Lisa
Female, Age 44

AZEDRA®
iobenguane I 131 injection for intravenous use

PROFILES IN PPGL

Pheochromocytoma Metastatic Recurrence After Surgery

Indication

AZEDRA® (iobenguane I 131) is indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Important Safety Information

Warnings and Precautions:

Risk from radiation exposure: AZEDRA contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. These risks of radiation associated with the use of AZEDRA are greater in pediatric patients than in adults. Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with AZEDRA consistent with institutional good radiation safety practices and patient management procedures.

Myelosuppression: Severe and prolonged myelosuppression occurred during treatment with AZEDRA. Among the 88 patients who received a therapeutic dose of AZEDRA, 33% experienced Grade 4 thrombocytopenia, 16% experienced Grade 4 neutropenia, and 7% experienced Grade 4 anemia. Five percent of patients experienced febrile neutropenia. Monitor blood cell counts weekly for up to 12 weeks or until levels return to baseline or the normal range. Withhold and dose reduce AZEDRA as recommended in the prescribing information based on severity of the cytopenia.

Secondary myelodysplastic syndrome, leukemia, and other malignancies: Myelodysplastic syndrome (MDS) and acute leukemias were reported in 6.8% of the 88 patients who received a therapeutic dose of AZEDRA. The time to development of MDS or acute leukemia ranged from 12 months to 7 years. Two of the 88 patients developed a non-hematological malignancy.

Hypothyroidism: Hypothyroidism was reported in 3.4% of the 88 patients who received a therapeutic dose of AZEDRA. Initiate thyroid-blocking medications starting at least 1 day before and continuing for 10 days after each AZEDRA dose to reduce the risk of hypothyroidism or thyroid neoplasia. Evaluate for clinical evidence of hypothyroidism and measure thyroid-stimulating hormone (TSH) levels prior to initiating AZEDRA and annually thereafter.

For important risk and use information about AZEDRA, please see additional Important Safety Information throughout, and the accompanying Full Prescribing Information.

Patient name and photo are for illustrative purposes but clinical details are derived from an individual treated in the Phase II trial of AZEDRA. Individual results may vary in clinical use of AZEDRA in patients with pheochromocytoma and paraganglioma (PPGL).

Lisa
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Patient background and medical history

Relevant medical history

Date of diagnosis: July 2006

Antihypertensive medication: Doxazosin 1 mg qd

Prior surgeries: Right adrenalectomy in July 2006

Prior systemic therapies: None

Tumor profile

Tumor type: Pheochromocytoma

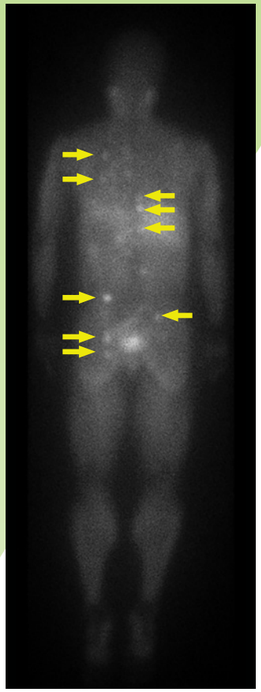
Secretory profile: Norepinephrine, epinephrine

Metastatic locations: Lung, small bowel

MIBG avidity: Confirmed through patient workup and dosimetric scan

Baseline labs

Test	Normal Range	Patient Value
Creatinine Clearance	90–140 mL/min	NR
Bilirubin	5.13–17.1 µmol/L	6.84 µmol/L
Hemoglobin	120–160 g/L	115 g/L
Leukocytes	4–11 x10^9/L	6.3 x10^9/L
Neutrophils	2–8.25 x10^9/L	3.92 x10^9/L
Platelets	150–450 x10^9/L	311 x10^9/L



Posterior I-131 MIBG

Scan following a therapeutic dose of AZEDRA (435 mCi). Numerous metastatic lesions in the lung and small bowel are best appreciated on this posterior scan and are indicated by arrows.

What treatment would you choose for Lisa?

Important Safety Information

Elevations in blood pressure: Eleven percent of the 88 patients who received a therapeutic dose of AZEDRA experienced a worsening of pre-existing hypertension defined as an increase in systolic blood pressure to ≥160 mmHg with an increase of 20 mmHg or an increase in diastolic blood pressure to ≥100 mmHg with an increase of 10 mmHg. All changes in blood pressure occurred within the first 24 hours post infusion. Monitor blood pressure frequently during the first 24 hours after each therapeutic dose of AZEDRA.

Renal toxicity: Of the 88 patients who received a therapeutic dose of AZEDRA, 7% developed renal failure or acute kidney injury and 22% demonstrated a clinically significant decrease in glomerular filtration rate (GFR) measured at 6 or 12 months. Monitor renal function during and after treatment with AZEDRA. Patients with baseline renal impairment may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. AZEDRA has not been studied in patients with severe renal impairment.

For important risk and use information about AZEDRA, please see additional Important Safety Information throughout, and the accompanying Full Prescribing Information.

Individual results may vary in clinical use.

Results following treatment with AZEDRA

AZEDRA® iobenguane I 131 injection for intravenous use

AZEDRA therapeutic dosing

First dose administered in March 2010, second dose 3 months later in June 2010

Primary endpoint: Antihypertensive medication reduction

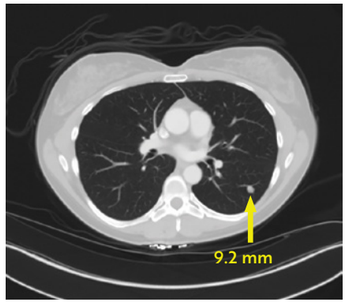
Responder: Yes, 100% (discontinuation) | **Duration of response:** 22.36 months

Secondary endpoint: Tumor marker response

Plasma Testing	Baseline Value	Value at 12 months	Percentage Change
Chromogranin A	27.4 µg/L	7 µg/L	– 74%
Metanephrine	1,292.85 pmol/L	1,034.28 pmol/L	– 20%
Normetanephrine	10,073.70 pmol/L	5,935.02 pmol/L	– 41%
24-hour Urine Testing			
Metanephrine	2,377 nmol/day	1,906.32 nmol/day	– 20%
Normetanephrine	8,905.26 nmol/day	6,715.80 nmol/day	– 25%

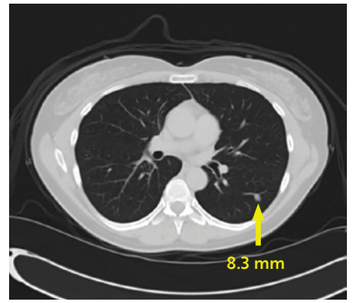
Secondary endpoint: Tumor response by RECIST v1.0

Responder: Yes, partial response



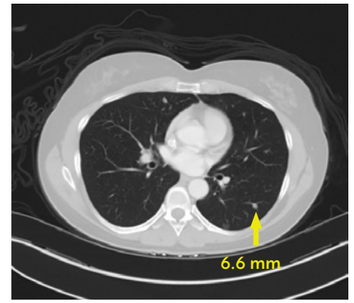
Axial Chest CT at baseline

Scan shows a 9.2 mm lesion in the superior segment of the left lower lobe of the lung.



Axial Chest CT at 6 months

Scan 6 months after the first therapeutic dose of AZEDRA shows reduction of the pulmonary lesion to 8.3 mm.



Axial Chest CT at 18 months

Scan 18 months after the first therapeutic dose of AZEDRA shows reduction of the pulmonary lesion to 6.6 mm.

Case discussion

Lisa was first diagnosed with a solitary pheochromocytoma in 2006, for which she had a right adrenalectomy. Believing she was cured, Lisa continued her life symptom-free. In 2010, however, her symptoms returned due to the appearance of metastases in her lungs and small bowel, requiring antihypertensive medication.

Lisa received AZEDRA first-line after the identification of iobenguane scan positive metastases, and she received the full treatment regimen on schedule. Following treatment, she discontinued her antihypertensive medication for 22 months and her tumor markers were reduced. Lisa achieved a partial tumor response as measured by RECIST, and one of her pulmonary metastatic lesions decreased by 28% over the 18 months following her first dose of AZEDRA.

Lisa is a person with metastatic recurrence of pheochromocytoma following surgical resection. She received AZEDRA first-line after the identification of iobenguane scan positive metastases, and she responded positively as measured by both the primary and secondary endpoints of the study.

AZEDRA was proven effective in the largest prospective clinical trial of advanced PPGL patients

The efficacy of AZEDRA was established based on the results of a Phase II, prospective, multicenter, single-arm trial in which 68 patients were treated. The primary endpoint was reduction or discontinuation of antihypertensive medication by at least 50% for at least six months. One of the key secondary endpoints was overall tumor response assessed radiographically per RECIST 1.0.

First and only FDA-approved therapy for advanced PPGL

Significant and sustained reduction in antihypertensive medication in 25% of patients (n=17/68, 95% CI: 16–37%)

Demonstrated tumor control in 22% of patients (n=15/68, 95% CI: 14–33%)

Important Safety Information

Warnings and Precautions:

Pneumonitis: Fatal pneumonitis occurred 9 weeks after a single dose in one patient in the expanded access program. Monitor patients for signs and symptoms of pneumonitis and treat appropriately.

Embryo-fetal toxicity: Based on its mechanism of action, AZEDRA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with AZEDRA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose.

Risk of infertility: Radiation exposure associated with AZEDRA may cause infertility in males and females. Radiation absorbed by testes and ovaries from the recommended cumulative dose of AZEDRA is within the range where temporary or permanent infertility can be expected following external beam radiotherapy.

Adverse Reactions:

The most common severe (Grade 3–4) adverse reactions observed in AZEDRA clinical trials (≥10%) were lymphopenia (78%), neutropenia (59%), thrombocytopenia (50%), fatigue (26%), anemia (24%), increased international normalized ratio (18%), nausea (16%), dizziness (13%), hypertension (11%), and vomiting (10%). Twelve percent of patients discontinued treatment due to adverse reactions (thrombocytopenia, anemia, lymphopenia, nausea and vomiting, multiple hematologic adverse reactions).

Drug Interactions:

Based on the mechanism of action of iobenguane, drugs that reduce catecholamine uptake or that deplete catecholamine stores may interfere with iobenguane uptake into cells and therefore interfere with dosimetry calculations or the efficacy of AZEDRA. These drugs were not permitted in clinical trials that assessed the safety and efficacy of AZEDRA. Discontinue the drugs listed in the prescribing information for at least 5 half-lives before administration of either the dosimetry dose or a therapeutic dose of AZEDRA. Do not administer these drugs until at least 7 days after each AZEDRA dose.

For important risk and use information about AZEDRA, please see the accompanying Full Prescribing Information.

To report suspected adverse reactions, contact Progenics Pharmaceuticals, Inc. at 844-668-3950 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reference: AZEDRA® prescribing information. New York, NY: Progenics Pharmaceuticals, Inc.; 08 2018.

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