Abstract # 4108

Long-term Survival and Safety from a Multi-Center, Open-Label, Pivotal Phase 2 Study of AZEDRA® in Patients with Unresectable, Locally Advanced or Metastatic Pheochromocytoma or Paraganglioma

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BACKGROUND

- Pheochromocytomas and paragangliomas (PPGLs) are rare diseases[1]
- Approximately 10-35% of PPGLs are metastatic and/or locally invasive at initial diagnosis or treatment[2,3]
- Because of the catecholamine secreting nature of these tumors, PPGL tumors can manifest in various serious symptoms and signs that often go undiagnosed or are misdiagnosed
- More than 100 symptoms and signs (e.g. hypertension, headaches, palpitations, and diaphoresis) have been described in association with these tumors
- The 5-year survival rate of patients with malignant pheochromocytoma has been reported to be as low as 11.8%[4]
- Patients endure significant burdens resulting from hormonal dysfunction and tumor progression
  - Because malignancy is defined by the presence of distant metastases, curative surgery is not an option[5]
  - In the absence of a cure, there are two goals for treating advanced PPGL: symptom reduction and tumor control[6,7]
- MIBG (iobenguane) is a known substrate for the norepinephrine reuptake transporters
- Neuroendocrine tumors (NETs), such as PPGL, express high levels of these transporters on their cell surfaces
- MIBG is a biomarker that identifies neuroendocrine tumors

AZEDRA® (high specific activity (HSA) I-131 MIBG)

- AZEDRA® (iobenguane I 131) is a high specific activity I-131 MIBG manufactured using the Ultratrace® process involving a solid-phase precursor
- AZEDRA® (iobenguane I 131) is the first and only FDA-approved therapeutic radiopharmaceutical 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[8]
- The drug product has very high specific activity (minimal unlabeled MIBG) **(Table 1)**

Table 1. Differences between low specific activity (LSA) and HSA I-131 MIBG

Characteristics	LSA I-131 MIBG	HSA I-131 MIBG
Manufacturing process	Simple isotope exchange methodology	Solid phase precursor "Ultratrace" process
Unlabeled MIBG in each dose	Large amount	None
Chemical mass of MIBG in a 18.5 GBq (500 mCi) dose	~12 mg	~0.2 mg
Specific activity of final drug product	~ 1.59 MBq/µg[9] (low)	~92.5 MBq/µg (very high)
Efficacy	Low levels of radioactivity delivered to tumor per dose	High levels of radioactivity delivered to tumor per dose
Safety	Excess cold MIBG and increased risk for cardiovascular issues	No cold MIBG, low cardiovascular risk

METHODS

Table 2: AZEDRA® pivotal study IB12B (NCT00874614)

Study Design	• Phase 2, multi-center, open-label, single-arm study
Key Inclusion Criteria	• At least 12 years of age • Diagnosis of PPGL • Ineligible for curative surgery, failed prior therapy or not candidates for chemotherapy • MIBG-avid • On a stable antihypertensive medication for at least 30 days

Key Efficacy Endpoints	• Primary endpoint
	  ▪ Proportion of subjects with a reduction (including discontinuation) of all antihypertensive medication(s) by at least 50% for ≥6 months
	• Key secondary endpoints
	  ▪ Objective tumor response by RECIST 1.0
	  ▪ Tumor biomarker response
	  ▪ Overall survival (OS) up to 5 years post-first therapeutic dose
	  ▪ Safety

Study Duration	• 12-month efficacy phase followed by 4-years long-term follow-up
Treatment	• Dosimetric dose: 111-222 MBq (3-6 mCi) • Up to 2 therapeutic doses, each at ~18.5 GBq (500 mCi) (or 296 MBq/kg [8 mCi/kg] for patients ≤62.5 kg), approximately 3 months apart

Rationale for primary endpoint

- Primary Endpoint:
  - Proportion of subjects with a reduction of all antihypertensive medication by ≥50% for at least 6 months, after receiving at least one therapeutic dose of AZEDRA®
- Because of the catecholamine secreting nature of PPGL tumors, the disease can manifest with serious cardiovascular symptoms, such as sustained hypertension
- Primary cause of death is disease progression
- FDA agreed that a sustained reduction in the requirement for antihypertensive medication with adequate control of blood pressure is a clinical benefit
- Supported by data from tumor response and tumor biomarker response

Tumor Biomarker Response

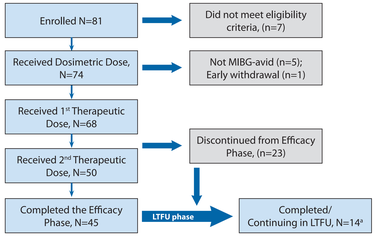
- Clinical presentation of PPGL is secondary to the tumor's secretion of catecholamines
- Biochemical marker data can provide plausible mechanistic support to the reduction in the use of antihypertensive medication results observed in the study
- Responses were analyzed for markers that were ≥1.5 times the upper limit of normal (ULN) at baseline
- Biomarker response were evaluated per modified WHO criteria:
  - Responder = Confirmed response of Complete Response (CR) or Partial Response (PR)
    - Biochemical CR = normalization
    - Biochemical PR = >50% decrease from baseline value but remaining above ULN
    - Biochemical stable disease (SD) = ≤50% decrease from baseline value or increase by ≤50% of baseline value
    - Biochemical progressive disease (PD) = >50% increase from baseline value

RESULTS

Disposition of Patients

- Of 81 PPGL patients who were screened for enrollment, 74 received a dosimetric dose of AZEDRA®
- Of these 74 patients, 68 had MIBG-avid tumors and received at least one therapeutic dose; 50 of these 68 patients received two therapeutic doses **(Figure 1)**

Figure 1: Disposition of Patients



[a]Analysis cut-off: Jan 25, 2019
LTFU: Long-term follow-up

Demographic and Baseline Characteristics

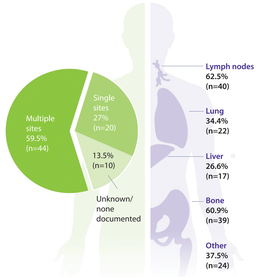
- Of the 74 patients who received a dosimetric dose of AZEDRA®, 55.4% were men and 44.6% were women with a median age of 54.5 years (range: 16-76 years)
- At the time of enrollment, 53 (71.6%) patients had a primary diagnosis of pheochromocytoma and 21 (28.4%) had paraganglioma **(Table 3)**
- Most patients had extensive disease at multiple metastatic locations. A total of 44 out of 74 (59.5%) patients had high tumor burden **(Figure 2)**

Table 3: Demographics and Baseline Characteristics

Characteristic	All Dosed (N=74)
Sex, n (%)	
Male	41 (55.4)
Female	33 (44.6)
Age at enrollment (years)	
Mean (SD)	51.1 (13.77)
Median (Min, Max)	54.5 (16, 76)
Age group, n (%)	
<18	1 (1.4)
18–30	7 (9.5)
30–64	54 (73.0)
≥65	12 (16.2)
Primary diagnosis at enrollment, n (%)	
Pheochromocytoma	53 (71.6)
Paraganglioma	21 (28.4)
Patients were heavily pre-treated and the majority had widely metastatic disease	
Prior Treatments, n (%)	
Includes Surgery	66 (89.2)
Includes Conventional I-131 MIBG	22 (29.7)
Includes Chemotherapy (CVD and/or others)	28 (37.8)
Number of Prior Treatment Modalities, n (%)	
One	20 (27.0)
Two	26 (35.1)
Three	20 (27.0)
Four	6 (8.1)
None documented	2 (2.7)
Location of Metastases, n (%)a	
Lymph nodes	40 (62.5)
Lung	22 (34.4)
Liver	17 (26.6)
Bone	39 (60.9)
Others	24 (37.5)

[a]Based on N=64 with evaluable target lesions
CVD: cardiovascular disease; Max: maximum; MIBG: metaiodobenzylguanidine; Min: minimum; SD: standard deviation

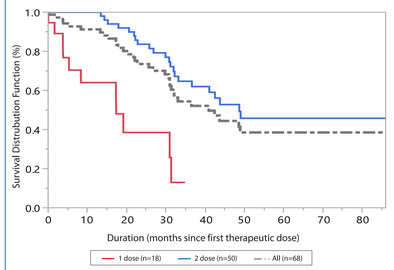
Figure 2: Location of multiple metastatic tumor sites



With a Median Follow Up of 41 Months, A Tail of Survival of 40% was observed

- The 12-month OS was 91%
- Median OS for all patients was 41.1 months (95% CI 31.1, 91.2). Median OS was 17.5 months (95% CI 4.0, 31.5) and 48.7 months (95% CI 33.2, 91.2) in patients receiving one and two doses, respectively
- A tail of survival was observed, with OS of 73.1% at 2 years and 44.2% at 4 years **(Figure 3)**

Figure 3: Overall survival* following first therapeutic dose, Kaplan-Meier Model (N=68)



*Survival time was to the date of death, or censored at the last date the patient was known to be alive. Analysis cutoff: January 25, 2019.

Primary Endpoint

- The primary endpoint was met by 25% (17/68) (95% CI 16%-37%) of all patients who received at least one therapeutic dose, achieving pre-specified success criteria
- Clinical benefit (reduction of all antihypertensive medication by ≥50% for at least 6 months following the first therapeutic dose) was achieved in 32% (16/50) (95% CI 21%–46%) of patients who received two therapeutic doses

High Clinical Benefit Rates were observed

- Overall, 92.2% of patients achieved tumor response of confirmed PR or SD
- A total of 49 out of 50 (98%) patients who received two therapeutic doses of AZEDRA® achieved clinical benefit of confirmed PR or SD **(Table 4)**

Table 4: Best confirmed overall tumor response by RECIST 1.0 following AZEDRA® treatment

Best confirmed overall tumor response[a] per RECIST	At least one therapeutic dose (N=68)	One therapeutic dose(N=18)	Two therapeutic doses (N=50)
Evaluated patients*, n	64	14	50
Complete response	0	0	0
Partial response[a]	15 (23.4)	0	15 (30.0)
Stable disease[b]	44 (68.8)	10 (71.4)	34 (68.0)
Progressive disease	3 (4.7)	2 (14.3)	1 (2.0)
No assessment	2 (3.1)	2 (14.3)	0
Clinical benefit (confirmed response + SD)	59 (92.2)	10 (71.4)	49 (98.0)

*Patients evaluable for response were done by central review; No assessment signifies patients who discontinued therapy before the first scan
[a]Per RECIST, partial response required confirmation at a subsequent visit
[b]Including moderate response (MR)

High Biochemical Response Rates Were Observed in the Majority of Patients

- The best overall biochemical response rates (CR+PR) for chromogranin A (CgA), total metanephrines (TM), and vanillylmandelic acid (VMA) were 80%, 70%, and 64%, respectively **(Table 5)**

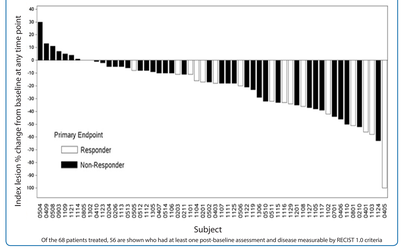
Table 5: Best overall tumor biomarker response

	Chromogranin A (CgA)		Total Metanephrines (TM)		Vanillylmandelic Acid (VMA)	
	n	%	n	%	n	%
Baseline 1.5x ULN	49	100	53	100	44	100
Complete Response (CR)	22	45	12	23	14	32
Partial Response (PR)	17	35	25	47	14	32
Stable Disease (SD)	8	16	15	28	14	32
Progressive Disease (PD)	2	4	1	2	2	5
Best Overall Response Rate (CR+PR)	39	80	37	70	28	64

Tumor Response and Primary Endpoint

- Confirmed PR occurred in 41.2% (7/17) of patients who were considered responders for the primary endpoint, and 17.0% (8/47) of patients who were not responders for the primary endpoint
- 100% (17/17) of primary endpoint responders achieved PR/SD during the efficacy phase
- In total, 89.3% (41/47) of primary endpoint non-responders achieved PR/SD; 6.4% (3/47) had PD **(Figure 4)**

Figure 4: Maximum confirmed reduction in measurable target lesion size by RECIST 1.0 criteria



Of the 68 patients treated, 56 are shown who had at least one post-baseline assessment and disease measurable by RECIST 1.0 criteria

Safety

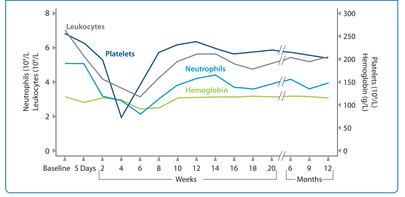
- The most common (≥50%) treatment-emergent adverse events (TEAEs) in all patients who received any dose of the drug were nausea, myelosuppression, and fatigue **(Table 6)**
- No severe acute hypertension or hypertensive crises were observed in patients during or immediately following drug administration
- Hematological toxicity was transient and manageable following treatment **(Figure 5)**
- Myelosuppressive events resolved within 4-8 weeks without requiring stem cell transplantation
- Hematological supportive care was provided for 23% of treated patients and stem cell transplantation was not required
- Late radiation toxicity included 7 patients with secondary malignancies (myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), colon cancer, and lung carcinoma) of which MDS, ALL and AML were considered related to I-131 radiotherapy

Table 6: Incidence of all-grade TEAEs occurring in at least 20% of patients*

Adverse Event (AE) by Preferred Term	Treatment-related, all grade, n (%)	Treatment-related, grade 3-5, n (%)	Any AE, all grades, n (%)
Nausea	52 (70.3)	1 (1.4)	53 (71.6)
Thrombocytopenia	49 (66.2)	28 (37.8)	49 (66.2)
Anemia	40 (54.1)	14 (18.9)	43 (58.1)
Leukopenia	41 (55.4)	28 (37.8)	41 (55.4)
Fatigue	32 (43.2)	7 (9.5)	41 (55.4)
Neutropenia	39 (52.7)	26 (35.1)	39 (52.7)
Vomiting	33 (44.6)	1 (1.4)	36 (48.6)
Dry mouth	27 (36.5)	0	28 (37.8)
Dizziness	16 (21.6)	1 (1.4)	28 (37.8)
Headache	16 (21.6)	0	21 (28.4)
Hypotension	8 (10.8)	1 (1.4)	18 (24.3)
Decreased appetite	14 (18.9)	1 (1.4)	17 (23.0)
Diarrhea	11 (14.9)	2 (2.7)	16 (21.6)
Constipation	4 (5.4)	1 (1.4)	16 (21.6)

*The safety population included all 74 patients who received any dose of the drug.

Figure 5: Hematological toxicities resolved within 4-8 weeks and without the need for stem cell transplantation



SUMMARY

- Study IB12B, the largest prospective clinical trial to date, has demonstrated multiple clinical benefits of AZEDRA® (iobenguane I 131) treatment
  - Control of catecholamine-associated hypertension and sustained reduction of antihypertensive medications
  - Clinical benefit rates (objective confirmed tumor responses and stable disease) were observed in 71.4% and 98.0% of patients receiving one and two therapeutic doses, respectively
    - Both primary endpoint responders and non-responders derived clinical benefit
  - A tail of survival was observed, with OS of 73.1% at 2 years and 44.2% at 4 years
  - Best overall biomarker responses (CR+PR) for CgA, TM, and VMA were observed in 80%, 70%, and 64%, respectively
- The most common treatment-emergent adverse events were consistent with expected radiation-related risks of hematologic toxicities, nausea/vomiting, fatigue, and dizziness
  - Hematological toxicities resolved within 4-8 weeks and without the need for stem cell transplantation
  - In contrast to low specific activity I-131 MIBG, no severe hypertension, hypertensive crises or acute CV side effects were observed

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Disclosure

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