Piflufolastat (18F) (Pylclari®) for the diagnosis of prostate cancer

General information [1]

Drug description	Indication
The active substance of Pylclari® is piflufolastat (^{18}F) - formerly known as (18F)-DCFPyL - a diagnostic radiopharmaceutical for tumour detection. Piflufolastat is a fluorine-18 labelled small-molecule prostate-specific membrane antigen (PSMA) inhibitor that enables positron emission tomography (PET). It binds to cells expressing PSMA, including malignant prostate cancer cells which overexpress PSMA.	Piflufolastat (Pylclari®) is indicated for the detection of PSMA positive lesions with PET in adults with prostate cancer in the following clinical settings: ❖ primary staging of patients with high-risk prostate cancer prior to initial curative therapy ❖ to localise recurrence of prostate cancer in patients with a suspected recurrence based on increasing serum prostate-specific antigen (PSA) levels after primary treatment with curative intent.

Incidence of prostate cancer [2]

- ❖ In Austria, in 2020, 6,126 men were newly diagnosed with prostate cancer.
- ❖ The age-standardised incidence rate[1] in 2020 was 149,9 per 100,000 men.

Current treatment [3][2]

- ❖ For **screening, early detection and diagnosis** of prostate cancer, the ESMO recommends:
  - Population-based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of over-diagnosis and overtreatment and is not recommended.
  - Early PSA testing (baseline PSA followed by risk-adapted follow-up) can be offered to men >50 years, men >45 years with a family history of prostate cancer, African Americans >45 years and BRCA1/2 carriers >40 years.
  - Testing for prostate cancer in asymptomatic men should not be done in men with a life expectancy <10 years.
  - mpMRI should be carried out before prostate biopsy.
  - A prostate cancer risk calculator and/or mpMRI should be used to confirm the indication for biopsy in men with elevated PSA.
  - Transperineal biopsies are recommended, rather than transrectal ultrasound-guided biopsies.
  - Each biopsy should be reported individually and evaluated using the International Society of Urological Pathology Consensus recommendations.
- ❖ For **staging and risk assessment,** the following is recommended:
  - Localised disease should be classified as low-, intermediate- or high-risk as a guide to prognosis and therapy.
  - Patients with intermediate-risk disease should be staged for metastases using MRI or CT (abdomen and pelvis) and bone scan.
  - Patients with high-risk disease should be staged for metastases using CT (chest, abdomen, and pelvis) and bone scan.

Regulatory status

EMA [1]	FDA [4, 5]
Approval status for this indication: On 25 May 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Pylclari®. UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 24/07/2023 <u>The full indication is:</u> ❖ Pylclari® is for diagnostic use only. ❖ Pylclari® is indicated for the detection of PSMA positive lesions with PET in adults with prostate cancer in the following clinical settings:	**Approval status for this indication**: On 27 May 2021, the FDA approved Pylarify® (piflufolastat F 18) for PET imaging of PSMA-positive lesions in men with prostate cancer • with suspected metastasis who are candidates for initial definitive therapy. • with suspected recurrence based on elevated serum PSA level. ✓ FDA granted approval to Progenics Pharmaceuticals, Inc. ✓ Priority review **Other indications**: none

[1] European Standard Population 2013.

[2] Due to an ongoing update, currently, there is no Onkopedia Guideline available.

- primary staging of patients with high-risk prostate cancer prior to initial curative therapy
- to localise recurrence of prostate cancer in patients with a suspected recurrence based on increasing serum PSA levels after primary treatment with curative intent.

Other indications: none

✓ Medicine is under additional monitoring

Manufacturer

The applicant for Pylclari®[3] in Europe is Curium Pet France [1].
The manufacturer of piflufolastat F 18 (trademark Pylarify®) is Progenics Pharmaceuticals, Inc. [5].

Costs

Currently, there is no cost information available.

Posology [5]

❖ **Radiation safety – drug handling**
- Pylarify® is a radioactive drug. Only authorised persons qualified by training and experience should receive, use, and administer Pylarify®.
- Handle Pylarify® with appropriate safety measures to minimise radiation exposure during administration.
- Use waterproof gloves and effective radiation shielding, including syringe shields, when preparing and handling Pylarify®.

❖ **Recommended dose**
- The recommended amount of radioactivity to be administered for PET imaging is 333 MBq (9 mCi) with an acceptable range of 296 MBq to 370 MBq (8 mCi-10 mCi) administered as a single bolus intravenous injection.

❖ **Preparation and administration**
- Use aseptic technique and radiation shielding when preparing and administering Pylarify®.
- Visually inspect the radiopharmaceutical solution. Do not use if it contains particulate matter or if it is discoloured (Pylarify® is a clear, colourless solution).
- Calculate the necessary volume to administer based on calibration time and required dose.
- Pylarify® may be diluted with 0.9% Sodium Chloride Injection, USP. Assay the dose in a suitable dose calibrator prior to administration.

❖ **Post administration instructions**
- Follow the Pylarify® injection with an intravenous flush of 0.9% Sodium Chloride Injection USP.
- Dispose of any unused Pylarify® in compliance with applicable regulations.

❖ **Patient preparation**
- Instruct patients to drink water to ensure adequate hydration prior to administration of Pylarify® and to continue drinking and voiding frequently for the first few hours following administration to reduce radiation exposure.

❖ **Image acquisition**
- The recommended start time for image acquisition is 60 minutes after Pylarify® injection. Starting image acquisition more than 90 minutes after injection may adversely impact imaging performance.
- Patients should void immediately prior to image acquisition.
- Position the patient supine with arms above the head.
- Image acquisition should start from mid-thigh and proceed to the skull vertex.
- Scan duration is 12 minutes to 40 minutes depending on the number of bed positions (typically 6-8) and acquisition time per bed position (typically 2-5 minutes).

❖ **Image display and interpretation**
- Pylarify® binds to PSMA. Based on the intensity of the signals, PET images obtained using Pylarify® indicate the presence of PSMA in tissues.

[3] Piflufolastat (18F) is formerly known as (18F)-DCFPyL.

- Lesions should be considered suspicious if uptake is greater than physiologic uptake in that tissue or greater than adjacent background if no physiologic uptake is expected. Tumours that do not express PSMA will not be visualised.
- Increased uptake in tumours is not specific for prostate cancer.

❖ **Radiation dosimetry**
- Radiation absorbed dose estimates are shown in label information for organs and tissues of adult male patients from intravenous administration of Pylarify®.
- The radiation effective dose resulting from administration of 370 MBq (10 mCi) of Pylarify® to an adult weighing 70 kg is estimated to be 4.3 mSv.
- The radiation doses for this administered dose to the critical organs, which are the kidneys, liver, and spleen, are 45.5 mGy, 13.7 mGy, and 10 mGy respectively.
- When PET/CT is performed, exposure to radiation will increase by an amount dependent on the settings used in the CT acquisition.

Warnings and precautions [5, 6]

❖ **Risk of image misinterpretation**
- Pylarify® uptake can be seen in a variety of tumour types as well as in non-malignant processes and normal tissues.
- Image interpretation errors can occur with Pylarify® imaging.

❖ **Hypersensitivity reactions**
- Monitor patients for hypersensitivity reactions, particularly patients with a history of allergy to other drugs and foods.

❖ **Radiation risk**
- Ensure safe drug handling to protect patients and health care workers from unintentional radiation exposure.

❖ **Individual benefit/risk justification**
- For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should, in every case, be as low as reasonably achievable to obtain the required diagnostic information.

❖ **Renal impairment**
- Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

❖ **Patient preparation**
- The patient should be well hydrated before the start of the examination and urged to void before the examination in order to reduce bladder activity and as often as possible during the first hours after the examination in order to reduce radiation exposure.
- A diuretic expected to act within the uptake time period may be administered to improve interpretation of piflufolastat (18F) PET/CT as it results in less activity depositions in ureters and the bladder.

❖ **After the procedure**
- Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

Study characteristics: CONDOR trial [7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
CONDOR NCT03739684	208	18F-DCFPyL at a dose of 9 mCi (333 MBq) administered IV 1–2 hours before PET/CT	-	correct localisation rate (CLR)[4]	-	prospective, multicentre, open label, single-arm, phase III study	18F-DCFPyL	Progenics Pharmaceuticals, Inc.	CONDOR trial [8]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline
❖ ≥ 18 years of age ❖ Histopathologically confirmed prostate adenocarcinoma per original diagnosis, with subsequent definitive therapy	❖ Subjects administered any high energy (>300 KeV) gamma-emitting radioisotope within five physical half-lives prior to day 1	❖ Median age: 68 years (range, 43–91) ❖ Age ≥65 years: n=141/208 (67.8%)

[4] Defined as positive predictive value with an additional requirement of anatomic lesion colocalisation between 18FDCFPyL-PET/CT and a composite standard of truth (SOT). The SOT consisted of, in descending priority (i) histopathology, (ii) subsequent correlative imaging findings, or (iii) post radiation PSA response.

❖ Suspected recurrence of prostate cancer based on rising PSA after definitive therapy based on: • Post-radical prostatectomy: Detectable or rising PSA that is ≥ 0.2 ng/mL with a confirmatory PSA ≥ 0.2 ng/mL • Post-radiation therapy, cryotherapy, or brachytherapy: Increase in PSA level that is elevated by ≥ 2 ng/mL above the nadir ❖ Negative or equivocal findings for prostate cancer on conventional imaging performed as part of standard of care workup within 60 days prior to day 1 ❖ Life expectancy ≥6 months as determined by the investigator ❖ Able and willing to provide informed consent and comply with protocol requirements	❖ Ongoing treatment with any systemic therapy (ADT, antiandrogen, GnRH, LHRH agonist or antagonist) for prostate cancer ❖ Treatment with ADT in the past 3 months of day 1 ❖ Receipt of investigational therapy for prostate cancer within 60 days of day 1 ❖ Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise the safety or compliance of the subject to produce reliable data or completing the study	❖ Median time from prostate cancer diagnosis: 71 months (range, 3–356) ❖ Prior prostate cancer therapies: • Radical prostatectomy only: n=103/208 (49.5%) • Radiation therapy only: n=31/208 (14.9%) • Radical prostatectomy and radiation therapy: n=74/208 (35.6%) ❖ At least one prior systemic therapy: n=58/208 (27.9%) ❖ Total Gleason score: • <8: n=153/208 (73.6%) • ≥8: n=55/208 (26.4%) ❖ Median PSA (ng/mL) (n=202): 0.8 (range, 0.17–98.45) ❖ Median PSA sample collection study day prior to administration of 18F-DCFPyl (study day): 1 (-29-1) ❖ PSA group: • <2.0 ng/mL: n=139/202 (68.8%) • ≥2.0 ng/mL: n=63/202 (31.2%) ❖ ^{18}F-DCFPyL dosing and uptake time: • Median administered activity, mCi: 9.42 (range, 7.49–11.07) • Median administered activity, MBq: 349 (range, 277–410) • Median time from injection to imaging: 79 minutes (range, 59–115)

Efficacy (I vs. C)	**Safety**[5] (n=208)
❖ 18F-DCFPyL-PET/CT detected ≥1 lesion in 59.1% to 65.9% patients as assessed by 3 independent blinded central readers. ❖ The PE of CLR was met as the lower limit of 95% CI exceeded 20% for all three readers. ❖ The **CLR ranged from 84.8% to 87.0% among the 3 readers** (the lower bound of the 95% CI ranged from 77.8% -80.4%). ❖ The performance of 18F-DCFPyL-PET/CT by CLR and PPV was maintained through all categories of the SOT: histopathology (n=31): 78.6%–82.8% and 92.9%–93.3% for CLR and PPV, respectively; correlative imaging (n=100): 86.1%–88.6% and 87.0%–89.5% for CLR and PPV, respectively; and PSA response (n=1): 100% for both CLR and PPV. ❖ Further analyses of the correlative imaging results showed CLR remained high across the different modalities used (i) 18F-fluciclovine-PET/CT (n=71): 86.8%–90.9%; (ii) MRI (n=23): 80.0%–86.7%; and (iii) CT (n=6): 80.0%–100%. ❖ The CLRs for each reader also were maintained across prior treatment regimens and increased with the within-patient maximum standardised uptake value of lesions identified on 18F-DCFPyL-PET/CT. **CLR by baseline PSA and detection rate:**	**AEs:** 6.7% ❖ **E.g., headache:** 1.9% ❖ **E.g., fatigue:** 1.0% ❖ **E.g., hypertension:** 1.0% **Serious grade 3 AEs (hypersensitivity, headache, paraesthesia):** 0.5% **Grade 4 AEs or deaths:** 0

[5] Safety assessments included monitoring for the incidence of treatment-emergent adverse events (AE) from the time of 18F-DCFPyL dosing up to 7 ± 3 days post-dose.

- In patients with baseline PSA levels <0.5 ng/mL, the median CLR was 73.3% while patients with a PSA of ≥5 ng/mL had a median CLR of 96.4%.
- The detection rate rose with increasing PSA levels ranging from 36.2% (<0.5 ng/mL) to 96.7% (≥5 ng/mL).

PPV by anatomic region:

- PPV of 18F-DCFPyL-PET/CT was determined in detection of recurrent disease by anatomic regions (prostate/prostate bed, pelvi PFS and extrapelvic regions) from the composite SOT in patients with at least one 18F-DCFPyL-positive lesion.
- The PPV was consistently high across all anatomic regions.
- The PPV in the prostatic region ranged between 75.0% and 83.3% among the three independent readers.
- For pelvic lymph nodes, the PPV was between 67.2% and 72.7%, and for the extrapelvic regions, it ranged from 67.3%-69.8%.

Inter-reader and intra-reader agreement:

- Inter-reader agreement had a concordance of 75% and Fleiss' kappa of 0.65 (95% CI, 0.58–0.73).
- Agreement between the central and local readers had concordances of 83.2%-83.7% and kappas of 0.62 (95% CI, 0.50–0.73), 0.65 (95% CI, 0.54–0.75), and 0.64 (95% CI, 0.53–0.74) for the three readers.
- Intra-reader agreement had kappas of 0.94 (95% CI, 0.82–1.0), 1.0 and 0.81 (95% CI, 0.64–0.98) for the three readers.

Change in planned medical management:

- The treating physicians completed pre- and post-18F-DCFPyLPET/CT medical management questionnaire for 205 patients.
- Nearly two-thirds (n=131; 63.9%) of these patients had a change in intended disease management plan.
- Of these 131 patients, 103 (78.6%) were associated with positive 18F-DCFPyL-PET/CT findings, and 28 (21.4%) were associated with negative findings.
- Of the 144 patients that had a positive 18F-DCFPyL scan, 103 (72.5%) had a recommended change in management. The most frequent changes to treatment management plans after the 18F-DCFPyL-PET/CT imaging results included salvage local therapy that was either supplemented or replaced by systemic therapy (n=58; 28.3%), observation to initiating therapy (n=49; 23.9%), systemic therapy to salvage local therapy (n=43; 21.0%), and planned treatment to observation (n=9; 4.4%).

Patient-reported outcomes

In CONDOR trial, the evaluation of patients-reported outcomes is not provided.

Risk of bias - study level (case series) [9]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[6]	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?

[6] Baseline characteristics were heterogenous.

yes	yes	yes	unclear[7]	no[8]	yes	yes	yes	yes	
Overall risk of bias: moderate									

Study characteristics: OSPREY trial [10, 11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
OSPREY NCT02981368	385[9]	single dose of 9 mCi (333 MBq) 18F-DCFPyL via intravenous injection, followed by PET/CT 1 to 2 hours thereafter (both cohorts)	-	**specificity** of 18F-DCFPyL PET/CT imaging to determine the absence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology + **sensitivity** of 18F-DCFPyL PET/CT imaging to determine the presence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology	-	prospective, multicentre, multi-reader, open-label, phase 2/3 study	18F-DCFPyL	Progenics Pharmaceuticals, Inc.	OSPREY trial [10]

Inclusion criteria

All cohorts:
- Adults ≥18 years; signed informed consent
- Histologically confirmed adenocarcinoma of the prostate

Cohort A only:
- At least high-risk prostate cancer defined by NCCN Guidelines Version 3.2016 (clinical stage ≥T3a or PSA >20 ng/mL or Gleason score ≥8)
- Scheduled or will be scheduled to undergo radical prostatectomy with PLND

Cohort B only:
- Radiologic evidence of local recurrence or new or progressive metastatic disease demonstrated on anatomical imaging (CT, MRI, or ultrasound), whole-body bone scan (99mTc-MDP or Na18F) within 4 weeks of day 1
- If prior treatment with radiation or ablative therapy, evidence of recurrence outside the confines of prior treated site(s)
- Scheduled or will be scheduled for percutaneous biopsy of at least one amenable lesion

Exclusion criteria

All cohorts:
- Subjects administered any high energy (>300 KeV) gamma-emitting radioisotope within 5 physical half-lives, or any IV iodinated contrast medium within 24 hours, or any high-density oral contrast medium (oral water contrast is acceptable) within 5 days, prior to study drug injection.
- Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise obtaining reliable data, achieving study objectives, or completion.

Cohort A only:
- Patients with prior ADT or any investigational neoadjuvant agent or intervention.

Cohort B only:

Patient characteristics at baseline
High-risk disease (cohort A)/ Recurrent or metastatic disease (cohort B)

- Number of patients: 268[10]/117[11]
- Median age at informed consent: 65/68 years
- Median months since last prostate cancer staging evaluation: 1.7/31.1
- AJCC primary tumour (T) stage:
  - TX (3.0/10.3 %); T1a (0.4/0 %); T1b (0.7/0.9 %); T1c (32.5/13.7 %); T2 (2.6/2.6 %); T2a (16.8/8.5 %); T2b (11.2/6.0 %); T2c (5.2/8.5 %); T3 (1.1/2.6 %); T3a (20.9/20.5 %); T3b (5.2/14.5 %); T4 (0.4/7.7 %); Missing (0/4.3 %)
- AJCC regional lymph node (N) stage:
  - NX (38.4/33.3 %); No (58.2/39.3 %); N1 (3.4/23.1 %); Missing (0/4.3 %)

[7] 132 patients had a lesion follow-up, but the point in time is unclear.
[8] Loss to follow-up rate was not reported.
[9] Two patient populations underwent 18F-DCFPyL-positron PET/CT. Cohort A (n=252) enrolled men with high-risk prostate cancer undergoing radical prostatectomy with pelvic lymphadenectomy. Cohort B (n=93) enrolled patients with suspected recurrent/metastatic prostate cancer on conventional imaging.
[10] Cohort A: Of 268 patients who underwent Pyl PET/CT, 16 patients did not undergo RP-PLND and 252 patients underwent surgery and have PLN pathology results.
[11] Cohort B: of 117 patients who underwent Pyl PET/CT, 93 patients had extra-prostatic biopsies.

	❖ Prior radiation or ablative therapy to intended site of biopsy, if within the prostate bed. ❖ Initiation of new systemic therapy for recurrent and/or progressive metastatic disease since radiographic documentation of recurrence/progression	❖ AJCC distant metastases (M) stage: • MX (17.9/ 0.9 %); Mo (80.6/ 58.1 %); M1 (0.4/28.2 %); M1a (0/5.1 %); M1b (0.4/3.4 %); M1c (0/0) ❖ Gleason grade: • 6 (1.1/3.4 %); 7 (18.3/33.3 %); 8 (44.8/27.3 %); 9 (34.3/31.6 %); 10 (1.5/0.9 %); Missing (0/3.4 %) ❖ Median PSA (ng/ml, range): 9.7 (1.2-125.3)/ 7.1 (0.03-596.9) ❖ Prior prostatectomy: 0/47.1 % ❖ Prior prostate radiation therapy: 0.4/58.1 % ❖ Prior systemic therapy: 1.5/63.2 % ❖ Median18F-DCFPyL dosing and uptake time (mCi/MBq administered: 9.14/338 ❖ Median minutes from injection to imaging (range): 74 (25—194)

Efficacy (I vs. C)	**Safety** (I vs. C)
Cohort A ❖ The specificity co-primary endpoint was met, as the lower limits of the 95% CIs for all readers exceeded the prespecified 80% success threshold. ❖ Of the 75.4% of patients with pathologically negative pelvic lymph nodes, **specificity** across all 3 readers ranged from 96.3% to 98.9% (lower limits of the 95% CI, 93.6%-96.0%). ❖ The sensitivity endpoint was not met, as the lower bounds of the 95% CI (19.2%-29.7%) did not reach the success threshold of 40%. ❖ Of 24.6% of patients with at least 1 pathologically proven pelvic nodal metastasis, **sensitivity** for the 3 readers ranged from 30.6%-41.9%. ❖ Results for **PPV and NPV** were 78.1%-90.5% (lower bounds of 95% CI, 63.8-69.9) and 81.4%-83.8% (lower bounds of 95% CI, 76.4%-78.9%), respectively. ❖ Primary tumour in the prostate gland was identified on 18F-DCFPyL-PET/CT by the blinded readers in 95.2%-99.3% of cases. ❖ In a post hoc sensitivity analysis, we evaluated PET/CT for detection of nodal metastases >5 mm in diameter based on the assumption that smaller tumour deposits are below PET detection limits. ❖ After exclusion of the 27 patients whose largest nodal metastasis was ≤5 mm, sensitivity, and specificity both met the success criteria, and high PPV and NPV results were preserved. ❖ The median results of the 3 18F-DCFPyL-PET/CT readers for detecting pelvic lymph node metastases were compared with CT or MRI; 18F-DCFPyL-PET/CT demonstrated threefold higher PPV (86.7% vs. 28.3%), higher specificity (97.9% vs. 65.1%) and slightly higher NPV (83.2% vs. 77.8%), and similar sensitivity (40.3% vs. 42.6%). ❖ At least 1 reader detected extra pelvic lesions by 18F-DCFPyL-PET/CT in 12.3% (33/268) of high-risk patients, potentially up staging them from clinical Mo to M1 disease. **Cohort B** ❖ Median sensitivity was 95.8% (95% CI, 87.8%-99.0%) and median PPV was 81.9% (95% CI, 73.7%-90.2%). ❖ Across the readers, false-negative results ranged from 1.4%-7.1% and false-positive results from 12.2%-18.8%. ❖ Although the cohort included lesions that presumptively represented recurrent or metastatic disease on conventional imaging, 23.9% of patients (22/92) had negative histopathology for prostate cancer on biopsy. ❖ Sensitivities and PPVs for detection of prostate cancer within different anatomical regions were also determined.	Patients who experienced **at least 1 AE**: n=51/385 patients (13.2%) **Most frequent AEs**: dysgeusia (2.6%), headache (2.3%), and fatigue (1.3%) Patients who experienced **a serious AE**: n=7/385 (1.8%); none was considered related to 18F-DCFPyL

- All 93 evaluable patients underwent extra prostatic biopsy: 20 (21.5%) had pelvic lymph nodes, 19 (20.4%) had extra pelvic lymph nodes, 44 (47.3%) had osseous lesions and 10 (10.8%) had distant visceral/soft tissue lesions.
- 18F-DCFPyL-PET/CT demonstrated >88% sensitivity and ≥75% PPV in confirming prostate cancer within all sites of disease and extent of disease spread at the region level.
- Sensitivities and PPVs of 18F-DCFPyL-PET/CT across different baseline PSA levels were also evaluated.
- In men with low PSA (<2 ng/ml), sensitivity ranged from 88.9%-100% and PPV ranged from 61.5%-88.9%.
- Relative to conventional imaging (CT/MRI, bone scintigraphy) findings, 18F-DCFPyL-PET/CT indicated that distant metastasis was likely in 19/33 patients (57.6%) and unlikely in 18/82 patients (22.0%).

Patient-reported outcomes

In OSPREY trial, the evaluation of patients-reported outcomes is not provided.

Risk of bias - study level (case series) [9]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial[12]	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	yes	yes	yes	yes	yes

Overall risk of bias: low

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT03824275	18F-DCFPyL PET/CT in men with prostate cancer, a phase 2/3 trial.	12/2023
NCT03594760	PSMA-PET: Deep radiomic biomarkers of progression and response prediction in prostate cancer, a phase 3 study.	12/2024
NCT03459820	Differences in optimal prostate cancer patient management as proposed by a panel of experts before and after 18F-DCFPyL PET/CT, a phase 2/3 trial.	06/2027

Available assessments

- In November 2020, CADTH published "PET Diagnostic Imaging with Prostate-Specific Membrane Antigen for Prostate Cancer: A Review of Clinical Utility, Cost-Effectiveness, Diagnostic Accuracy, and Guidelines". The review focuses not only on 18F-DCFPyL [13].

[12] Baseline characteristics were heterogenous.

- There were no further assessments identified via NICE, G-BA, ICER and NIHR.

Other aspects and conclusions

- In May 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Pylclari®. It is indicated for the detection of PSMA-positive lesions with PET in adults with prostate cancer for the primary staging of patients with high-risk prostate cancer prior to initial curative therapy, and to localise recurrence of prostate cancer in patients with a suspected recurrence based on increasing serum PSA levels after primary treatment with curative intent. In May 2021, the FDA approved Pylarify® for PET imaging of PSMA-positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy and for patients with suspected recurrence based on elevated serum PSA level.
- CONDOR (NCT03739684) is a phase III, prospective, multicentre, open-label, single-arm study evaluating the diagnostic performance and safety of 18F-DCFPyL-PET/CT in 208 patients with suspected recurrent or metastatic prostate cancer. Men ≥18 years with biochemically recurrent adenocarcinoma of the prostate treated with radical prostatectomy or radiotherapy were included. Exclusion criteria included administration of any high-energy gamma-emitting radioisotope within 5 physical half-lives prior to 18F-DCFPyL injection, and ADT within 3 months of imaging, or investigational therapy for prostate cancer within 60 days of imaging:
  - CLR, the PE, was 84.8%–87.0% (lower bound of 95% CI, 77.8–80.4).
  - Patients-reported outcomes were not provided.
  - The ESMO-MCBS was not applicable because the primary endpoint could not be assessed.
  - Since baseline characteristics were heterogenous and it remained unclear when lesion follow-up was performed, the risk of bias was considered moderate.
- OSPREY (NCT02981368) is a prospective, multicentre, multi-reader, open-label, phase 2/3 study assessing the diagnostic performance of 18F-DCFPyL-PET/CT for detecting sites of metastatic prostate cancer in 385 patients, assigned to 2 cohorts. Patients ≥18 years of age with histologically confirmed prostate adenocarcinoma were eligible. Cohort A included patients with high-risk PCa (clinical stage ≥T3a or PSA >20 ng/ml or Gleason score ≥8) who were planned for radical prostatectomy with PLND. Patients with prior ADT were excluded. Cohort B included patients with radiological evidence of local recurrence or metastatic disease on anatomical imaging or whole-body bone scintigraphy and in whom lesion(s) were amenable to biopsy:
  - In cohort A, 18F- DCFPyL-PET/CT had median specificity of 97.9% (95% CI, 94.5%-99.4%) and median sensitivity of 40.3% (28.1%-52.5%, not meeting prespecified endpoint). In cohort B, median sensitivity was 95.8% (87.8%-99.0%).
  - Patients-reported outcomes were not provided.
  - The ESMO-MCBS was not applicable because the primary endpoint could not be assessed.
  - Although baseline characteristics were heterogenous, the overall risk of bias was considered low.
- 3 ongoing phase 2/3 trials, evaluating 18F-DCFPyL PET/CT in prostate cancer diagnosis, were identified.
- According to EMA, the benefit of piflufolastat is supported by 3 clinical studies [1] which were not specified. Beside CONDOR and OSPREY trial, the third trial may be PYTHON (NCT04734184), a prospective phase 3 study on 18F-DCFPyL PET/CT imaging in biochemical recurrence of prostate cancer. Although the estimated study completion date has passed [14], there is no data available for this trial.
- In conclusion, further phase 3 data is required to substantiate the role of piflufolastat for the detection of PSMA-positive lesions with PET in adults with prostate cancer.

First published: 06/2023
Last updated: 09/2023

Abbreviations: ADT=androgen deprivation therapy, AE=adverse event, AJ=adjustment, AJCC=American Joint Committee on Cancer, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CLR= correct localization rate, CT=computerized tomography; EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GnRH=gonadotropin-releasing hormone, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, LHRH=luteinizing hormone-releasing hormone, MG=median gain, mpMRI=multi-parametric magnetic resonance imaging, MRI=magnetic resonance imaging; n=number of patients, NCCN=National Comprehensive Cancer Network, NICE=National Institute for Health Care Excellence, NPV=negative predictive value, OS=overall survival, PE=primary endpoint, PET=positron emission tomography, PFS=progression-free survival, PLND=pelvic lymph node dissection, PM=preliminary grade, PPV=positive predictive value, PSA=prostate specific antigen, PSMA=prostate specific membrane antigen, QoL=quality of life, SAE=serious adverse event, SOT=standard of truth, ST=standard treatment

References:

1. European Medicines Agency (EMA). Medicines. Pylclari. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/pylclari].
2. Statistik Austria. Krebserkrankungen. Ausgewählte Krebslokalisationen nach Inzidenz. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
3. Parker C, Castro E, Fizazi K, et al., on behalf of the ESMO Guidelines Committee. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol VOLUME 31, ISSUE 9, P1119-1134, SEPTEMBER 2020.

4. U.S. Food and Drug Administration (FDA). FDA approves second PSMA-targeted PET imaging drug for men with prostate cancer. [Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-second-psma-targeted-pet-imaging-drug-men-prostate-cancer].
5. U.S. Food and Drug Administration (FDA). Pylarify. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214793s000lbl.pdf].
6. European Medicines Agency (EMA). Pylclari: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/pylclari-epar-product-information_en.pdf].
7. U.S. National Library of Medicine, ClinicalTrials.gov. Study of 18F-DCFPyL PET/CT Imaging in Patients With Suspected Recurrence of Prostate Cancer (CONDOR). [Available from: https://clinicaltrials.gov/ct2/show/results/NCT03739684].
8. Morris MJ, Rowe SP, Gorin MA, et al., and CONDOR Study Group. Diagnostic Performance of 18F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res 2021;27:3674–82.
9. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].
10. Pienta KJ, Gorin MA, Rowe AP, et al., OSPREY Study Group. A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with 18F-DCFPyL in Prostate Cancer Patients (OSPREY). J Urol 2021 July ; 206(1): 52–61.
11. U.S. National Library of Medicine, ClinicalTrials.gov. Study of 18F-DCFPyL PET/CT Imaging in Patients With Prostate Cancer (OSPREY). [Available from: https://clinicaltrials.gov/ct2/show/NCT02981368].
12. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://clinicaltrials.gov/ct2/home].
13. Canada´s Drug and Health Technology Agency (CADTH). PET Diagnostic Imaging with Prostate-Specific Membrane Antigen for Prostate Cancer: A Review of Clinical Utility, Cost-Effectiveness, Diagnostic Accuracy, and Guidelines. [Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2020/RC1321%20PSMA%20for%20Prostate%20Cancer%20Final.pdf].
14. U.S. National Library of Medicine, ClinicalTrials.gov. A Prospective Study on 18F-DCFPyL PET/CT Imaging in Biochemical Recurrence of Prostate Cancer (Python). [Available from: https://clinicaltrials.gov/ct2/show/NCT04734184].