stated a PPV of more than 50%, with an expected value of at least 75%. Sample size was calculated based on the superiority margin by Chow and colleagues using a power of 90% ( $1-\beta=0.9$ ),  $\alpha$  of 0.01, and a superiority margin of 25%.<sup>12</sup> To meet this threshold, at least 52 evaluable regions with histopathological confirmed FAP-positive tumours were required. Assuming PET sensitivity and specificity of 70%, and a per-region tumour prevalence of 30%, at least 124 participants with immunohistochemical staining were required. Accounting for a 20% dropout rate, the final sample size was set at 155 participants.

Primary and secondary endpoints were analysed in the intention-to-treat population (defined as all randomly assigned participants who received [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET-CT). For the primary endpoint analysis, availability of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET-CT, histopathological sampling (biopsy or surgery), and FAP immunohistochemistry was required. All participants who received [ $^{68}\text{Ga}$ ]Ga-FAPI-46 were included in the safety population.

Patient-based and region-based PPV (primary endpoint) and sensitivity (secondary endpoint) for detecting immunohistochemical FAP-positive tumours were calculated as preplanned in tabular form, indicating

95% CI, using the Wilson score method.<sup>13</sup> As one lesion per participant was assessed by immunohistochemistry, patient-based and region-based analyses were equivalent. A post-hoc expanded analysis classified participants as positive if at least one lesion showed increased [ $^{68}\text{Ga}$ ]Ga-FAPI-46 uptake, irrespective of whether this lesion corresponded to the immunohistochemically confirmed FAP-positive region.

The association between [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET uptake intensity and immunohistochemical FAP expression on a per-region basis (secondary endpoint) was assessed using Spearman correlation. Additionally, a post-hoc analysis was performed per-lesion.

Patient-based and region-based PPV and sensitivity of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET and [ $^{18}\text{F}$ ]FDG PET (as standard imaging), which was confirmed by histopathology and independent of immunohistochemical analyses, was calculated in tabular form, indicating the 95% CI (using the Wilson score method).<sup>13</sup> Validation mechanisms chosen for this endpoint are detailed in the appendix (p 4). Inter-reader agreement is reported at per-patient and per-region using Fleiss'  $\kappa$ , interpreted by Landis and Koch criteria.<sup>14</sup> Descriptive data on adverse events are shown.

A post-hoc analysis compared the highest patient-based, histopathologically validated  $\text{SUV}_{\text{peak}}$  values between [ $^{68}\text{Ga}$ ]Ga-FAPI-46 and [ $^{18}\text{F}$ ]FDG PET for all participants and the seven most common tumour types, using the Wilcoxon test. False-negative regions were assigned an  $\text{SUV}_{\text{peak}}$  of 0. Further analyses, including histopathologically validated and non-validated regions, were performed.

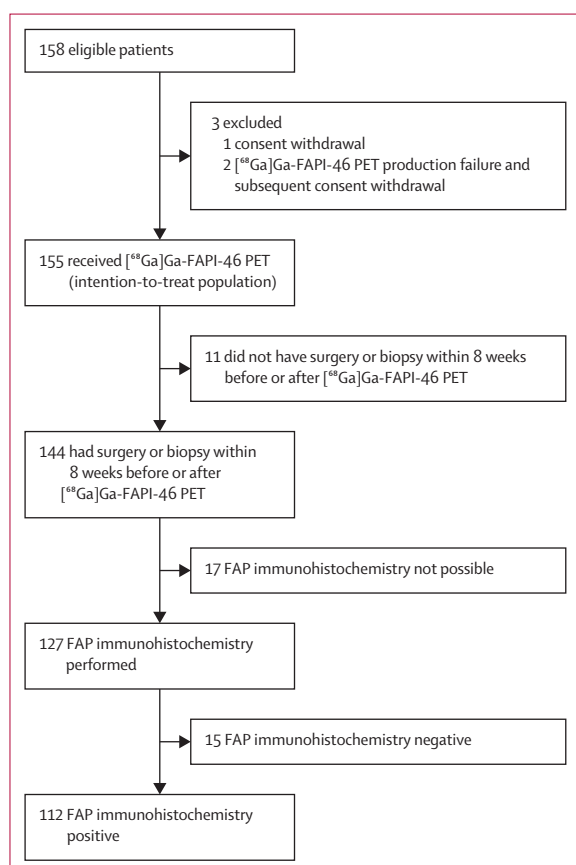
All analyses were performed using SPSS Statistics (version 27.0) and Python (version 3.11.8). A two-sided  $p$  value of less than 0.05 was considered statistically significant. The final analysis was performed on Jan 10, 2025.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

Between Dec 1, 2021 and Feb 6, 2024, 158 eligible participants were enrolled and three were excluded (one due to consent withdrawal and two due to [ $^{68}\text{Ga}$ ]Ga-FAPI-46 production failure and subsequent consent withdrawal; figure 1). The intention-to-treat population included 155 participants who received [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET-CT. 98 (63%) of 155 participants were male and 57 (37%) were female (table 1; appendix pp 5–6). One (1%) participant was African, two (1%) were Asian, and 152 (98%) were White. The median age of participants was 62 years (IQR 55–70). 99 (64%) participants received [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET-CT for staging at initial diagnosis and 56 (36%) for restaging. At the time of imaging, 107 (69%) participants had metastatic



**Figure 1: Trial profile**

FAP=fibroblast activation protein  $\alpha$ .

disease. Immunohistochemical FAP staining of tumour samples was feasible in 127 (88%) of 144 participants with histopathological validation (surgery or biopsy within 8 weeks); insufficient tumour material precluded analysis in the remaining 17 (12%). Biopsy samples were used for immunohistochemical staining in 78 (61%) of 127 participants, and surgical samples in 49 (39%).

An additional clinical [ $^{18}\text{F}$ ]FDG PET–CT was performed in 152 (98%) of 155 participants at a median of 1 day (IQR 1–2) before [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET–CT, with no change in therapy between scans. Histopathological validation of at least one region was available in 141 (93%) of 152 participants; reasons for missing data were due to patient death as a result of progression of the underlying tumour disease (n=1) and planned biopsy or surgery not being performed (n=10). The median follow-up time was 29 days (29–30).

The patient-based PPV of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET for detecting FAP-positive tumours based on immunohistochemical FAP staining was 90% (95% CI 84–95), and region-based PPV was 92% (85–96; appendix p 7). Specificity was not assessed due to the low number of false positives (11 [9%] of 127) and true negatives (four [3%]). Immunohistochemical validation was

[ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET (n=155)	
Age, years	62 (55–70)
Sex	
Female	57 (37%)
Male	98 (63%)
Race and ethnicity	
White	152 (98%)
Black or African	1 (1%)
Asian	2 (1%)
Tumour diagnosis	
Breast	7 (5%)
Cholangiocarcinoma	4 (3%)
Colorectal	4 (3%)
Endometrial	1 (1%)
Oesophageal	4 (3%)
Head and neck	2 (1%)
Lymphoma	10 (6%)
Multiple myeloma	2 (1%)
Neuroendocrine	3 (2%)
Non-small-cell lung cancer	15 (10%)
Pancreatic	8 (5%)
Prostate	3 (2%)
Renal cell carcinoma	33 (21%)
Sarcoma	28 (18%)
Seminoma	2 (1%)
Thyroid	1 (1%)
Unknown primary origin	3 (2%)
Urothelial carcinoma	14 (9%)
Other*	11 (7%)
Purpose of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET	
Staging at initial diagnosis	99 (64%)
Restaging	56 (36%)
Metastatic stage	
Yes	107 (69%)
No	48 (31%)
Previous therapies	
Yes	54 (35%)
No	101 (65%)
Type of previous therapies	
Surgery or local resection	49 (32%)
Radiotherapy or similar local targeting	9 (6%)
Chemotherapy	21 (14%)
Immunotherapy	10 (6%)
Other	3 (2%)
Eastern Cooperative Oncology Group performance status	
0	109 (70%)
1	41 (26%)
2	5 (3%)
Data are median (IQR) or n (%). *Other tumour diagnoses were anal carcinoma (n=1), metanephric adenoma (n=1), Ormond's disease (n=1), myxoid renal tumor (n=1), penile cancer (n=2), pseudomyxoma peritonei (n=2), schwannoma (n=1), tonsillar carcinoma (n=1), and urachus carcinoma (n=1).	
<b>Table 1: Patient characteristics</b>	



stratified by the seven most frequent tumour entities (RCC, sarcoma, NSCLC, urothelial carcinoma, lymphoma, PDAC, and other; appendix p 8). Region-based PPV was consistently 75% or higher across all subgroups (100% for urothelial carcinoma in 11 [9%] of 127 participants, 100% for lymphoma in ten [8%], 92% for sarcoma in 24 [19%], 92% for NSCLC in 13 [10%], 84% for RCC in 26 [20%], 80% for PDAC in five [4%], and 94% for other in 38 [30%]).

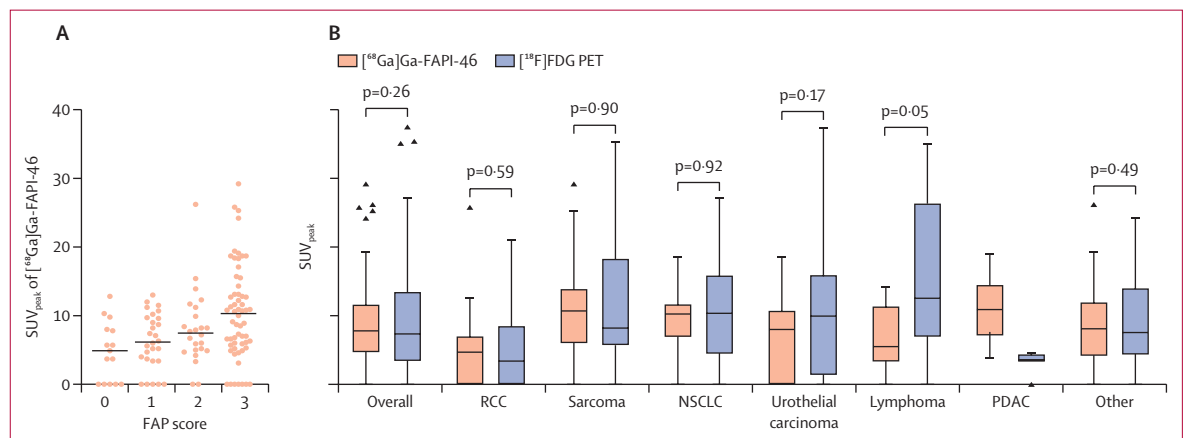
Comparison of patient-based, histopathologically confirmed PET SUV values in 141 (93%) of 152 participants are shown in figure 2. The patient-based histopathologically validated SUV<sub>peak</sub> values of [<sup>68</sup>Ga]Ga-FAPI-46 PET were median 4.7 (IQR 0.0–7.0) for RCC, 10.7 (6.0–13.9) for sarcoma, 10.3 (6.9–11.7) for NSCLC, 8.0 (0.0–10.8) for urothelial carcinoma, 5.5 (3.3–11.4) for lymphoma, 10.9 (7.1–14.5) for PDAC, and 8.1 (4.2–12.0) for other cancers. The corresponding values for [<sup>18</sup>F]FDG PET were median 3.4 (0.0–8.5) for RCC, 8.2 (5.7–18.3) for sarcoma, 10.4 (4.5–15.9) for NSCLC, 10.0 (1.4–15.9) for urothelial carcinoma, 12.6 (6.9–26.4) for lymphoma, 3.6 (3.3–4.4) for PDAC, and 7.6 (4.3–14.0) for other cancers. Region-based analyses are presented in the appendix (pp 16–17).

On a per-region basis, a low positive association between [<sup>68</sup>Ga]Ga-FAPI-46 PET uptake intensity (SUV<sub>peak</sub>) and immunohistochemical FAP expression was found (Spearman's  $r=0.33$ ,  $p=0.0002$ ; figure 2). The median SUV<sub>peak</sub> of [<sup>68</sup>Ga]Ga-FAPI-46 PET on the visual FAP expression scale was 4.9 (IQR 0.0–8.0) for score 0, 6.2 (3.5–9.7) for score 1, 7.5 (4.9–10.9) for score 2, and 10.3 (5.8–14.0) for score 3 (figure 2). A post-hoc analysis on a lesion level (101 [80%] of 127 participants) also

revealed a low association between SUV<sub>peak</sub> and immunohistochemical FAP expression (Spearman's  $r=0.38$ ,  $p=0.0001$ ; appendix p 15).

In a post-hoc analysis, accuracy for [<sup>68</sup>Ga]Ga-FAPI-46 and [<sup>18</sup>F]FDG PET were compared on a per-patient and per-region basis in the 141 participants with at least one histopathologically validated region. A total of 177 regions, all confirmed by histopathology (biopsy or surgery), were included in the analysis. Notably, this evaluation was performed independently of FAP immunohistochemistry and was based solely on PET findings and histopathological confirmation. The overall patient-based PPV was 98% (95% CI 94–100) and sensitivity was 86% (79–91) for [<sup>68</sup>Ga]Ga-FAPI-46 versus 100% (97–100) PPV and 85% (78–90) sensitivity for [<sup>18</sup>F]FDG PET (appendix p 9). The highest accuracy rates were reported for sarcoma (96% for [<sup>68</sup>Ga]Ga-FAPI-46 vs 96% for [<sup>18</sup>F]FDG PET) and PDAC (100% vs 86%). Conversely, lower patient-based accuracy rates were noted for RCC (65% for [<sup>68</sup>Ga]Ga-FAPI-46 vs 68% for [<sup>18</sup>F]FDG PET) and urothelial carcinoma (67% vs 75%).

The overall region-based PPV was 98% (95% CI 94–99) and sensitivity was 85% (78–89) for [<sup>68</sup>Ga]Ga-FAPI-46 versus 94% (89–97) PPV and 82% (75–87) sensitivity for [<sup>18</sup>F]FDG PET. Region-based PPV for [<sup>68</sup>Ga]Ga-FAPI-46 PET was 92% (74–98) for RCC, 100% (88–100) for sarcoma, 93% (69–99) for NSCLC, 100% (70–100) for urothelial carcinoma, 100% (65–100) for lymphoma, 100% (91–100) for PDAC, and 100% (91–100) for other cancers. For [<sup>18</sup>F]FDG PET, region-based PPV was 100% (85–100) for RCC, 97% (83–99) for sarcoma, 72% (49–88) for NSCLC, 91% (62–98) for urothelial carcinoma, 100% (76–100) for lymphoma, 100% (61–100)

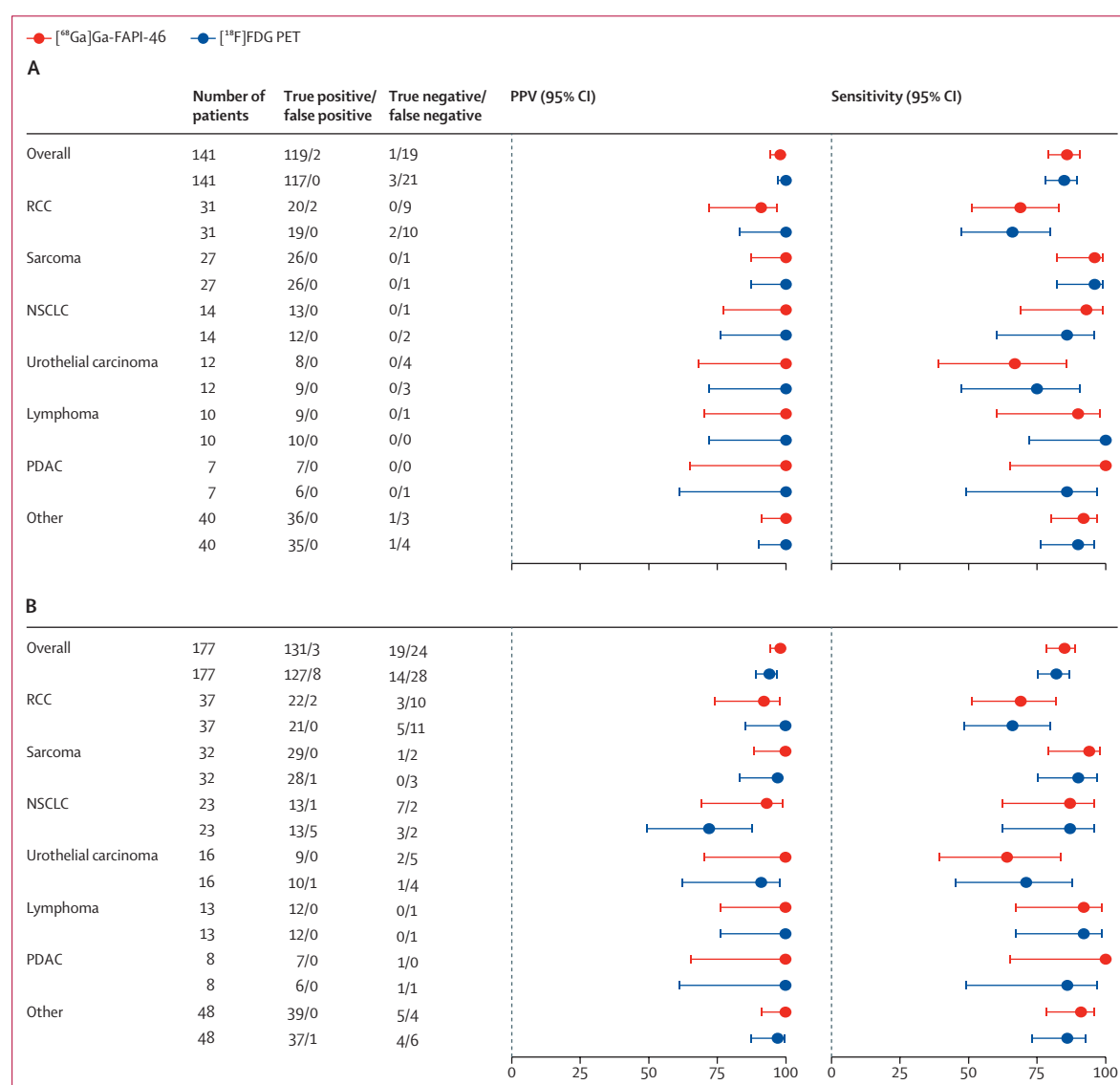


**Figure 2: Association between [<sup>68</sup>Ga]Ga-FAPI-46 PET uptake intensity and immunohistochemical FAP expression**

(A) Association between [<sup>68</sup>Ga]Ga-FAPI-46 PET uptake intensity and immunohistochemical FAP expression on a per-region basis (Spearman's  $r=0.33$ ,  $p=0.0002$ ). The dots represent individual tumour regions ( $n=127$ ) and horizontal black lines represent the median value. (B) Comparison of patient-based, histopathologically validated SUV<sub>peak</sub> values for [<sup>68</sup>Ga]Ga-FAPI-46 and [<sup>18</sup>F]FDG PET.  $p$  value of less than 0.05 was considered significant. Given the small sample size ( $n<10$ ) in the PDAC subgroup, the  $p$  value was omitted to avoid misinterpretation. Triangles represent outliers. The other cancers include breast cancer, cancer of unknown primary, cholangiocarcinoma, colorectal cancer, anal carcinoma, endometrial carcinoma, thyroid cancer, oesophageal cancer, head and neck cancer, tonsillar carcinoma, multiple myeloma, neuroendocrine carcinoma, prostate cancer, urachus carcinoma, seminoma, schwannoma, penile cancer, and pseudomyxoma peritonei. NSCLC=non-small-cell lung cancer. PDAC=pancreatic ductal adenocarcinoma. RCC=renal cell carcinoma. SUV=standardised uptake value.

for PDAC, and 97% (87–100) for other cancers. Region-based sensitivity for [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET was 69% for RCC (51–82), 94% (79–98) for sarcoma, 87% (62–96) for NSCLC, 64% (39–84) for urothelial carcinoma, 92% (67–99) for lymphoma, 100% (65–100) for PDAC, and 91% (78–96) for other cancers. For [ $^{18}\text{F}$ ]FDG PET, region-based sensitivity was 66% (48–80) for RCC, 90% (75–97) for sarcoma, 87% (62–96) for NSCLC, 71% (45–88) for urothelial carcinoma, 92% (67–99) for lymphoma, 86% (49–97) for PDAC, and 86% (73–93) for other cancers. Details on patient-based and region-based results by tumour entity are presented in figure 3 and the appendix (p 9). PPV and sensitivity for individual readers are shown in the appendix (p 10). There were 24 lesions

(including 15 participants with primary urinary tract tumours), for which findings of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET were judged negative by masked readers but biopsy or surgery (or both) confirmed tumour disease. In the unmasked clinical evaluation, 11 lesions showed no visible uptake and nine lesions showed only faint uptake (PET false-negative regions; appendix p 11). Four additional lesions showed measurable [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET uptake, with  $\text{SUV}_{\text{peak}}$  values ranging from 4.7 to 30.3. Two participants with RCC (1% of 141 total patients) were classified as false positive by masked readers, as the subsequent surgery identified one capillary haemangioma (FAP expression score of 3) and one focal nodular hyperplasia of the liver (FAP expression score of 0).



**Figure 3: Sensitivity and PPV for [ $^{68}\text{Ga}$ ]Ga-FAPI-46 versus [ $^{18}\text{F}$ ]FDG PET**

Patient-based (A) and region-based (B) PPV and sensitivity for [ $^{68}\text{Ga}$ ]Ga-FAPI-46 versus [ $^{18}\text{F}$ ]FDG PET, subdivided by tumour entities based on histopathologically confirmed regions, independent of FAP immunohistochemistry. FAP= fibroblast activation protein  $\alpha$ . NSCLC=non-small-cell lung cancer. PDAC=pancreatic ductal adenocarcinoma. PPV=positive predictive value. RCC=renal cell carcinoma.

	Grades 1–2	Grade 3	Grade 4	Grade 5
Any	5 (6%)	0	0	0
Nausea	2 (2%)	0	0	0
Papulopustular rash	1 (1%)	0	0	0
Dizziness	1 (1%)	0	0	0
Headache	1 (1%)	0	0	0

Possibly related adverse events (n=5) documented within 30 days after [<sup>68</sup>Ga]Ga-FAPI-46 PET-CT in four (3%) of 155 participants (n=90 adverse events in total). Graded according to Common Terminology Criteria for Adverse Events (version 5.0) and classified as possibly attributable to [<sup>68</sup>Ga]Ga-FAPI-46 PET. No [<sup>68</sup>Ga]Ga-FAPI-46-related serious adverse events were observed.

**Table 2: Possibly related adverse events**

Inter-reader reproducibility was assessed in 152 (98%) of 155 participants for [<sup>68</sup>Ga]Ga-FAPI-46 and [<sup>18</sup>F]FDG PET. Substantial to almost perfect agreement was found for [<sup>68</sup>Ga]Ga-FAPI-46 PET interpretation (Fleiss'  $\kappa$  0.71–0.83), whereas for [<sup>18</sup>F]FDG PET moderate-to-substantial agreement was identified (0.46–0.78). Reproducibility was higher for [<sup>68</sup>Ga]Ga-FAPI-46 than [<sup>18</sup>F]FDG PET, especially on a per-patient based analysis, and for per-region lymph node or visceral interpretations (appendix p 12).

In 39 (25%) of 155 participants, 90 adverse events were documented within 30 days after [<sup>68</sup>Ga]Ga-FAPI-46 PET-CT (appendix pp 13–14). The most common adverse events included nausea (16 [18%]), fatigue (ten [11%]), and constipation (six [7%]). Five (6%) of 90 adverse events (nausea [n=2], papulopustular rash [n=1], dizziness [n=1], and headache [n=1]) were classified as possibly related to [<sup>68</sup>Ga]Ga-FAPI-46 (table 2), all other events were attributed to medical history, tumour disease, or subsequent therapy. Seven (8%) adverse events were serious, none related to [<sup>68</sup>Ga]Ga-FAPI-46. One participant died during the 30-day follow-up period due to disease progression.

## Discussion

This single-centre phase 2 trial showed high accuracy, reproducibility, and safety of [<sup>68</sup>Ga]Ga-FAPI-46 PET in patients with FAP-expressing cancers. The primary endpoint (PPV  $\geq$ 75%) was met, reaching a PPV ranging from 80% to 100% for detecting immunohistochemical FAP-positive tumours across various tumour entities. [<sup>68</sup>Ga]Ga-FAPI-46 application was safe, with few grade 1–2 adverse events reported, including nausea or headache. Compared with previous retrospective trials, this study has notable strengths, including prospective enrolment, the implementation of multiple independent masked readings, masked histopathology rating, independent lesion validation, and comparison with the clinical standard, [<sup>18</sup>F]FDG PET.

The immunohistochemical FAP expression of tumour regions showed a low positive association with [<sup>68</sup>Ga]Ga-FAPI-46 PET uptake intensity (SUV<sub>peak</sub> Spearman's  $r=0.33$ ,  $p=0.0002$ ), which is slightly lower than the 95% CI (0.38–0.94) reported in previous

prospective lesion-based analyses.<sup>8</sup> This discrepancy might be attributed to methodological differences, since the present analysis was region-based. In a post-hoc lesion-level analysis including 101 (80%) of 127 participants, a similarly low association was observed (Spearman  $r=0.38$ ,  $p=0.0001$ ), corresponding to the lower bound of the previously reported CI. The use of biopsy samples for immunohistochemical analyses in 61% of participants might have introduced sampling errors.

Specific tumour entities had varying degrees of [<sup>68</sup>Ga]Ga-FAPI-46 PET uptake intensity. Patient-based median SUV<sub>peak</sub> of sarcoma was 10.7 (IQR 6.0–13.9) for [<sup>68</sup>Ga]Ga-FAPI-46 PET. As indicated in the distribution of tumour entities and subtypes, a heterogeneous sarcoma cohort was enrolled, predominantly including participants with soft tissue sarcoma (18 [64%] of 28; appendix p 5). High FAP radioligand uptake aligns with previous findings.<sup>15</sup> [<sup>68</sup>Ga]Ga-FAPI-46 PET showed low uptake in RCC, urothelial carcinoma, and lymphoma (4.7–8.0); whereas, PDAC showed markedly higher [<sup>68</sup>Ga]Ga-FAPI-46 PET uptake than [<sup>18</sup>F]FDG PET (10.9 vs 3.6) and lymphoma showed substantially lower uptake (5.5 vs 12.6). Overall, the radioligand uptake profile supports the future use of [<sup>68</sup>Ga]Ga-FAPI-46 PET-CT, especially in patients with sarcoma and PDAC.<sup>15,16</sup>

Overall PPV and sensitivity of [<sup>68</sup>Ga]Ga-FAPI-46 and [<sup>18</sup>F]FDG PET were high. The detection rate for urothelial carcinoma of [<sup>68</sup>Ga]Ga-FAPI-46 was lower than those in previous retrospective analyses, and although Novruzov and colleagues<sup>27</sup> reported a 30% higher detection rate for [<sup>68</sup>Ga]Ga-FAPI-46 compared with [<sup>18</sup>F]FDG PET, the region-based sensitivity obtained in our study is slightly higher for [<sup>18</sup>F]FDG PET (71% vs 64% for [<sup>68</sup>Ga]Ga-FAPI-46). RCC shows similarly low sensitivity (69% for [<sup>68</sup>Ga]Ga-FAPI-46 vs 66% for [<sup>18</sup>F]FDG PET). As previously published, [<sup>68</sup>Ga]Ga-FAPI-46 PET for sarcoma has shown high detection rates.<sup>15</sup> However, the wide CIs, which are partly due to the small sample sizes within tumour entity subgroups, indicate uncertainties in the measurements. Further studies with homogeneous patient cohorts are needed to enable accurate assessment of PPV and sensitivity for individual tumour entities.

In total, [<sup>68</sup>Ga]Ga-FAPI-46 PET false-negative lesions leading to low detection rates, were identified in 22 (16%) of 141 participants, mostly in primary urinary tract tumours (15 [68%] of 22). In the unmasked clinical evaluation, 11 lesions showed no visible uptake, whereas nine lesions showed faint uptake. Four lesions with measurable uptake (SUV<sub>peak</sub>) remained undetected by the masked readers, mostly due to their anatomical proximity to the urinary tract and based on urinary radioligand excretion.<sup>18</sup> However, it needs to be considered that the use of [<sup>68</sup>Ga]Ga-FAPI-46 PET-CT will not primarily focus on the characterisation of primary tumours of RCC and urothelial carcinoma, but rather on the detection of lymph node and distant metastases.



Masked reads resulted in [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET false-positive findings in two (1%) participants with RCC: one capillary haemangioma (FAP expression score of 3) and one focal nodular hyperplasia of the liver (FAP expression score of 0), confirmed by histopathology. Both of these benign entities have been associated with FAP expression and need to be considered as pitfalls of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET interpretation.<sup>19,20</sup>

We found substantial to almost perfect reproducibility of the masked [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET interpretations among three independent readers (Fleiss'  $\kappa$  0.71–0.83). Although some of the corresponding p values support statistical significance, Fleiss'  $\kappa$  remains a descriptive measure and should be interpreted accordingly. The high reproducibility of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET interpretation is consistent with previous findings for other radioligands, including [ $^{68}\text{Ga}$ ]labelled somatostatin receptor analogues and [ $^{68}\text{Ga}$ ]PSMA-11 PET.<sup>21,22</sup> [ $^{18}\text{F}$ ]FDG PET showed moderate-to-substantial reproducibility (Fleiss'  $\kappa$  0.46–0.78), with greater variability particularly in the assessment of lymph node and visceral metastases, likely reflecting challenges, such as non-specific uptake in reactive or inflammatory processes.<sup>23,24</sup> Previous data have highlighted superior accuracy of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 over [ $^{18}\text{F}$ ]FDG PET for lymph node staging, especially in patients with NSCLC.<sup>7</sup> The lower organ uptake of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET compared with [ $^{18}\text{F}$ ]FDG PET might enhance detection of visceral metastases.<sup>25,26</sup>

Compared with [ $^{18}\text{F}$ ]FDG PET–CT, [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET–CT provides several logistical advantages, including reduced uptake time and simpler patient preparation (ie, no fasting or blood glucose level control required).<sup>3,27</sup> In this study, an acquisition window of 15 (plus minus 5 min, protocol-defined range) post-injection for [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET–CT was selected based on our previous study showing equal tumour detection for early versus late scans.<sup>28</sup>

Our study has several limitations. The basket trial design allowed broad inclusion of tumour types previously identified as promising for FAP imaging, resulting in a heterogeneous cohort.<sup>29</sup> Although several subgroups (RCC, sarcoma, NSCLC, urothelial carcinoma, lymphoma, and PDAC) reached sufficient size for subgroup analyses, other entities had to be pooled for assessment. A subsequent trial will focus on gastrointestinal cancers (EUCT 2023-506030-70-00). Due to our study design and requirement for histopathological confirmation of tumour regions, approximately two-thirds (64%) of participants were examined for initial staging and a third (36%) for restaging. The value of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET–CT for therapy monitoring remains to be assessed in future studies, particularly for FAP-directed therapies.<sup>3</sup> Additionally, only three participants were African or Asian, limiting the feasibility of meaningful subgroup analyses based on race. This underrepresentation should be considered when interpreting the generalisability of these findings. Specificity and negative predictive value

were not assessed, limiting conclusions about overall diagnostic accuracy. However, the findings on PPV and sensitivity are highly relevant for clinical decision making. In our study, questionnaires before and after receiving [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET–CT were sent to the treating physicians to evaluate the effect on treatment management; however, given the short follow-up period and high relevance of this aspect, further investigation is being conducted in an ongoing study (NCT04571086), with a 12-month follow-up.

Watanabe and colleagues conducted off-protocol basket analyses involving 50 participants from our study cohort, focusing on overall survival prognostication using [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET–CT and a lesion based comparison of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET, [ $^{18}\text{F}$ ]FDG PET, and contrast-enhanced CT.<sup>30,31</sup> Although these imaging datasets were derived from participants in this prospective trial, the analysis did not incorporate direct data, study endpoints, or masked reader assessments from the results presented here and their findings provide complementary context to our trial.

In conclusion, this single-centre, single-arm, phase 2 trial confirms the safety and potential of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET as an imaging biomarker for detecting FAP-expressing cancers. Further studies are warranted to refine the specificity and define the role of [ $^{68}\text{Ga}$ ]Ga-FAPI-46 PET in clinical practice.

#### Contributors

KMP, WPF, KH, and MN were members of the protocol development working party that contributed to conceptualisation and writing the first version of the protocol. KMP, TB, FB, LEP, BAH, RH, DK, NvO, BvT, H-PK, CK, SK, AR-S, MS, JTS, VG, and WPF accrued patients and collected data. MMW, CL, PS, ATK, KMP, and LK performed image analysis. MT-A optimised the fibroblast activation protein (FAP) immunohistochemistry and supervised the staining. ME evaluated immunohistochemical FAP expression. KMP, EG, and WPF contributed to the statistical analysis plan. EG, KMP, and WPF led the statistical analysis. WPF, KMP, TB, EG, and KH accessed and verified the data. KMP wrote the first draft of the manuscript. WPF was the coordinating principal investigator and contributed to writing the original manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

KMP was funded by the Clinician Scientist Program of the University Medicine Essen Clinician Scientist Academy (UMEA; Faculty of Medicine and Deutsche Forschungsgemeinschaft (DFG)); received consultant and travel fees from Novartis, travel fees from Ipsen, and research funding from Bayer. MMW received personal fees from Boston Scientific, Terumo, Advanced Accelerator Applications, Ipsen, and Eli Lilly. CL received travel fees from Novartis. TB received travel fees from PARI and Novartis. ATK was funded by the Clinician Scientist Program of the UMEA (Faculty of Medicine and DFG). ME received research funding from BicycleTx; consulting fees from AstraZeneca, Genomic Health, Gilead, Merck, Johnson & Johnson (J&J), Diaceutics, MSD, and BicycleTx; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, J&J, Diaceutics, Eisai, BicycleTx, Roche, Owkin, Ferring, and Merck; payment for expert testimony from AstraZeneca, Genomic Health, Gilead, Merck, J&J, Diaceutics, MSD, and BicycleTx; travel fees from AstraZeneca, MSD, Diaceutics, Ferring, Merck, Roche, J&J, Astellas, Eisai, and BicycleTx; had a leadership or fiduciary role for the Clinical Advisory Board of BicycleTx, Board of European Society of Urological Pathology of the European Association of Urology, Board of

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#### Data sharing

Access to the summary of deidentified participant data (including data dictionaries) can be made available upon reasonable request after approval by an independent review committee after publication of the study primary and secondary endpoints. Requests should be directed to the corresponding author (kim.pabst@uk-essen.de).

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