cERianna™
(FLUOROESTRADIOL F 18) INJECTION

Seeing deeper into recurrent or metastatic breast cancer

Helping clinicians detect whole-body ER+ lesion status to better inform clinical decisions

INDICATIONS AND USAGE

CERIANNA is indicated for use with positron emission tomography (PET) imaging for the detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

Limitations of Use

Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. CERIANNA is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR).

CONTRAINDICATIONS

None.

ADVERSE REACTIONS

In Clinical Trials (n=1207) the most common adverse reactions seen occurred at a rate <1%: were injection-site pain and dysgeusia.

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Important Safety Information

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CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Risk of Misdiagnosis

Inadequate Tumor Characterization and Other ER-Positive Pathology: Breast cancer may be heterogeneous within patients and across time. CERIANNA images ER and is not useful for imaging other receptors such as HER2 and PR. The uptake of fluoroestradiol F18 is not specific for breast cancer and may occur in a variety of ER-positive tumors that arise outside of the breast, including from the uterus and ovaries. Do not use CERIANNA in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer.

False Negative CERIANNA Scan: A negative CERIANNA scan does not rule out ER-positive breast cancer. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative CERIANNA scan.

Radiation Risks

Diagnostic radiopharmaceuticals, including CERIANNA, expose patients to radiation. Radiation exposure is associated with a dose-dependent increased risk of cancer. Ensure safe drug handling and patient preparation procedures (including adequate hydration and voiding) to protect patients and health care providers from unintentional radiation exposure.

Pregnancy Status

Assessment of pregnancy status is recommended in females of reproductive potential before administering CERIANNA.

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USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary

All radiopharmaceuticals, including CERIANNA, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of radiation dose. Advise a pregnant woman of the potential risks of fetal exposure to radiation from administration of CERIANNA.

There are no available data on CERIANNA use in pregnant women. No animal reproduction studies using fluoroestradiol F18 have been conducted to evaluate its effect on female reproduction and embryo-fetal development.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Lactation Risk Summary

There are no data on the presence of fluoroestradiol F18 in human milk, or its effects on the breastfed infant or milk production. Lactation studies have not been conducted in animals. Advise a lactating woman to avoid breastfeeding for 4 hours after CERIANNA administration in order to minimize radiation exposure to a breastfed infant.

Pediatric Use

The safety and effectiveness of CERIANNA in pediatric patients have not been established.

Geriatric Use

Clinical studies of fluoroestradiol F18 injection did not reveal any difference in pharmacokinetics or biodistribution in patients aged 65 and over.

DRUG INTERACTIONS

Systemic Endocrine Therapies that Target Estrogen Receptors

Certain classes of systemic endocrine therapies, including ER modulators and ER down-regulators, block ER, reduce the uptake of fluoroestradiol F18, and may reduce detection of ER-positive lesions after administration of CERIANNA. Drugs from these classes such as tamoxifen and fulvestrant may block ER for up to 8 and 28 weeks, respectively. Do not delay indicated therapy in order to administer CERIANNA. Administer CERIANNA prior to starting systemic endocrine therapies that block ER.

To report SUSPECTED ADVERSE REACTIONS, contact Zionexa US Corp, a GE Healthcare Company, at +1.800.654.0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Role of ER in breast cancer

Breast Cancer Heterogeneity

Breast cancer (BC) is a complex disease characterized by considerable heterogeneity at both the tumor and molecular levels.[1-4] This heterogeneity harbors divergent tumor biological behaviors and emerges as diverse molecular subtypes of BC, with potentially different treatment sensitivities or mixed responses to therapy.[3,4] One of the most common molecular subtypes is ER-positive (ER+) BC.[4] An estimated 70% to 75% of primary breast tumors initially express the ER at diagnosis and start out as estrogen dependent.[5-9]

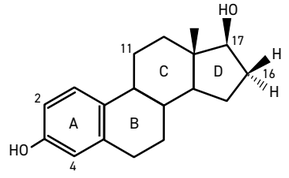
Importance of Estrogen Receptor

Breast Cancer Proliferation

The ER and endogenous estrogen play important roles in regulating growth and differentiation of normal breast epithelium as well as in the development and progression of BC.[9-11] The biological effects of estrogen are primarily mediated by estradiol binding to one of the structurally and functionally distinct ER subtypes (ERα and ERβ).[6,9] These subtypes are encoded by different genes (*ESR1 and ESR2*).[6]

Upon the binding of estradiol to ER, the ligand-activated receptors trigger a cascade of complex biological processes and ER-mediated signals involving coregulatory proteins, genomic actions, and extranuclear actions, which ultimately stimulate the transcription of estrogen-responsive genes.[6,9,12,13] Alterations in these biological processes (e.g., genetic dysfunction of coregulatory proteins) can contribute to a pathologic outcome by modulating ER-mediated signals, which has potential to drive BC cell proliferation, promote BC cell migration, and mediate metastasis.[9,14] As an example, metastatic tumor antigen 1 (MTA1) is a commonly deregulated coregulator protein in BC that promotes transcriptional repression of the ER, leading to BC cell growth and metastatic progression.[9,14,15]

Image 1. Molecular Structure of Estradiol[6]



The 17β-estradiol structure consists of four cycloalkane rings and two hydroxyl groups. The numbers indicate commonly used positions for substituents.[6]

Response to Therapy

The ER-mediated signals are potential targets for BC treatments, especially endocrine therapy (ET) that targets either estradiol production or ER function.[9] In clinical practice, ER status (i.e., positive or negative) of the primary breast tumor is routinely used as a prognosis indicator and a predictor of treatment response to ET, allowing clinicians to identify patients who will likely benefit from or otherwise may be resistant to ET.[7,10,16,17] Predicting response to ET is important both to spare non-responders from the side effects that come along with treatment and to minimize the overall cost by only treating patients that have a good chance to respond.[2]

Because a majority of primary breast tumors are ER+ and most metastatic lesions retain their original ER expression,[1,9,18] a large portion of patients with BC are *predicted* to respond positively to ET, including many treated for metastatic breast cancer (MBC).[9] Clinical practice guidelines from professional oncology organizations, such as the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO), recommend ET for treatment of BC with any degree of ER positivity.[19-22] Unfortunately, not all patients respond to first-line ET (i.e., *de novo* resistance), and even some patients who have an initial response will eventually relapse (i.e., acquired resistance).[5,7,23-27] One factor most prominently contributing to unpredictable initial response and acquired resistance to ET is lack or loss of ER expression and/or ER expression discordance.[1,5,7,12,13]

There is unequivocal evidence that ET effectiveness relies on sufficient and functional ER expression in BC lesions,[8,26-29] which is why regularly determining whole-body ER status in metastatic disease is critical

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Importance of ER discordance

ER expression may be discordant between BC lesions (i.e., inter-tumor discordance) and may change over time in the same patient (i.e., temporal discordance)[7,8,30]

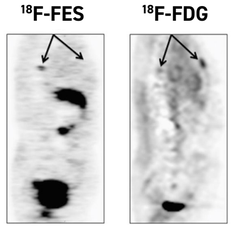
Discordant ER expression between the primary tumor and metastatic lesions occurs in up to 30% of patients with MBC[7,17,30-32]

- Patients with ER+ primary BC at diagnosis may eventually present with ER- metastases,[1,8,30] demonstrating molecular phenoconversions in ER status between primary tumors and metastatic lesions[1]
- These phenoconversions may occur naturally (e.g., genetic or epigenetic loss of the receptor) or following treatment with ET (e.g., clonal selection of ER- cells or receptor down-regulation)[5,7,11,12,17,23,33]
- Considering these findings, clinical practice guidelines recommend re-biopsy, at least once, during recurrent or metastatic BC to reassess ER status,[21,22,34] preferably using validated immunohistochemistry (IHC) analysis of large core biopsies[28]
- Despite clear indications, re-biopsy in advanced disease may not always be feasible because of the characteristics of the lesion (e.g., location) or the patient (e.g., comorbidity), and IHC analysis may be hampered by technical difficulties (e.g., decalcification with bone lesions, inadequate sample yield)[7,8,16,19,30,35-37]

~15-20% **of patients may eventually need a therapy change due to a switch in ER status between the primary tumor and metastatic lesions[17,19,36,38]**

In some patients with BC, the progression to the ER- phenotype might not be permanent or could be reversible, which has implications for possibly restoring endocrine sensitivity and responsiveness to ET in recurrent or metastatic disease[24,33,39-41]

Image 2. Inter-Tumor ER Discordance: Patient with MBC with Concurrent ER+ and ER- Lesions[5*]

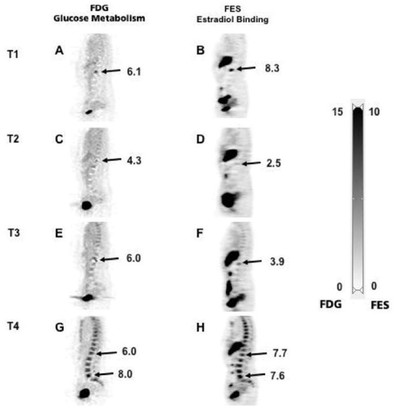


*FDG = ^{18}F-fluorodeoxyglucose, FES = F18 fluoroestradiol.

Because levels of ER expression may be heterogenous within the same patient, biopsy of a single tumor site may not be representative of ER expression of the tumor burden as a whole[5,7,8,30,35]

Torso survey images (sagittal view) from a 52-year-old patient with MBC from an ER+ (PR+ and HER2-) primary histology. A spinal lesion was visible on both F18 fluoroestradiol PET and FDG PET images and a sternal lesion was visible on FDG PET image but not on F18 fluoroestradiol PET image, indicating mixed F18 fluoroestradiol uptake.[5]

Image 3. Temporal ER Discordance: Case of ER Phenoconversion and Restored Sensitivity to ET in a Patient with Bone-Dominant MBC[33]



Measuring temporal changes in ER expression requires serial biopsies, which are impractical and poorly tolerated by most patients[33]

A case report of a 45-year-old woman with bone-dominant MBC from a historically ER+ primary tumor who underwent serial, observational molecular imaging over the course of several treatments. A bone biopsy was not performed because of a lack of an accessible non-bone site of metastasis and patient refusal. Images of FDG and F18 fluoroestradiol PET scans shown side by side to illustrate the temporal changes in tracer uptake at four time points, with corresponding standardized uptake values listed. T1 indicated before initiation of ET; T2 indicated after response to ET; T3 indicated at subsequent disease progression on ET; and T4 indicated at disease progression on chemotherapy, before initiation of diethylstilbestrol (DES).[33]

At T1, the arrow showed spinal metastasis at L1 with strong uptake at initial metastatic presentation by FDG PET (A) and F18 fluoroestradiol PET (B). The patient experienced response to ET, as shown in T2, with a notable decrease in FDG uptake (C) and F18 fluoroestradiol uptake (D). The tumor then progressed on anastrozole, shown in T3, with increasing FDG uptake (E) but less prominent F18 fluoroestradiol uptake (F) compared with baseline. Her disease then responded to chemotherapy clinically (with a decrease in pain and a decline in tumor markers), but eventually progressed on chemotherapy, as shown in T4, with the emergence of diffuse spinal metastasis, as shown in two representative lesions by FDG PET (G) and F18 fluoroestradiol PET (H). The latter indicated an increase in the tumor's capability to bind estradiol at the time of disease progression on chemotherapy, suggesting increased ER expression. The patient subsequently experienced response to salvage ET with DES.[33]

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Key Take-Away Messages

- ER status is one of the most powerful predictive biomarkers in BC, especially for helping clinicians predict response to ET
- Historically, assessment of ER status has been carried out on the primary breast tumor, assuming no change in biological features or receptor expressions of the recurrent or metastatic disease compared with the original primary
- This approach is no longer considered tenable given the mounting evidence proving that ER expression may be discordant between BC lesions and may change over time in the same patient
- Given the plasticity of endocrine-resistant BC, treatment strategies should be based on the phenotype of the tumor at relapse rather than at diagnosis
- Clinicians who continue to treat patients according to ER status of the primary breast tumor may potentially be misidentifying patients with recurrent or metastatic BC who are appropriate (or not appropriate) for ET, leading to suboptimal treatment
- There is an unmet need for alternative approaches to clarify the full extent of ER expression in recurrent or metastatic BC to help inform clinical decisions

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References: 1. Aitken SJ, Thomas JS, Langdon SP, Harrison DJ, Faratian D. Quantitative analysis of changes in ER, PR and HER2 expression in primary breast cancer and paired nodal metastases. *Ann Oncol.* 2010;21(6):1254-1261. **2.** Russnes HG, Navin N, Hicks J, Borresen-Dale AL. Insight into the heterogeneity of breast cancer through next-generation sequencing. *J Clin Invest.* 2011;121(10):3810-3818. **3.** Fisher R, Pusztai L, Swanton C. Cancer heterogeneity: implications for targeted therapeutics. *Br J Cancer.* 2013;108(3):479-485. **4.** Tang J, Cui Q, Zhang D, Liao X, Zhu J, Wu G. An estrogen receptor (ER)-related signature in predicting prognosis of ER-positive breast cancer following endocrine treatment. *J Cell Mol Med.* 2019;23(8):4980-4990. **5.** Kurland BF, Peterson LM, Lee JH, Linden HM, Schubert EK, Dunnwald LK, et al. 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