Why We Did What We Did: PSMA-PET/CT Selection Criteria for the VISION Trial

Running short title: Origin of VISION Trial and PET Criteria

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Key words: theranostics, prostate cancer, PET, selection criteria, PSMA

Endocyte: A Phoenix Risen from the Ashes

Endocyte was founded in 1996 to develop small molecule drug conjugates (SMDCs) and imaging agents targeting the folate receptor¹. In 2012, Endocyte entered into a license agreement with Merck & Co for co-development of a folate-targeted theragnostic for women with platinum-resistant ovarian cancer. Two years later, Endocyte received a positive opinion for conditional marketing authorization from the Committee for Human Medicinal Products (CHMP) for the combination of the folate-targeted SMDC and a companion SPECT diagnostic for patient selection. Shortly after, Endocyte withdrew the conditional marketing authorization application, due to the Phase III trial failing the pre-defined futility analysis. During that same time, Endocyte expanded its portfolio to include PSMA-targeted theragnostics and initiated a Phase I trial investigating a PSMA-targeted SMDC and ^{99m}Tc-based PSMA-targeted SPECT tracer for prostate cancer².

While analyzing the failure of the folate-targeted theragnostic trial³, Endocyte restructured the organization and explored in-licensing opportunities. Leveraging the company's history with theragnostics and patient selection experience, along with the growing recognition of the potential of PSMA-targeted radioligand therapy (RLT), Endocyte announced the worldwide licensing agreement for [¹⁷⁷Lu]Lu-PSMA-617 with ABX GmbH in October 2017. The team then quickly worked to initiate the Phase 3 trial Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer (VISION). Endocyte decided to use [⁶⁸Ga]Ga-PSMA-11 PET/CT for patient selection and entered into a supply agreement with Telix to use their PSMA-11 kit for sites that did not have an active [⁶⁸Ga]Ga-PSMA-11 investigational new drug authorization. Less than a year after

acquisition of PSMA-617, the first patient was enrolled in the VISION study. Along with overall survival (OS), Endocyte negotiated with the Food and Drug Administration to have imaging-based progression free survival (PFS) as an alternate primary endpoint. In October 2018, Novartis announced its intent to acquire Endocyte which completed the story of Endocyte rising from the ashes. On March 23, 2021, Novartis announced the successful results of the VISION trial, approximately three and a half years after Endocyte's acquisition of the exclusive license for PSMA-617 ⁴.

Formulating the PSMA-PET Selection Criteria

The first decision was whether to even use imaging for patient selection. For example, if imaging only excluded less than 10% of patients, would it be worth the added effort, expense, and complexity to the trial? On the other hand, if selection were too restrictive, patients could be excluded who might otherwise benefit from [¹⁷⁷Lu]Lu-PSMA-617. After consulting with a variety of opinion leaders, a 10-20% exclusion rate by imaging was targeted as an optimal compromise between too restrictive and not restrictive enough which was achieved in the trial. At the time (and arguably still), there was not enough robust data in the public domain to inform a definitive exclusion rate and set expectations based on efficacy outcomes in this patient population using PSMA-PET. In addition to the complex task of maximizing the likelihood of successfully reaching efficacy endpoints, one must balance feasibility and thus reproducibility of the read criteria. Relating novel criteria to existing, familiar criteria may improve likelihood of successful implementation.

The next decision was either to utilize PSMA-PET alone or combine PSMA- and FDG-PET. At that time, the combination of PSMA- and FDG-PET had been advantageously utilized to evaluate for low PSMA uptake by PSMA-PET as well as discordant lesions by combining PSMA- and FDG-PET⁵. After careful consideration, it was decided to utilize PSMA-PET/CT in combination with the diagnostic CT, as adding FDG-PET presented potential operational complexity and cost in the execution of a large global clinical trial. However, when considering patients in a standard of care clinical setting, addition of FDG-PET/CT to improve patient selection could save money⁶. In a large global clinical trial setting, two scans versus one could increase variability in reads. Future issues with reimbursement of PET could occur with both FDG- and PSMA-PET, but PSMA-PET was considered more essential given the patent necessity for assessing PSMA-expression of tumors for this targeted therapy.

A definition for “PSMA-positive” and “PSMA-negative” was created specifically for this trial. In this context, the definition of “PSMA-positivity” was designed not to localize prostate cancer but to identify tumors with sufficient target expression which would likely respond to therapy. The use of an SUV (standardized uptake value) cut-off was not chosen for this global trial given the variability of SUV across clinical sites and known challenges of standardization/certification. Visual assessment against an appropriate internal reference was chosen. Blood pool was too low as a reference and using multiples of the blood pool would require measuring SUVs. Spleen was considered which often has high uptake and thus the possible advantage of a more stringent threshold. Preliminary evaluation of splenic uptake in PSMA-PET scans revealed there was too much variability (unpublished data). Finally, some patients might not have a

spleen which would preclude that as a universal reference organ. The commonly used Deauville criteria for FDG-PET for lymphoma uses the liver as a reproducible visual internal reference standard⁷. The team defined PSMA-positivity as “greater than liver” rather than “equal to or greater than liver” to provide more stringent selection. Given the prior Endocyte experience with grading levels of activity on folate-receptor imaging, a binary assessment of “PSMA-positivity or negativity” was chosen.

CT can be used to identify aggressive tumors which would then be assessed on the PET/CT for level of PSMA uptake. To aid with reproducibility, we used the familiar RECIST 1.1 criteria as a foundation. Assessment of anatomic imaging was divided into three systems: lymph node, solid organ, and skeleton. The need to identify and accurately measure lesions for determination of PSMA-status requires high-quality anatomic imaging and careful reads by imagers.

First, the lymph node category was addressed. The ALSYMPCA trial with radium-223 chloride included patients with lymphadenopathy up to 3 cm in short axis and showed benefit in overall survival could be achieved in patients with bone metastases without treating nodes up to 3 cm⁸. If a patient had extensive, non-nodal disease with intense uptake on PSMA-PET but “PSMA-negative” nodes, we surmised that patients would still likely benefit. Instead of a 3 cm threshold, 2.5 cm in short axis was ultimately used for greater stringency.

Next, the solid organ/parenchymal metastases were considered. Like the size criteria for target lesions in RECIST 1.1, only disease 1.0 cm in short axis or greater would be assessed for PSMA-status. The need to identify metastases down to 1.0 cm in short axis emphasizes the need for careful evaluation of the anatomic imaging, since a “PSMA-

negative” metastasis could be more difficult to identify on PET imaging. Unfortunately, at 1.0 cm in short axis, activity could be underestimated due to partial volume effect, but it would be critical to include metastases down to this size given the impact of parenchymal metastases on survival.

Finally, the skeletal system was particularly challenging. The patient population in the VISION trial would be previously treated with multiple therapies, so it would have been difficult to distinguish between healed, sclerotic metastases or active sclerotic disease on CT. Thus, focus on aggressive/destructive bone disease with a soft tissue component was pursued. Like the size criteria for target lesions in RECIST 1.1, the reader would only assess bone metastases with a soft tissue component 1.0 cm in short axis or greater, and only the soft tissue component would be assessed for level of activity.

The first step in the read criteria is assessing the PSMA-PET for at least one “PSMA-positive” lesion (of any size) to ensure presence of targetable disease (Fig. 1). The reader then evaluated the anatomic imaging for lesions that met size criteria for assessment of PSMA-status (Fig. 1). One or more “PSMA-negative” lesions resulted in exclusion (Figs. 1 and 2). The rationale was that one “PSMA-negative” lesion of adequate size for assessment could represent only a portion of the PSMA-negative disease reservoir that would not respond to PSMA-targeted therapy. This was also important for the imaging-based PFS endpoint. Theoretically, PSMA-positive disease would respond promptly after the initial cycles of [¹⁷⁷Lu]Lu-PSMA-617, but even one PSMA-negative lesion would continue to grow and therefore the sum of the diameters of the target lesions would increase to progression of disease soon after nadir. A major concern was potentially excluding good responders who have high uptake in many

lesions except one. Using cut-offs such as greater than 70%, 80%, or 90% of lesions positive were considered. Prior unpublished Endocyte experience with folate imaging demonstrated that this methodology adds significant variability and complexity to the read. Ultimately, the original exclusion criterion of one or more “PSMA-negative” lesions was maintained.

By synthesizing the knowledge of radiotherapeutic trials with prior experience in developing read criteria for theragnostics, novel imaging selection criteria saw their first use in the successful VISION trial. Future correlation with outcomes and advanced PSMA-PET analyses are needed to further refine these selection criteria to optimize patient care and management decision algorithms^{9,10}.

Acknowledgements: The authors would like to thank the entire Endocyte and Novartis teams for their contributions to the VISION trial.

Figure 1. Read methodology of the VISION trial for patient selection.

Figure 2: Example of a patient that would have been excluded by the imaging selection criteria used in the VISION trial. (A) Anterior maximum-intensity-projection from [^{68}Ga]Ga-PSMA-11 PET/CT has readily evident PSMA-positive disease, for example, in the sacrum (arrow); thus, the next step is to evaluate the diagnostic CT for lesions that fulfill size criteria for possible exclusion. (B) On contrast-enhanced diagnostic CT, a 1.8 cm metastasis is identified in the right hepatic lobe (arrow). Trans-axial low-dose CT (C), PET (D), and fused PET/CT (E) images show that the metastasis (arrows) has activity similar to normal liver, is therefore PSMA-negative, and would result in exclusion. Level of uptake in the hepatic metastasis was importantly confirmed in sagittal and coronal planes (not shown) in case of misregistration.

Disclosures:

P.H. Kuo is an employee of Invicro. He is a consultant and/or speaker for Amgen, Eisai, Endocyte, General Electric Healthcare, Novartis, Invicro, Bayer, Chimerix, Fusion Pharma, and UroToday. He is a recipient of research grants from Blue Earth Diagnostics and General Electric Healthcare.

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¹ Leamon CP, Low PS. Delivery of Macromolecules into Living Cells: A Method that Exploits Folate Receptor Endocytosis. *Proc. Natl. Acad. Sci. USA* 1991; 88:5572-76.

² Phase 1 study of EC1169 in patient with recurrent mCRPC NCT02202447

³ Study for Women with Platinum Resistant Ovarian Cancer Evaluating EC145 in Combination with Doxil®(PROCEED) NCT01170650

⁴ Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med* 2021; 385(12): 1091-1103.

⁵ Hofman MS, Violet J, Hicks RJ, et al. Lu-177-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): single center, single-arm, phase 2 study. *Lancet Oncol.* 2015; 19: 825-833.

⁶ Calais J, Czernin J. PSMA Expression Assessed by PET Imaging Is a Required Biomarker for Selecting Patients for Any PSMA-Targeted Therapy. *J Nuc Med* 2021; 62(11):1489-1491

⁷ Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. *Eur J Nucl Med Mol Imaging.* 2017; 44(suppl 1): 97-110.

⁸ Parker C, Nilsson S, Heinrich D, et al. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. *N Engl J Med* 2013; 369(3): 213-223.

⁹ Srinivas S, Iagaru A. To Scan or Not to Scan: An Unnecessary Dilemma for PSMA Radioligand Therapy. *J Nuc Med* 2021; 62(11): 1487-1488.

¹⁰ Herrmann K, Krause B J. Nuclear Medicine Theranostics Comes of Age. *Lancet Oncol* 2021; 22(11): 1497-1498.