Title: OSPREY and CONDOR: Results from Two Registrational Clinical Studies Assessing the Diagnostic Performance of Piflufolastat F 18 (PYLARIFY®) PET/CT in Patients with High-Risk and Recurrent Prostate Cancer

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Introduction and overall goal: Piflufolastat F 18 (PYLARIFY; previously known as ^{18}F-DCFPyL) is a novel PSMA targeted radiotracer approved by the FDA for imaging men at risk for metastasis prior to initial treatment and for recurrence following prior therapy.[1] The overall goal of the OSPREY and CONDOR clinical trials was to determine the safety and diagnostic performance of piflufolastat F 18-PET/CT in the initial and recurrent disease setting, respectively.[2,3]

Specific aims: The primary objective of the OSPREY study (Cohort A) was determination of pelvic lymph node metastases with specificity and sensitivity at the patient level serving as co-primary endpoints. The primary objective of the CONDOR study was to determine the correct localization rate (CLR) defined as positive predictive value (PPV) with correct anatomic lesion co-localization between piflufolastat F 18 and a composite standard of truth in men with biochemical recurrence and uninformative conventional imaging.

Rationale and background: Non-PSMA PET based imaging modalities are considered inadequate for localizing and characterizing metastatic disease in prostate cancer patients that are high-risk prior to definitive therapy (RP and/or RT) or have biochemical recurrence, particularly early in patients with low PSAs (<2 ng/mL). Given the need for improved imaging agents to better inform treatment planning, a clinical development plan was implemented for piflufolastat F 18, a novel PET imaging agent that binds selectively with high affinity to PSMA.

Methods and materials: In OSPREY, piflufolastat F 18 was evaluated in men with high-risk prostate cancer who were planned for radical prostatectomy with lymphadenectomy (Cohort A, n=268). Specificity and sensitivity were determined for detecting metastases in pelvic lymph nodes with histopathology serving as the standard of truth; these results were then compared to conventional imaging. Cohort A provided 80% power to test the null hypotheses for specificity at 80% and for sensitivity at 40%. The CONDOR primary endpoint, CLR, was successfully met if the lower bound of the 95% confidence interval exceeded 20% for at least two of three independent, blinded central PET/CT reviewers. For both studies, 9 mCi (333 MBq) of piflufolastat F 18 was administered 1-2 hours prior to PET/CT; and three central, blinded, and independent readers evaluated the piflufolastat F 18 scans. Safety was a secondary objective for both studies.

Results: For OSPREY (n=252 evaluable), piflufolastat F 18-PET/CT demonstrated a sensitivity among the three readers ranging from 30.6-41.9% (lower bound of 95% CI: 19.2-29.7%), specificity of 96.3-98.9% (lower bound of 95% CI: 93.6-96.0%), and PPV and NPV ranging from 78.1-90.5% (lower bound of 95% CI: 63.8-69.9) and 81.4-83.8% (lower bound of 95% CI: 76.4-78.9%), respectively. When excluding patients with micrometastasis ≤5 mm, sensitivity improved to a range of 48.6-62.9% (lower bound of 95% CI: 32.0-46.9%) meeting both co-primary endpoints. For CONDOR, 208 men (median PSA 0.8 [0.2-98.4] ng/mL) underwent piflufolastat F 18-PET/CT. The study achieved its primary endpoint: CLR of 84.8% to 87.0% among three readers; the lower bound of 95% CI for CLR by all three reviewers was >77%. Based on local radiology assessment, PSMA-avid lesion(s) were identified in 69.2% (144/208) of patients. Additionally, 63.9% (131/205) had a change in intended management, the study's secondary endpoint, after piflufolastat F 18-PET/CT. Most frequently reported adverse reactions were headaches, dysgeusia and fatigue, occurring at rate of ≤2% between both clinical studies.

Discussion and conclusion: Piflufolastat F 18 demonstrated high PPV, NPV, and specificity as well as acceptable sensitivity for pelvic lymph node metastases in a high-risk prostate cancer cohort. In patients with biochemically recurrent prostate cancer and negative or equivocal imaging, piflufolastat F 18 demonstrated high CLRs and PPVs across three independent readers and led to substantial recommended changes in patient management. Piflufolastat F 18 was safe and well tolerated. ClinicalTrials.gov identifiers NCT02981368 and NCT03739684.

References:

1. PYLARIFY® [package insert]. North Billerica, MA: Progenics Pharmaceuticals, Inc., a Lantheus company
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3. Morris MJ, Rowe SP, Gorin MA, et al. 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;27:3674–3682.