Considerations for Treatment with Azedra: A Medical Oncologist's Perspective

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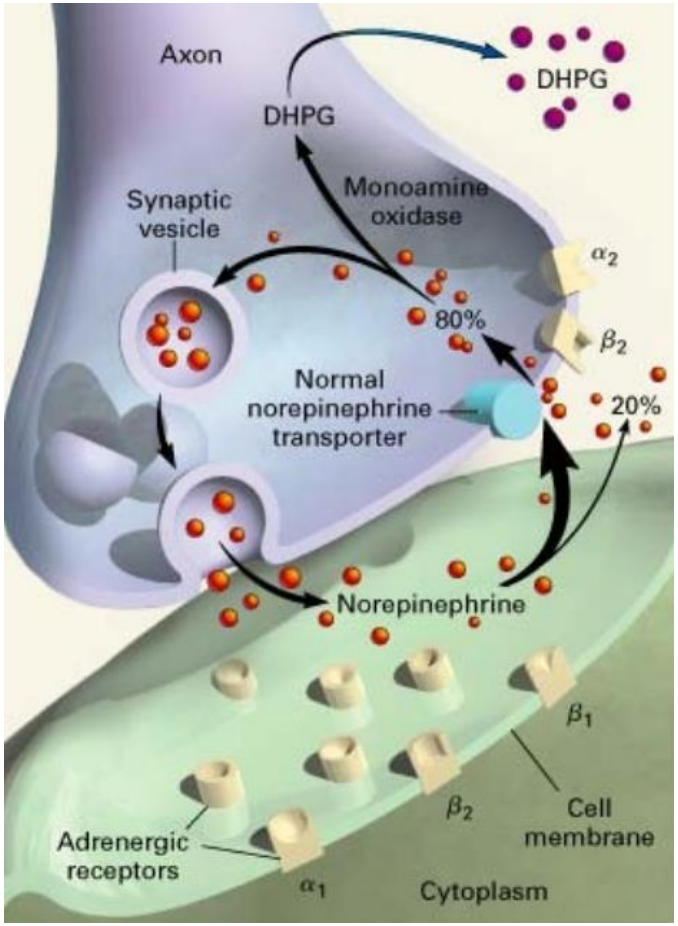
Relevant Financial Disclosures

- Research support to institution: Eli Lilly and Company, Crinetics
- Consulting: GE Health and Lantheus
- I will be discussing investigational and/or off-label use and/or of products in my presentation

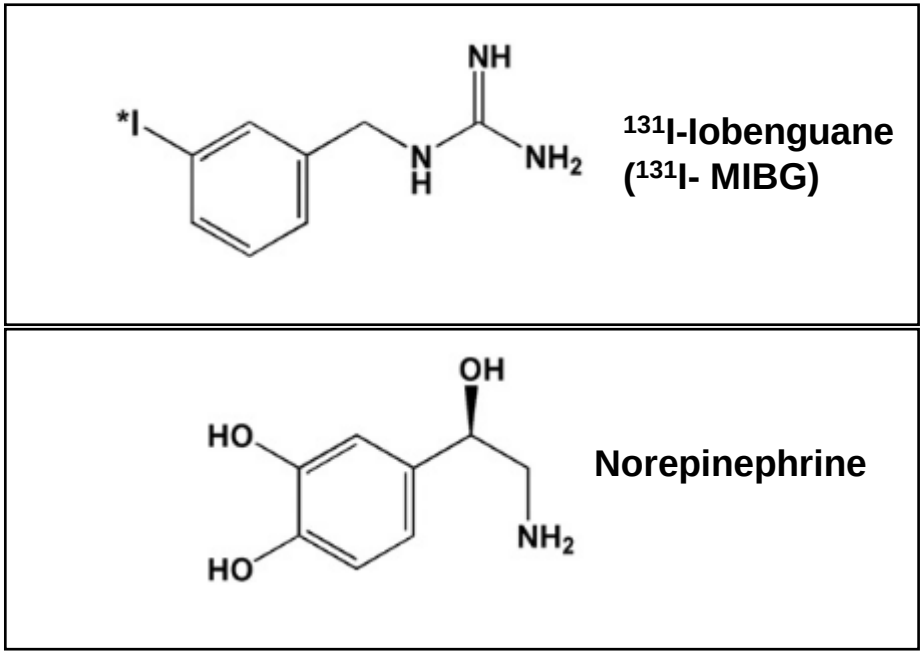
Acknowledgements

- Dr. Bhavana Konda and Akram Husain

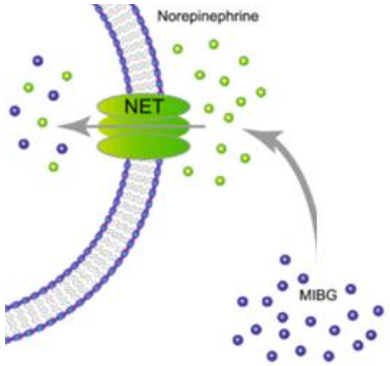
^{131}I-Iobenguane (Meta-Iodobenzylguanidine, MIBG) - Basics



Shannon *et al.* New Engl J Med 2000



Vallabhajosula. *et al.* Semin Nucl Med 2011



Disadvantages of LSA I-131 Iobenguane

- LSA-I-131- is produced by isotope exchange.
- Ratio of radioactive MIBG to non-radioactive MIBG molecules: 1:2000.
- Non-radiolabeled MIBG competes with radiolabeled MIBG for the NET: less effective.
- Saturation of the NET by cold molecules of MIBG prevents the reuptake of norepinephrine, exacerbating the manifestations of catecholamine excess.

Advantages of HSA I-131 Iobenguane

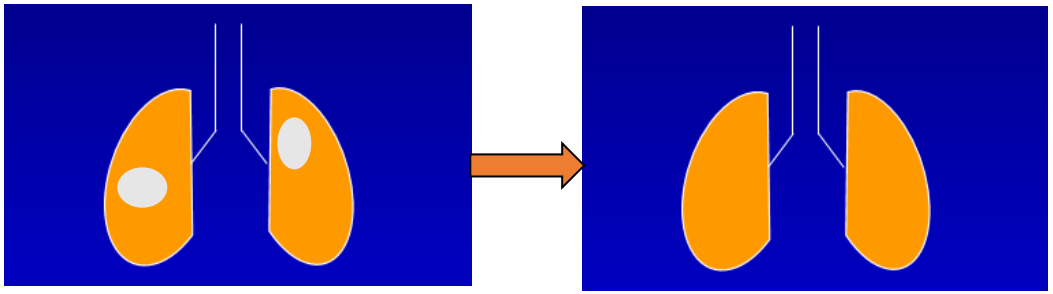
- HSA I-131 Iobenguane >99.9% of MIBG is labelled with I-131 (vs. 0.05% for LSA)
- Increased cellular uptake of radioactivity, approximately 150 times higher than that of LSA-I-131-MIBG
- 2500mCi/mg vs 16 mCi/mg

Phases of Clinical Trials

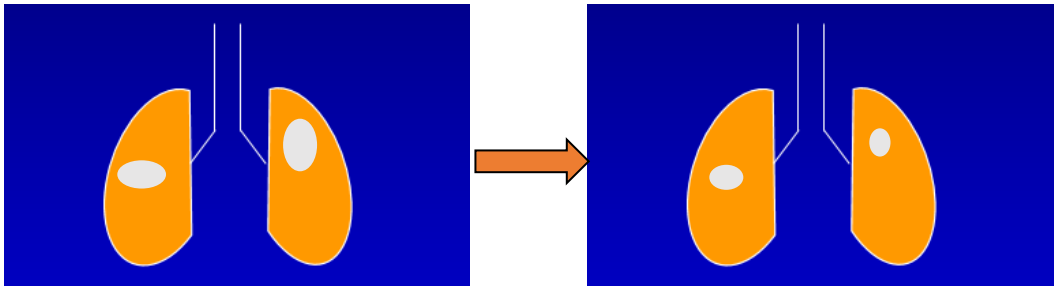
	Phase 1	Phase 2	Phase 3	FDA APPROVAL
Purpose	Safety Dosage	Efficacy Safety	Compares different treatments Efficacy Safety	
No. of participants	20-100	Few hundred	300-3000	
Length of study	Several months	Several months-2 years	1-4 years	
% of drug that move to next phase	70%	33%	25-30%	

https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405382.htm

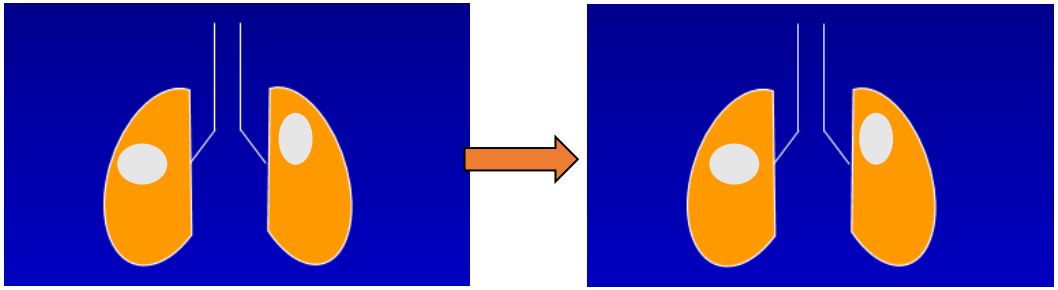
Evaluating response in clinical trials



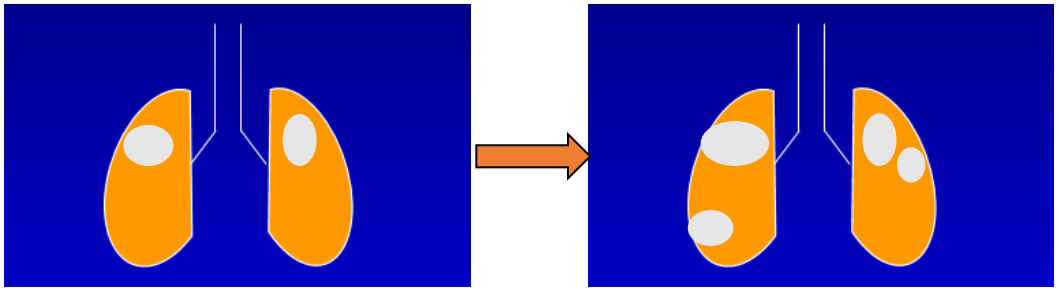
Complete response (CR)



Partial response (PR)



Stable response (SD)



Progressive disease (PD)

Other endpoints in clinical trials

- Progression-free survival

  How long from the start of study treatment do patients live without the cancer growing?

- Overall survival

  How long do patients live on the study treatment?

- Objective response rate

  What percentage of patients have at least a 30% decrease in size of their tumors on study treatment?

HSA ^{131}I-Iobenguane in Pheo / Paraganglioma
Efficacy data

Pryma *et al.* J Nuc Med 2019

- Open-label, single-arm, prospective study
- 68 patients received at least 1 therapeutic dose
- Primary endpoint: 50% reduction in baseline antihypertensive medication lasting at least 6 mo, without the introduction of new long-term (>14 d) antihypertensive medication or increases in the doses of the baseline regimen.
- Secondary objectives included radiographic tumor response, biochemical tumor marker response, overall survival (OS), and safety

Study Procedures

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

Dosimetry dose 3-6 mCi and up to two therapy cycles (3 months apart)

Patient Population

Prior treatments	
Included surgery	66 (89)
Included conventional ^{131}I-MIBG therapy or HSA ^{131}I-MIBG	22 (30)
Included chemotherapy with CVD or others	28 (38)
No. of prior treatment modalities	
1	20 (27)
2	26 (35)
3	20 (27)
4	6 (8)
None documented	2 (3)
Location of metastases*	
Lymph nodes	40 (63)
Bone	39 (61)
Lung	22 (34)
Liver	17 (27)
Lung or liver	32 (50)
Bone and lung or liver	20 (31)
Others†	24 (38)

Results

- Primary end point: 17/68 (**25%)** had at least a 50% reduction in baseline antihypertensive medication use lasting >=6 mo
- Median duration: 13 mo
- Objective response rate: 23%.
- Median overall survival: 37 mo (44 mo/2 doses vs 18 mo/1 dose)

	One dose n=18	Two doses n=50	>=1 dose n=68
CR	0	0	0
PR	**0**	**15 (30%)**	**15 (23%)**
SD	10 (71%)	34 (68%)	44 (69%)
PD	2 (14%)	1 (2%)	3 (5%)

HSA ^{131}I-Iobenguane in Pheo / Paraganglioma
Treatment-related adverse events

Most common Adverse events
Thrombocytopenia, anemia, leukopenia, neutropenia, nausea, vomiting, fatigue, dry mouth, dizziness

Adverse event	Frequency
Hematologic SAE	72%
Required transfusions/GCSF/erythropoietin	25%
Myelodysplastic syndrome	4%
Acute leukemia (AML/ALL)	3%
Pulmonary embolism	3%

Pryma *et al.* J Nuc Med 2019

Azedra (HSA I-131 iobenguane)

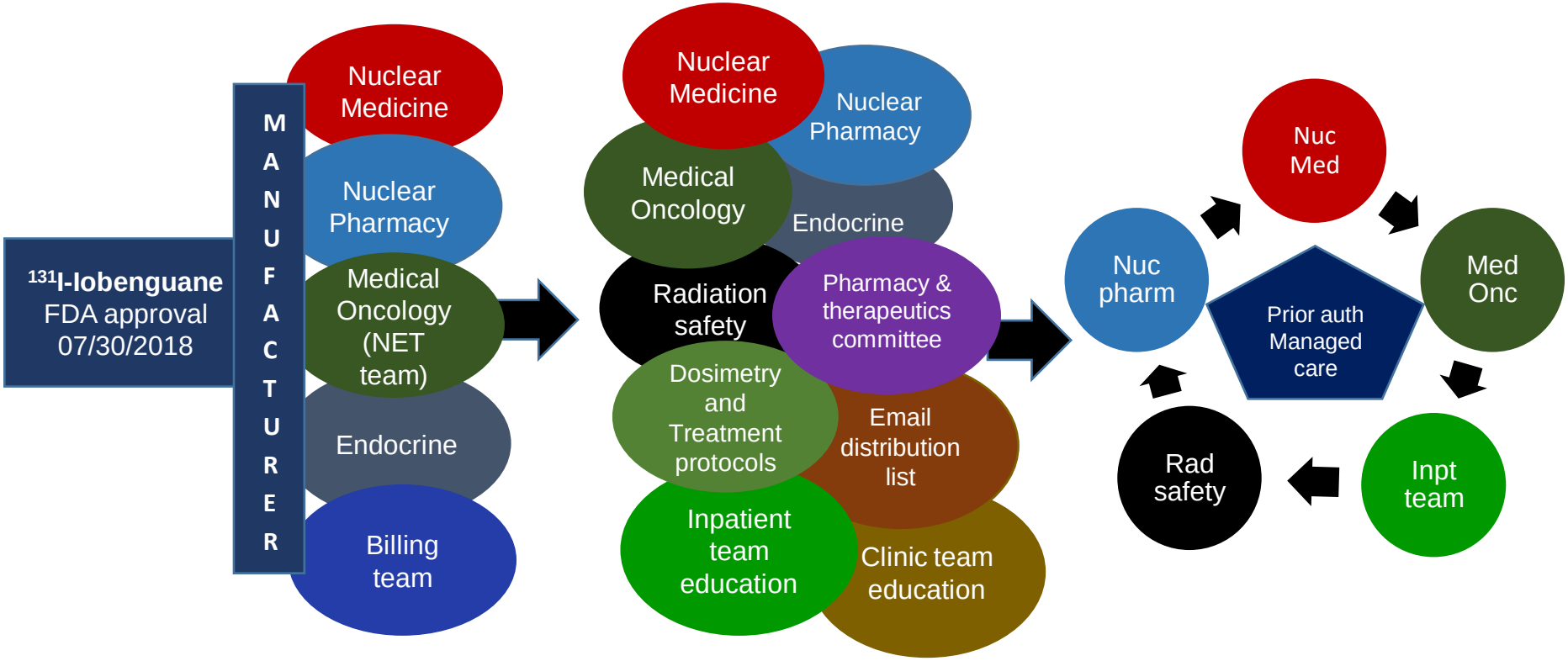
- On July 30, 2018 the FDA approved Azedra as the first and only FDA-approved therapy for non-resectable, locally-advanced or metastatic PHEO/PGL.

  Adult and pediatric patients 12 years and older

  Iobenguane scan positive disease

  Dosimetry based individualized treatment

Multi-disciplinary Team Effort



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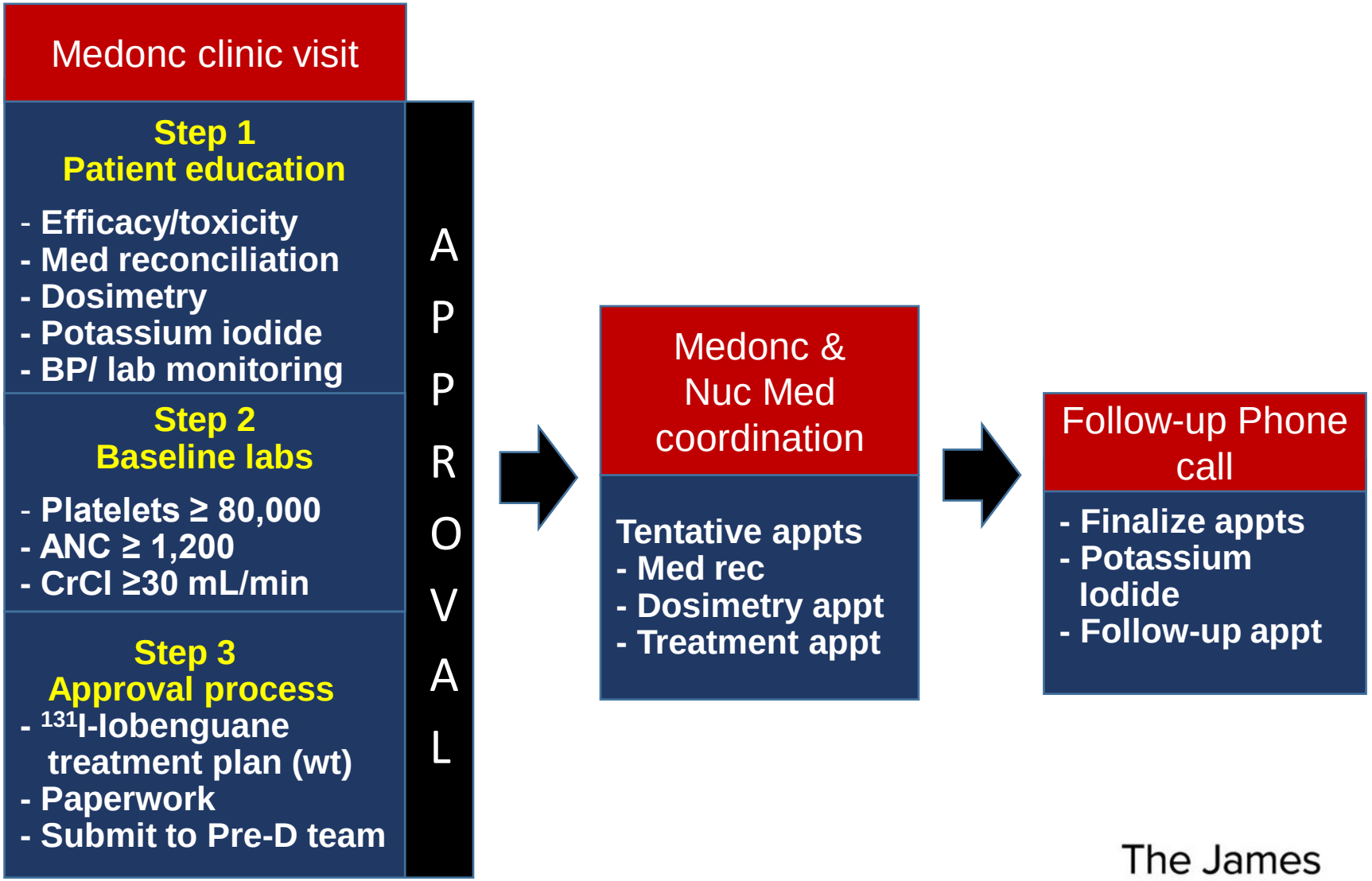
Work Flow



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Dosimetric Dose

The recommended dosimetric dose is:

- Patients weighing greater than 50 kg: 185 to 222 MBq (5 to 6 mCi)
- Patients 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)

Source: AZEDRA [prescribing information]. New York, NY: Progenics Pharmaceuticals, Inc.; 2018.

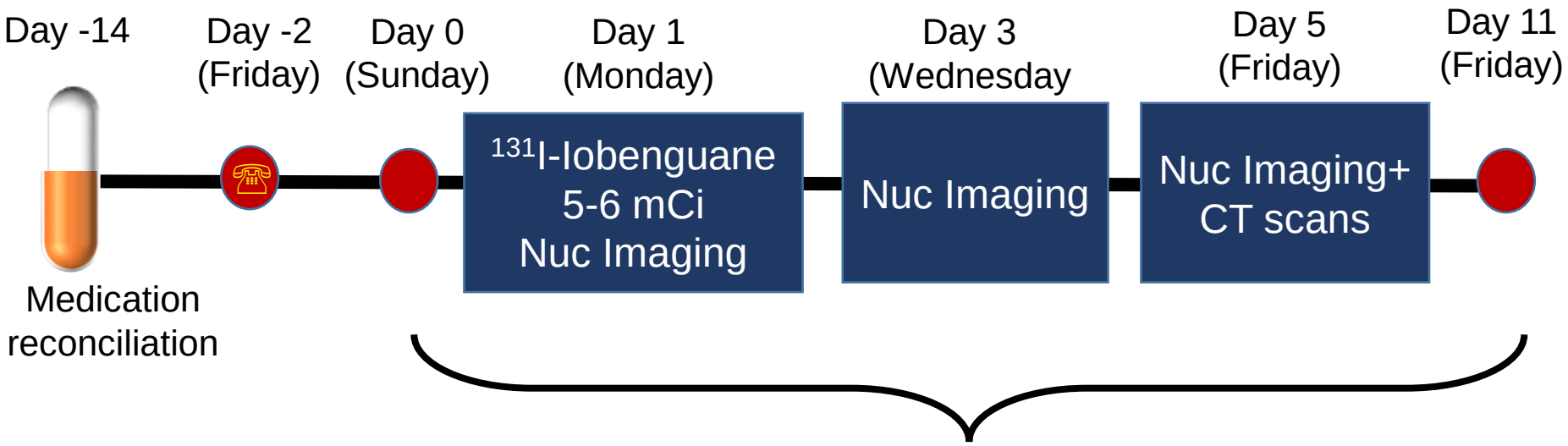
Stop medications that affect NE reuptake and storage

- Discontinue for ≥5 half-lives before dosimetry / therapeutic dose
- Do not administer these drugs until ≥7 days after a dose

CNS stimulants or amphetamines: cocaine, methylphenidate, dextroamphetamine, caffeine
Tricyclic antidepressants or norepinephrine reuptake inhibitors: amitriptyline, buproprion, duloxetine, mirtazapine, venlafaxine
Norepinephrine & dopamine reuptake inhibitors: phenteramine
Norepinephrine and serotonin reuptake inhibitors: tramadol
Antipsychotics:, olanzapine, quetiachlorpromazine, prochlorperazine, haloperidolpine, risperidone, clozapine
Monoamine oxidase inhibitors: phenelzine, linezolid
Non-select beta adrenergic blocking drugs: labetalol
Ca channel blockers: amlodipine, diltiazem, nifedipine
Alpha agonists or alpha/beta agonists: pseudoephedrine,
B2 stimulants: salbutamol, terbutaline
Sedating antihistamines: promethazine

Bombardier et al. Eur J Nucl Med Mol Imaging (2010) 37:2436–2446

Dosimetry



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Azedra Dosimetry Calculation

Patient MRN:
Date of Birth:
Gender:
Patient weight (kg): 74.3

Weight Based Dose per Cycle (mCi): 500

Patient Specific Kidney Mass	
Selected Standard Kidney Mass (g) =	310
Patient Kidney Mass (g) =	268

Predicted and Limiting Organ Doses

Therapeutic Activity(Nominal): 1000 mCi
37000 MBq

Target Organs	Unreduced Dose (Gy)	Limiting Dose (Gy)	Reduced Total Activity(mCi)
Left Kidney	24.8	18	727
Right Kidney	41.1	18	438
Liver	25.4	31	1220
Lungs	27.5	16.5	599
Red Marrow	6.5	12	1411
Small Intestines	8.4	40	4769

Therapeutic Dosage

max Weight Based Dose per Cycle :	500 mCi
Reduced Therapeutic Total Activity:	438 mCi
Therapeutic Dose per Cycle	**219 mCi**

Reviewed and Approved by: David Hunterlong 1/21/2022

Physicist

Reviewed and Approved by:

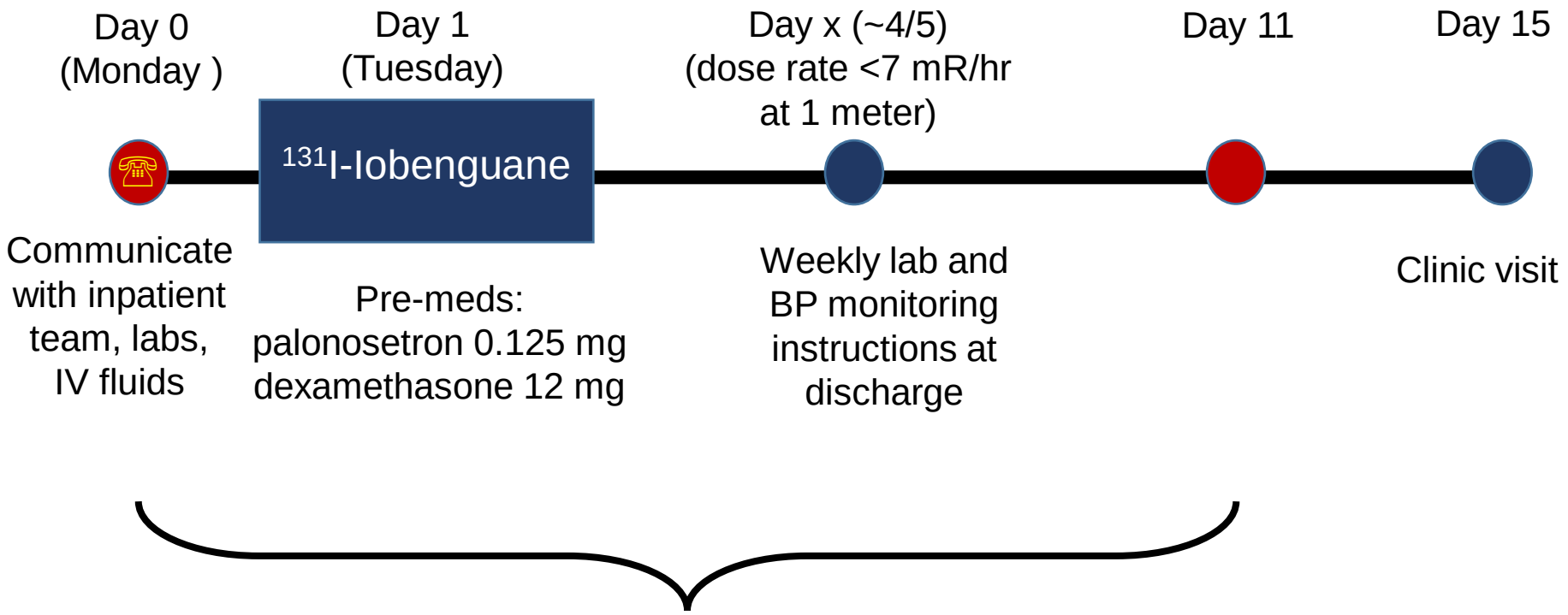
Authorized User

Treatment

- Weight >62.5 kg: **500mCi** and <62.5 kg: 8 mCi/kg
- Thyroid Blockade (Potassium Iodide): 24 hours before and 10 days after
- Hydration : 2L/day one day before and 7 days after
- Platelets >80,000 /mm3 and ANC >1200/mm3

^{131}Iobenguane therapy- dose #1

2-4 weeks after dosimetry



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Post-therapy

- Labs and Clinic visit 2 weeks post Azedra
- Monitor CBC weekly until post-nadir recovery
- BP log
- Labs and Restaging scans at ~10 weeks

Dose Modification for 2nd dose

- Platelet and ANC should have returned to baseline or normal
- Plt nadir of <25,000
- ANC<500
- Life threatening anemia for more than 7 days
- Febrile neutropenia
- Platelet count<50,000 with bleeding
- Reduce dose to either 425mCi or 85% of first dose
- **If pneumonitis: STOP treatment**

Administration of dosimetry dose

- Dosimetry dose
  - *Thaw vial to room temp (take 90 min)*
  - *Dilute with saline*
  - *Dispense dosimetry dose in10 ml syringe with 8 hour BUD*
  - *Administer over 1 minute*

Administration of therapy dose

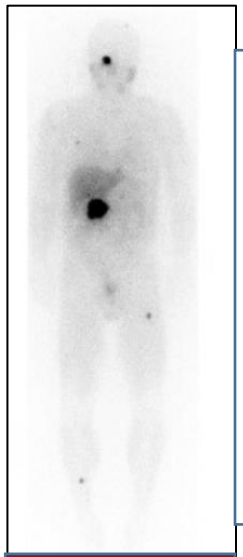
- Therapeutic dose
  - *Thaw vials (two or three 30 ml vials) to room temp and mix*
  - *Transfer needed amount from both vials to a 50 mL vials or 60 mL syringe*
  - *Dispense dose with 8 hour BUD*
  - *Administer over **30 minutes** for adults and 60 minutes pediatric*

Shielding for dose injection

Radiation safety preparation

50 year old male with tongue deviation

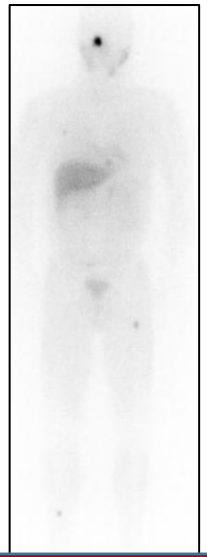
10 year history of HTN; 2 yr history of palpitations, diaphoresis; tongue deviation to the right, R ear pain, hoarseness of voice; Right CN X, XI, XII paresis

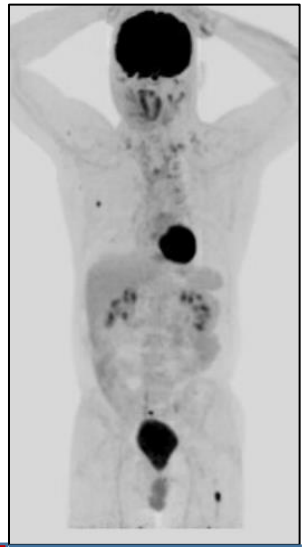


DOXAZOSIN

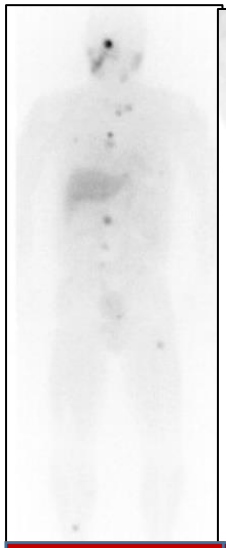
Surgery

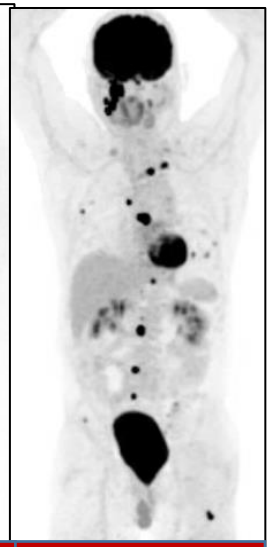
SRS





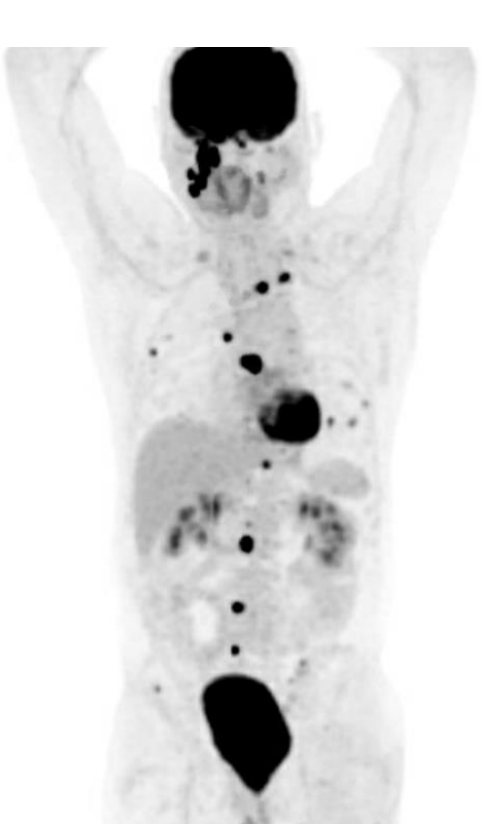
Surveillance



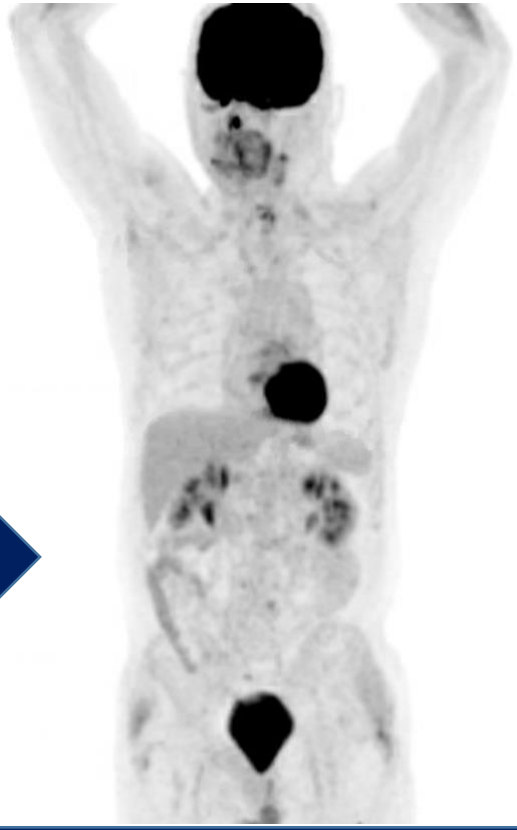


^{123}MIBG		^{123}MIBG	FDG PET	^{123}MIBG	FDG PET
2014		2015		2020	
6 cm RP mass, 2 cm R skull base mass, bone mets		Palpitations, diaphoresis resolved		^{131}Iobenguane offered	

Response to ^{131}I-Iobenguane



Baseline FDG PET



Following 2 doses of ^{131}I-Iobenguane

Challenging situations

- **MIBG negative disease*:*** 30% of *SDHB* mutated tumors are negative on MIBG scan (Zelinka ERC 2008).
- **Sequencing treatments**: Prior chemotherapy may exacerbate low blood counts.
- **Dual Tracer Positivity:** Both Dotatate PET (SSTR2 receptor) and MIBG scan positive (NE Transporter)
- **Future:** Combination strategies with medications that target VEGF (sunitinib)

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Questions?

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