Lilly A MEDICINE COMPANY

[Ac-225]-PSMA-62

RADIOLIGAND THERAPY

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyloxooncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

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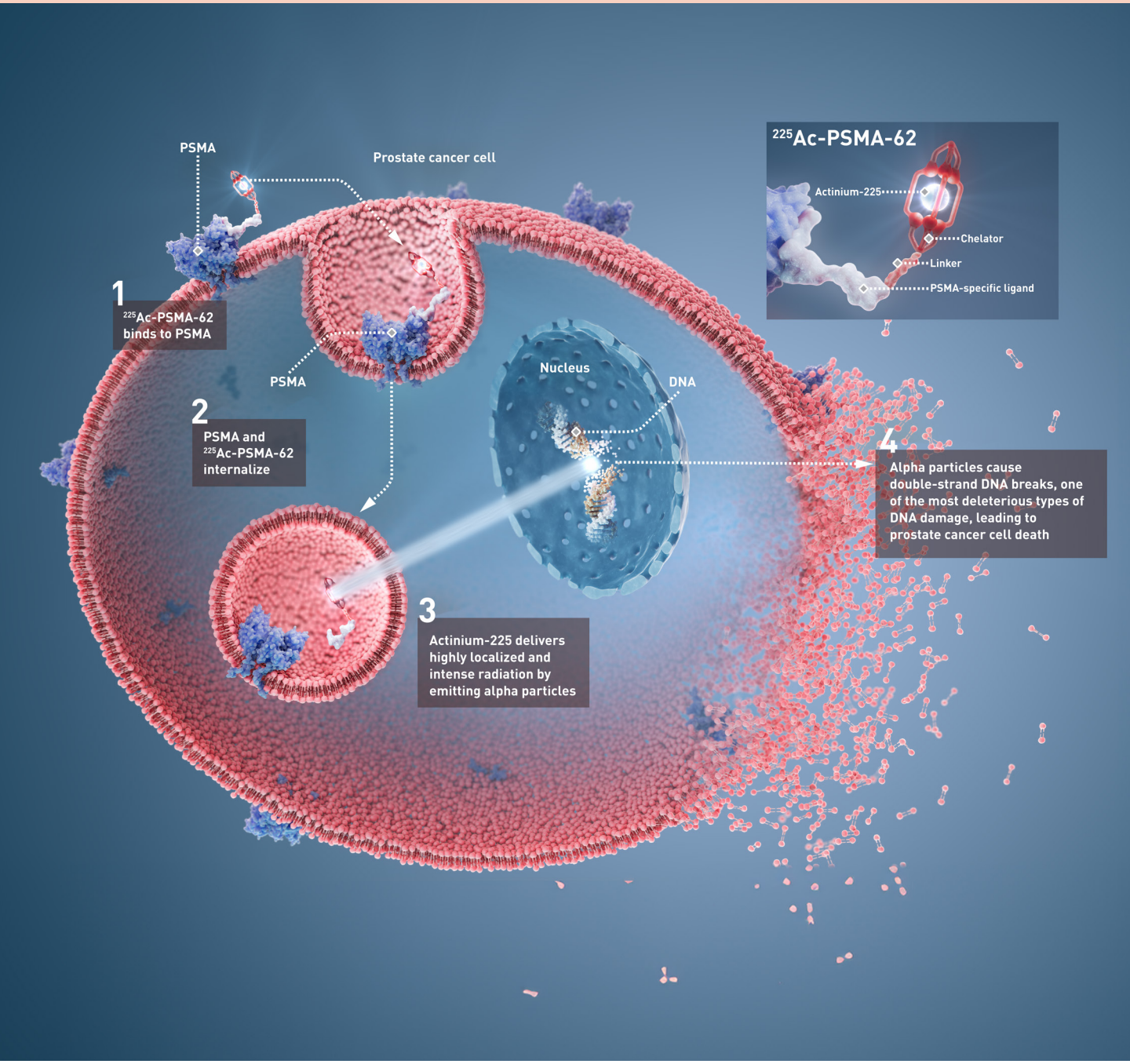

References: 1. Vito A, et al. *Eur J Nucl Med Mol Imaging*. 2022;49(suppl 1):S440:EP-039. **2.** Jang A, et al. *Ther Adv Med Oncol*. 2023;15:1-12. **3.** Pomykala KL, et al. *Ann Oncol*. 2023;34(6):507-519.

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TARGET

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein that is weakly expressed in normal prostate tissue but strongly upregulated in prostate cancer.[1] PSMA expression increases with higher Gleason scores and further increases in metastatic disease and when resistance to androgen therapy emerges.[2,3] Upon binding to its ligand, PSMA internalizes, thereby facilitating endocytosis and intracellular accumulation of PSMA-targeted compounds.[4]

MOLECULE

[Ac-225]-PSMA-62 is a next-generation PSMA-targeting radioligand comprised of the alpha-emitting radioisotope actinium-225, a chelating moiety, linker, and PSMA-62, a small peptide PSMA inhibitor. In nonclinical models, PSMA-62 showed high PSMA binding affinity, increased cellular internalization, and improved biodistribution, including high tumor retention and rapid renal clearance.[5]

CLINICAL DEVELOPMENT

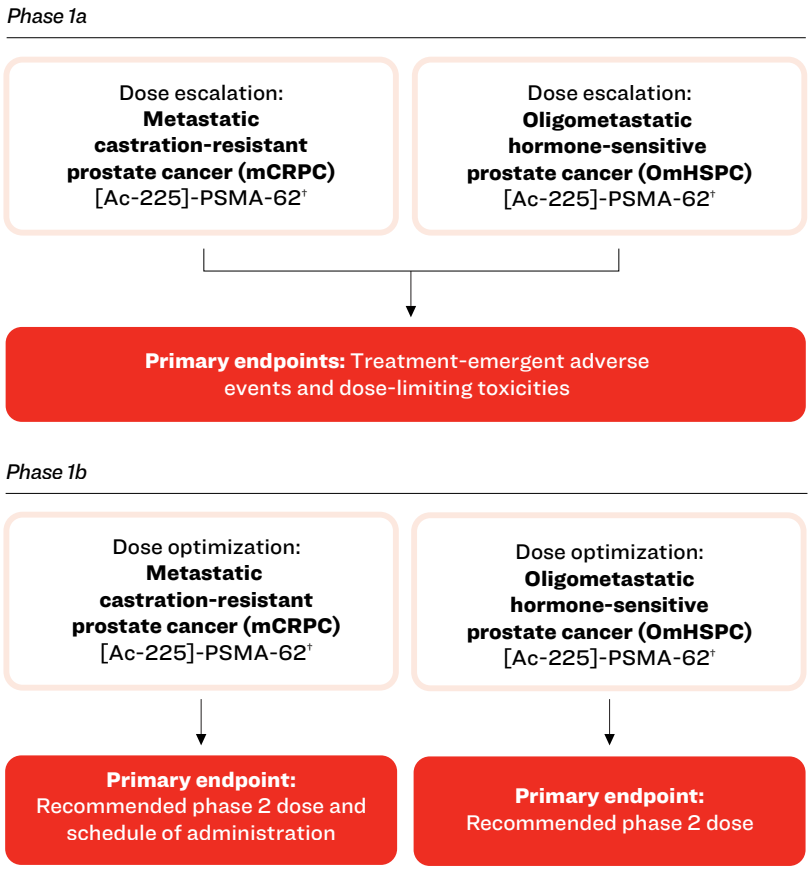
[Ac-225]-PSMA-62 is being studied in a phase I/II clinical trial for patients with metastatic castration-resistant prostate cancer (mCRPC) and patients with oligometastatic hormone-sensitive prostate cancer (OmHSPC).

References: 1. Silver DA, et al. *Clin Cancer Res*. 1997;3(1):81-85. **2.** Kasperzyk JL, et al. *Cancer Epidemiol Biomarkers Prev.* 2013;22(12):2354-2363. **3.** Meller B, et al. *EJNMMI Res.* 2015;5(1):66. **4.** Rajasekaran SA, et al. *Mol Biol Cell.* 2003;14(12):4835–4845. **5.** Vito A, et al. *Eur J Nucl Med Mol Imaging*. 2022;49(suppl 1):S440:EP-039.

[Ac-225]-PSMA-62 RADIOLIGAND THERAPY

ACCEL

[Ac-225]-PSMA-62 Phase I/II Clinical Trial to Characterize Efficacy, Safety, Tolerability, and Dosimetry in Oligometastatic Hormone-Sensitive and Metastatic Castration-Resistant Prostate Cancer*



* This clinical trial is currently being conducted in Canada.
† [Ac-225]-PSMA-62 is administered intravenously.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06229366].

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[Ac-225]-PSMA-62 Phase I/II Clinical Trial to Characterize Efficacy, Safety, Tolerability, and Dosimetry in Oligometastatic Hormone-Sensitive and Metastatic Castration-Resistant Prostate Cancer

KEY INCLUSION CRITERIA

- Histological, pathological, and/or cytological confirmation of adenocarcinoma of the prostate
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- Criteria specific for patients with metastatic castration-resistant prostate cancer (mCRPC):
  - Previously received:
    - An androgen receptor pathway inhibitor (ARPI)
    - Taxane-based chemotherapy, or was deemed ineligible for taxane by the investigator, or refused taxane
    - A maximum of 3 prior systemic therapy regimens in the mCRPC setting
  - Progressive mCRPC at the time of consent based on at least 1 of the following criteria being met in the context of castrate levels of testosterone:
    - Prostate-specific antigen (PSA) progression defined as rising PSA values at a minimum of 1-week intervals, with the last result being at least 1.0 ng/mL
    - Soft tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions
    - Progression of bone disease defined as the appearance of two or more new lesions by bone scan
  - At least one prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) positive lesion for prostate cancer
- Criteria specific for patients with oligometastatic hormone-sensitive prostate cancer (OmHSPC):
  - PSA recurrence after radical prostatectomy (RP) or definitive radiation therapy (RT), with or without adjuvant/salvage local therapy (radiation or surgery), with or without (neo)adjuvant androgen deprivation therapy (ADT)
    - PSA must be ≥0.2 ng/mL for patients with prior RP ± RT, or
    - PSA must be ≥2 ng/mL above nadir for patients with only prior RT
  - 1-5 positive lesions identified outside the prostate bed or remaining gland

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KEY EXCLUSION CRITERIA

- Patients receiving medications that are known to cause xerostomia or xerophthalmia (eg, darifenacin) are excluded if they are not on stable doses for at least 4 weeks prior to screening
- Existing grade 1 dry mouth (xerostomia) or symptomatic grade 1 dry eye (xerophthalmia) for any reason
- Criteria specific for patients with mCRPC:
  - Patient has received any PSMA-directed radioligand therapy (eg, [Lu-177]-PSMA-617, [Lu-177]-PNT2002, [Ac-225]-J591)
  - Patient has received any therapeutic systemic radionuclides (eg, radium-223, rhenium-186, strontium-89) or non-PSMA-directed therapeutic radioligands (eg, Lu-177-Dotatate) within 5 half-lives of starting the study treatment
- Criteria specific for patients with OmHSPC:
  - Patient has received any systemic anticancer therapy for prostate cancer with the exception of (neo)adjuvant ADT for management of localized disease
  - Presence of liver or central nervous system (CNS) metastases

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06229366].

Pipeline information is current through July 2024.