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REVIEW ON FDA APPROVED NEW DRUGS ON ONCOLOGY

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ABSTRACT

Cancer remains the second leading cause of death globally. The number of new medicines targeting cancer has grown impressively since the 1990s. On average, ten new drugs are introduced each year. Such growth has partly been achieved by emphasizing biologics and orphan indications, which account for one-quarter and one-half of new oncology drugs, respectively.The new drugs approved by FDA on oncology were Erleada (apalutamide) and Lutathera (lutetium Lu 177 dotatate).The objective was to compare FDA approved new drugs for Oncology. Erleada is the first FDA approved therapy to treat patients with Non-metastatic castration-resistant prostate cancer. Lutathera is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors. The study compared the characteristics of new human drugs approved by the FDA. The study included the mechanism, doses, Route of administration and other characters of the drug. Many of these drugs contain the active moiety which were not previously approved by the FDA, either as a single ingredient drug or as part of a combination product; these products frequently provide important therapies for patient .The availability of the new drugs and biological products often means new treatment options for patients and for advances in health care.

KEYWORDS: Cancer, Erleada, Lutathera, Therapy.

INTRODUCTION

1.Prostate cancer

Prostate cancer is currently the most frequently diagnosed cancer in men, and the third leading cause of male cancer death, in developed countries. There is an observable increasing

trend in the incidence of prostate cancer worldwide, in the context of increasing use of prostate specific antigen (PSA) testing. However, mortality rates for prostate cancer have fallen in developed countries, and this has been attributed to improved treatment and earlier detection.

Prostate cancer that is detected early is usually treated with local therapy, mainly surgery or radiotherapy.

Metastatic prostate cancers progress to castration resistant disease within two years of follow-up. Metastatic castrate resistant prostate cancer (mCRPC) is broadly defined as disease progression despite established androgen depletion therapy; signs and symptoms of progression include sequential PSA rises, progression of pre-existing disease, and/or the appearance of new metastases evident on imaging (CT, MRI or radionuclide bone scintigraphy).

1a.Treatment options for Metastatic castration-resistant disease

Treatment for mCRPC aims to 'control' rather than 'cure' the disease. Prior to the introduction of novel androgen receptor targeted therapies, chemotherapy was the mainstay of treatment for mCRPC. Chemotherapy acts to interrupt cell division (mitosis), which results in decreased cancer cell proliferation. Those most commonly used in prostate cancer(taxanes) do this by inhibiting microtubule disassembly, an important step in chromosomal replication during the M phase of the cell-cycle.

Androgen receptor antagonists and androgen synthesis inhibitors are the mainstay of androgen receptor targeted therapies. The first generation AR antagonist was flutamide followed by second-generation bicalutamide and nilutamide. Bicalutamide, a derivative of flutamide, remains the most commonly used AR antagonist, but more recent attention has focussed on third-generation AR antagonist enzalutamide. First and second-generation AR antagonists, though developed to inhibit AR function, were later found to provide incomplete inhibition due to partial or weak AR co-activator and agonist actions. Bicalutamide is usually administered at 50 mg daily, with studies having shown similar responses with this lower dose when compared to higher doses of 200 mg daily and 150 mg daily.

Abiraterone and enzalutamide, the most recently licenced hormone agents. Both have been approved as oral agents for mCRPC having been shown to improve overall survival in men with disease progression.

Table 1: Summary of mechanism of action, side effects, and contraindications for recently approved anti-androgen oral agents for mCRPC.

Drug	Mode of administration	Mechanism of action	Side effect profile	Contraindications
Abiraterone acetate	Oral	Inhibits androgen synthesis via CYP-17	Hepatotoxicity, hypokalaemia, hypertension, gastrointestinal upset	Severe liver dysfunction, hypokalaemia, heart failure
Enzalutamide	Oral	Inhibits AR and AR translocation	Seizures, encephalopathy, hypertension, fatigue, Ggastrointestinal upset	Seizures

1b. ENZALUTAMIDE

Mechanism of action of enzalutamide: Enzalutamide has high affinity for the androgen receptor (AR) and does not promote translocation of the AR to the nucleus and its binding to DNA, thus leading to tumour death.

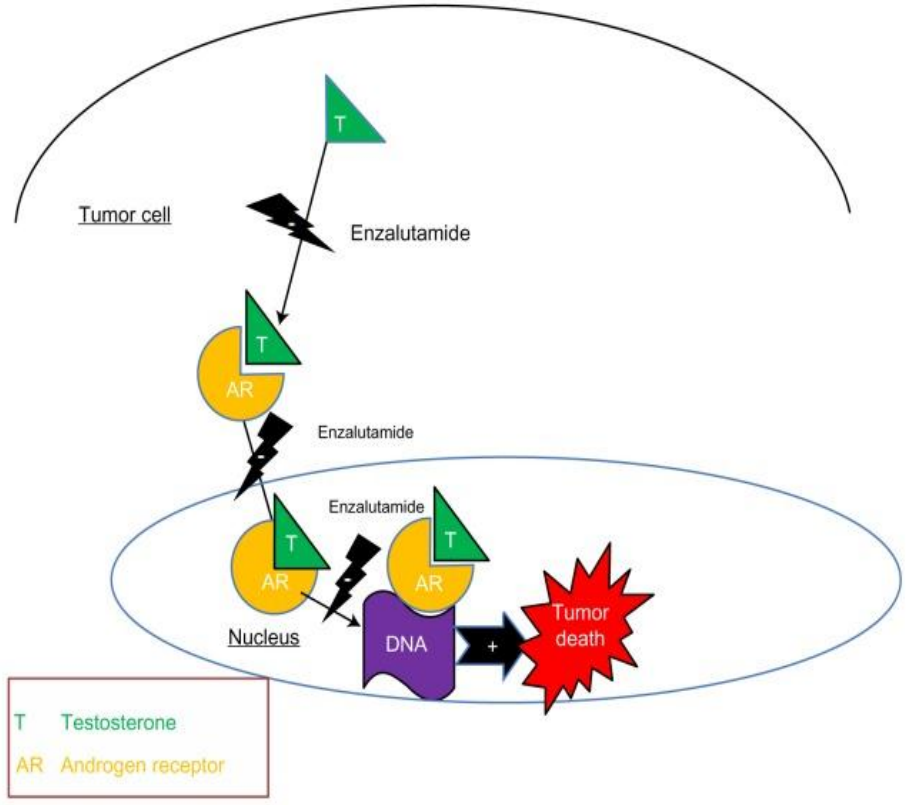


Fig. 1: Mechanism of action of enzalutamide.

Uses

Enzalutamide is used for the treatment, control, prevention, & improvement of Prostate cancer.

Enzalutamide Side-effects

These side-effects are possible, but do not always occur.

a)Weakness

b)Tiredness

c)Joint pain

d)Muscle weakness or stiffness

e)Headache

f)Dizziness

g)Burning, numbness, or tingling in the arms, hands, or feet

h)Decreased sense of touch or ability to feel sensation

i)Difficulty falling asleep

j)Anxiety

1c. ERLEADA (apalutamide)

ERLEADA is the first FDA-approved therapy to treat patients with non-metastatic castration-resistant prostate cancer.

Approval is based on Phase 3 SPARTAN clinical trial data which showed ERLEADA decreased the risk of distant metastasis or death by 72 percent and improved median metastasis-free survival by more than two years.

The major efficacy outcome was supported by statistically significant improvements for secondary endpoints, including time to metastasis, progression-free survival, and time to symptomatic progression.

Mechanism: ERLEADA is an AR inhibitor that binds directly to the ligand-binding domain of the AR. ERLEADA inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription. A major metabolite, N-desmethyl apalutamide, is a less potent inhibitor of AR, and exhibited one-third the activity of ERLEADA in an in vitro transcriptional reporter assay.ERLEADA administration caused decreased tumor cell

proliferation and increased apoptosis leading to decreased tumor volume in mouse xenograft models of prostate cancer.

Absorption

Oral bioavailability: 100%

Peak plasma time: 2 hr; delayed by ~2 hr with food

Peak plasma concentration: 6 mcg/mL; 5.9 mcg/mL (active metabolite)

AUC: 100 mcg·h/mL; 124 mcg·h/mL (active metabolite)

Steady-state achieved: 4 weeks

Distribution

Protein bound: 96% (apalutamide); 95% (N-desmethyl apalutamide)

Vd: ~276 L.

Metabolism

Metabolism is the main route of elimination

Primarily metabolized by CYP2C8 and CYP3A4 to form active metabolite, N-desmethyl apalutamide

The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose, but changes to 40% and 37%, respectively, at steady-state

Apalutamide represented 45% and N-desmethyl apalutamide represented 44% of the total AUC following a single oral dose.

Elimination

Half-life: 3 days

CL/F: 1.3 L/hr (single dose); 2 L/hr (steady-state)

Excretion: 65% urine; 24% feces

Administration

- **Oral Administration**

May take with or without food

Swallow tablets whole; do not chew, crush, or split

Storage

Store at controlled room temperature (20-25°C [68-77°F]); excursions permitted to 15-30°C (59-86°F)

Store in the original package

Do not discard desiccant

Protect from light and moisture

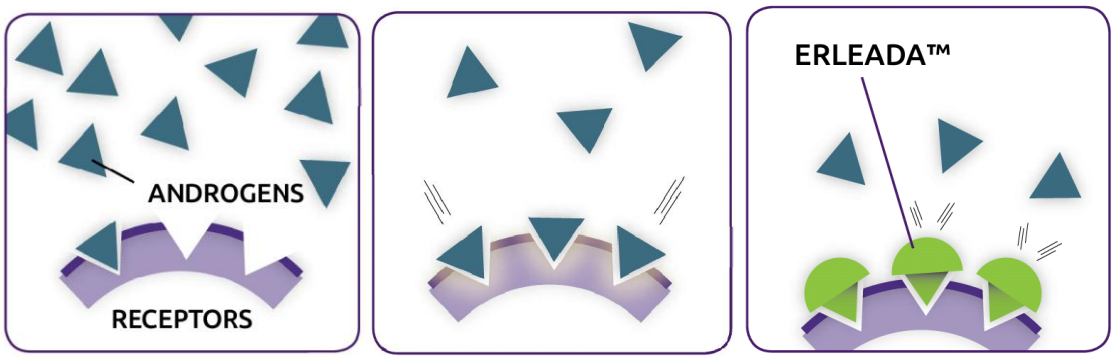
How ERLEADA™ (apalutamide) + ADT(androgen deprivation therapy) works

- Androgens can fuel cancer growth.
- Androgens are male hormones, primarilyυ testosterone, that are needed for the prostate to function normally.
- However, when androgens attach toυ androgen receptors, they can help fuel prostate cancer cell growth. ERLEADA works differently than ADT. ERLEADA blocks androgens from attachingυ to receptors to help prevent cancer cells from growing.

The goal of ADT is to lower testosterone levels, but in certain cases, the cancer adapts.

- Medical or surgical treatments that lowerυ testosterone are also referred to as androgen deprivation therapy (ADT). ADT includes treatment to suppress or block the production or action of male hormones called androgens, primarily testosterone.
- While ADT is often effective, in certainυ men prostate cancer adapts to low levels of androgens.

Erleada blocks the androgen fuel from reaching the receptors to slow cancer cells from growing. Erleada keep cancer cells growing. Erleada blocks the androgen fuel from reaching the receptors to slow cancer cells from growing. Androgens receptor erleada, an androgen receptor inhibitor, is the first prescription medicine approved for men with nmCRPC.



ERLEADA received FDA approval based on the Phase 3 data from the SPARTAN clinical trial, which assessed the efficacy and safety of Erleada versus placebo in patients with NM-CRPC who had a rapidly rising PSA while receiving continuous androgen deprivation therapy.

SPARTAN, a Phase 3, randomized, double-blind, placebo-controlled, multi-center study, enrolled 1, 207 patients with non-metastatic castration-resistant prostate cancer. Patients were randomized 2:1 to receive either Erleada orally at a dose of 240 mg once daily (n=806), or placebo once daily (n=401).All patients in the SPARTAN trial received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy.

Dosage Forms & Strengths

Tablet-60mg

Indicated for nonmetastatic, castration-resistant prostate cancer (NM-CRPC)

240 mg (ie, four 60-mg tablets) PO.

Dosage Modifications

≥Grade 3 toxicity or intolerable adverse effect

1)Hold dosing until symptoms improve to ≤Grade 1 or original grade, THEN

2)Resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted

Dosing Considerations

Patients receiving antiandrogens (eg, apalutamide) should also receive a gonadotropin-releasing hormone (GnRH) analog (eg, leuprolide, triptorelin, goserelin, histrelin) concurrently or should have had a bilateral orchiectomy.

CONTRAINDICATIONS

Pregnancy - ERLEADA can cause fetal harm and potential loss of pregnancy.

WARNINGS AND PRECAUTIONS

Falls and Fractures - In the SPARTAN study, falls and fractures occurred in 16% and 12% of patients treated with ERLEADA compared to 9% and 7% treated with placebo respectively. Falls were not associated with loss of consciousness or seizure. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

Seizure - In a randomized study (SPARTAN), two patients (0.2%) treated with ERLEADA™ experienced a seizure. Permanently discontinue Erleada in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with Erleada. Advise patients of the risk of developing a seizure while receiving Erleada and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

ADVERSE REACTIONS:- The most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema.

LABORATORY ABNORMALITIES

Hematology: anemia, leukopenia, lymphopenia, hypercholesterolemia, hypertriglycemia, hypertriglyceridemia, Hyperkalemia.

Rash: Rash was most commonly described as macular or maculo-papular. Adverse reactions were 24% .Grade 3 rashes (defined as covering > 30% body surface area [BSA]).

The onset of rash occurred at a median of 82 days. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four (4%) of patients treated with ERLEADA received systemic corticosteroids. Rash recurred in approximately half of patients who were re-challenged with ERLEADA.

Hypothyroidism: Hypothyroidism was reported for 8% of patients treated with ERLEADA™ based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

2: Neuroendocrine Tumors

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs), also known as carcinoids and islet cell tumors, are tumors derived from neuroendocrine cells that can occur anywhere along the gastrointestinal tract and comprise a heterogeneous family of neoplasms with a wide and complex spectrum of clinical behavior. These tumors have been considered rare diseases.

GEP-NETs are more prevalent than many other tumors of the gastrointestinal tract, including stomach and pancreatic carcinomas combined. Age at diagnosis is generally younger than for carcinomas (5th decade) and they may arise sporadically or as a result of hereditary predisposition syndromes such as multiple endocrine neoplasia type 1, Von Hippel-Lindau's disease or neurofibromatosis type 1.

GEP-NET	Secretion product	Clinical symptoms/ syndrome
Functional carcinoid	Serotonin	Carcinoid syndrome (flushing, diarrhea and heart disease)
Gastrinoma	Gastrin	Zollinger–Ellison syndrome (acid hypersecretion, dudoenal ulceration, esophagitis and diarrhea)
Insulinoma	Insulin	Hypoglicemia
Glucagonoma	Glucagon	Diabetes and necrolytic migratory erythema
VIPoma	VIP	Verner-Morrison or WDHA syndrome (watery diarrhea-hypokalemiaachlorhydria)

GEPNETs, gastroenteropancreatic neuroendocrine tumors; VIP, vasoactive intestinal peptide

2a.Lutathera (lutetium Lu 177 dotatate)

Lutathera (lutetium Lu 177 dotatate) is a radiolabeled somatostatin analog.

Lutathera is specifically indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors in adults.

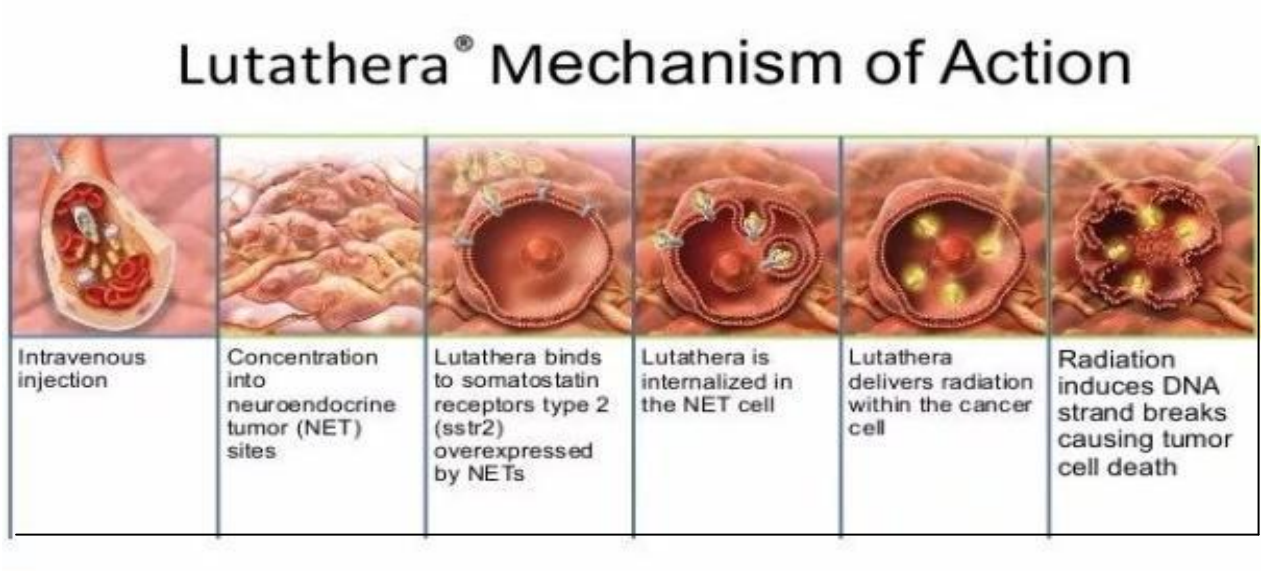
Pharmacology

Mechanism of Action

Radiolabeled somatostatin analog; binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2).

Upon binding to somatostatin receptor-expressing cells, including malignant somatostatin receptor-positive tumors, the compound is internalized.

Beta emission from Lu 177 induces cellular damage by forming free radicals in somatostatin receptor-positive cells and in neighboring cells.



Absorption

Peak plasma concentration: 10 ng/mL (mean) at end of IV infusion

AUC: 41 n·gh/mL (mean).

Distribution

Protein bound: 43%

Vd: 640 L; within 4 hr drug is distributed in kidneys, tumor lesions, liver, spleen, and in some patients, pituitary and thyroid glands.

Coadministration of amino acids reduces median radiation dose to the kidneys by 47% (34-59%) and increases mean beta-phase blood clearance by 36%.

Metabolism

Does not undergo hepatic metabolism

Elimination

Half-life, blood elimination: 3.5 hr

Half-life, terminal: 71 hr

Clearance: 4.5 L/hr

Excretion

Primarily eliminated renally

44% within 5 hr after dose

58% within 24 hr after dose

65% within 48 hr after dose.

Dosage Forms & Strengths

Injection, solution for IV use

370 MBq/mL (10 mCi/mL) single-dose vial

Solution volume in each vial adjusted from 20.5-25 mL to provide a total of 7.4 GBq (200 mCi) of radioactivity per vial.

Premedication and concomitant medications

Somatostatin analogs

1)Before initiating lutetium Lu 177-dota-tate: Discontinue long-acting somatostatin analogs (eg, long-acting octreotide) for at least 4 weeks beforehand; administer short-acting octreotide as needed; discontinue at least 24 hr before initiating lutetium Lu 177-dota-tate.

2)During treatment: Administer long-acting octreotide 30 mg IM between 4-24 hr after each lutetium Lu 177-dota-tate dose; do not administer long-acting octreotide within 4 weeks of each subsequent lutetium Lu 177-dota-tate dose; short-acting octreotide may be given for symptomatic management, but must be withheld for at least 24 hr before each lutetium Lu 177-dota-tate dose.

3)Following lutetium Lu 177-dota-tate treatment: Continue long-acting octreotide 30 mg IM q4weeks after completing lutetium Lu 177-dota-tate until disease progression or for up to 18 months following treatment initiation.

Antiemetic

1) Administer antiemetics 30 min before recommended amino acid solution

Amino acid solution

1) Initiate IV amino acid solution 30 min before administering lutetium Lu 177-dota-tate

2) IV amino acid solution contains: L-lysine (18-24 g) and L-arginine (18-24 g) per 1.5-2.2 L; osmolarity <1060 mOsmol

3) Use a 3-way valve to administer amino acids using the same venous access as lutetium Lu 177-dota-tate or administer amino acids through a separate venous access in the patient's other arm

4) Continue the infusion during, and for at least 3 hr after, lutetium Lu 177-dota-tate infusion

4) Do not decrease amino acid solution dose if the dose of lutetium Lu 177-dota-tate is reduced

Dosage Modifications

Renal impairment

Mild-to-moderate (CrCl 30-70 mL/min): No dose adjustment required; however, patients may be at greater risk of toxicity; perform more frequent assessments of renal function

Severe (CrCl <30 mL/min) or end-stage renal disease: Not studied.

Hepatic impairment

Mild-to-moderate: No dose adjustment required

Severe (TB >3 x ULN and any AST): Not studied

Thrombocytopenia

Grade 2, 3, or 4

1)Withhold dose until complete or partial resolution (grade 0 to 1), then resume dose at 3.7 GBq (100 mCi) with complete or partial resolution

2)If reduced dose does not result in grade 2, 3, or 4 thrombocytopenia, administer at 7.4 GBq (200 mCi) for next dose

3)Permanently discontinue for ≥grade 2 thrombocytopenia requiring a treatment delay ≥16 weeks

Grade 2, 3, or 4 recurrence

Permanently discontinue

Anemia and neutropenia

Grade 3 or 4

1) Withhold dose until complete or partial resolution (grade 0, 1, or 2), then resume dose at 3.7 GBq (100 mCi) with complete or partial resolution

2) If reduced dose does not result in grade 3 or 4 anemia or neutropenia, administer at 7.4 GBq (200 mCi) for next dose

3) Permanently discontinue for ≥grade 3 thrombocytopenia requiring a treatment delay ≥16 weeks

Grade 3 or 4 recurrence

Permanently discontinue

Renal toxicity

Renal toxicity definition

1) CrCl <40 mL/min OR

2) CrCl decreased 40% from baseline OR

3) Baseline serum creatinine increased 40%

Actions

1) Withhold dose until complete resolution

2) Resume dose at 3.7 GBq (100 mCi) in patients with complete resolution

3) If reduced dose does not result in renal toxicity, administer at 7.4 GBq (200 mCi) for next dose.

4) Permanently discontinue for renal toxicity requiring a treatment delay ≥16weeks

Hepatotoxicity

Hepatotoxicity definition

1) Bilirubinemia >3x ULN (Grade 3 or 4) OR

2) Hypoalbuminemia <30 g/L with a decreased prothrombin ratio <70%

Actions

1) Withhold dose until complete resolution

2) Resume dose at 3.7 GBq (100 mCi) in patients with complete resolution

3) If reduced dose does not result in hepatotoxicity, administer at 7.4 GBq (200 mCi) for next dose

4) Permanently discontinue for hepatotoxicity requiring a treatment delay ≥16weeks

Other nonhematologic toxicity

Grade 3 or 4

1) Withhold dose until complete or partial resolution (grade 0-2), then resume dose at 3.7 GBq (100 mCi) with complete or partial resolution

2) If reduced dose does not result in grade 3 or 4 toxicity, administer at 7.4 GBq (200 mCi) for next dose

3) Permanently discontinue for ≥grade 3 toxicity requiring a treatment delay ≥16 weeks

Grade 3 or 4 recurrence.

Permanently discontinue

Dosing Considerations

Verify pregnancy status of females of reproductive potential prior to initiating.

Administration

IV Preparation

Use aseptic technique and radiation shielding when administering solution

Use tongs when handling vial to minimize radiation exposure

Do not inject directly into any other IV solution

Confirm the amount of radioactivity in the radiopharmaceutical vial with an appropriate dose calibrator prior to and after administration

Inspect the product visually for particulate matter and discoloration under a shielded screen prior to administration; solution should appear clear and colorless to slightly yellow; discard vial if particulates or discoloration are present

Handling radiopharmaceuticals

1) Radiopharmaceutical; handle with appropriate safety measures to minimize radiation exposure

2) Use waterproof gloves and effective radiation shielding when handling

3) Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals

IV Administration

1) Insert a 2.5-cm, 20-gauge needle (short needle) into the lutetium Lu 177-dota-tate vial and connect via a catheter to 500 mL 0.9% NaCl solution.

2) Ensure that the short needle does not touch the lutetium Lu 177-dota-tate solution in the vial and do not connect this short needle directly to the patient.

3) Do not allow 0.9% NaCl solution to flow into the lutetium Lu 177-dota-tate vial prior to the initiation of the infusion and do not inject lutetium Lu 177-dota-tate directly into the 0.9% NaCl solution.

4) Insert a second needle that is 9 cm, 18 gauge (long needle) into the lutetium Lu 177-dota-tate vial, ensuring that this long needle touches and is secured to the bottom of the vial during the entire infusion.

5) Connect the long needle to the patient by an IV catheter that is prefilled with 0.9% NaCl and that is used exclusively for the lutetium Lu 177-dota-tate infusion into the patient.

6) Use a clamp or pump to regulate the flow of the 0.9% NaCl solution via the short needle into the lutetium Lu 177-dota-tate vial at a rate of 50-100 mL/hr for 5-10 minutes and then 200-300 mL/hr for an additional 25-30 minutes.

7) The 0.9% NaCl solution entering the vial through the short needle will carry the lutetium Lu 177-dota-tate from the vial to the patient via the catheter connected to the long needle over a total duration of 30-40 minutes.

8) Do not administer lutetium Lu 177-dota-tate as an IV

9) During the infusion, ensure that the level of solution in the lutetium Lu 177-dota-tate vial remains constant

10) Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least 5 minutes

11) Follow the infusion with an IV flush of 25 mL of 0.9% NaCl

12) Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

Adverse Effects

>10% All Grades:-Lymphopenia (90%), Creatinine increased (85%), Hyperglycemia (82%)Anemia, (81%), IncreasedGGT(66%), Increasedalkalinephosphatase(65%), Nausea(65%), Leukopenia(55%), Vomiting(53%), Thrombocytopenia(53%), ASTincreased(50%), ALT increased, Fatigue Hyperuricemia, Hypocalcemia, Blood bilirubinincreased, Hypokalemia, Abdominal pain, Diarrhea, Neutropenia, Decreased appetite, Hyperkalemia, Hypernatremia, Headache, Dizziness, Peripheral edema, Hypoglycemia, Flushing, Anxiety, Renalfailure, Alopecia, Hypertension, Pain in extremity, Cough.

>10% Grades 3-4

Lymphopenia (44%)

Increased GGT (20%)

Storage

Store in the original package (ie, lead-shielded container placed in a plastic sealed container)

Store at temperature below 25°C (77°F).

Shelf life is 72 hr; discard appropriately at 72 hr.

ABBREVATIONS

(mCRPC): Metastatic castration-resistant disease

(NM-CRPC):-nonmetastatic, castration-resistant prostate cancer

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