

Gallium-68 Information Session

Michael Graham, PhD, MD
University of Iowa
Co-Chair SNMMI Clinical Trials Network

SNMMI Annual Meeting June 9, 2014

SNMMI SOCIETY OF
NUCLEAR MEDICINE
AND MOLECULAR IMAGING
CLINICAL TRIALS NETWORK

CTN Mission: Facilitate the use of molecular imaging radiopharmaceuticals in clinical trials

- Ensure quality imaging is conducted in drug development clinical trials
- Facilitate access to investigational radiopharmaceuticals, including PET and SPECT agents
- Provide education and training for molecular imaging professionals performing clinical research
- Develop partnerships to enhance use of new radiopharmaceuticals

SNMMI/CTN Ga68-related Activity

- Bi-annual meetings to raise awareness
- Initial focus on identifying best agent
- More recently:
 - Common end-product specifications
 - Standardized protocols
 - Helping new sites
 - (IND template, consent forms, data forms)
 - Obtained orphan drug designation for DOTATOC
 - Assisting commercialization

Orphan Drugs

The FDA Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in USA (not more than 5 in 10,000 in EU)

- Fewer subjects needed in pivotal trial
- Application fees are waived
- Eligible for FDA grant funding
- Designation does not mean approved for clinical use
- Designated indication: management of patients with known disease

SNMMI/CTN Plan for Ga68 DOTATOC

- NDA approval of DOTATOC
- Waive exclusivity
- Help sites obtain aNDA

Implications

- Other sites can obtain DOTATOC aNDA

Compounding Model

- Companies can develop kits and seek NDA for kits
- Pharmacies will be able to compound and distribute

Current North American Activity

- DOTATOC
 - Iowa, UCSF, JHU (MGH, Wash U, Mt. Sinai, U Penn ...)
- DOTATATE
 - Vanderbilt, UCLA, NIH, RadioMedix, Stanford
(MD Anderson, LSU ...)
- DOTANOC
 - Indiana, Edmonton

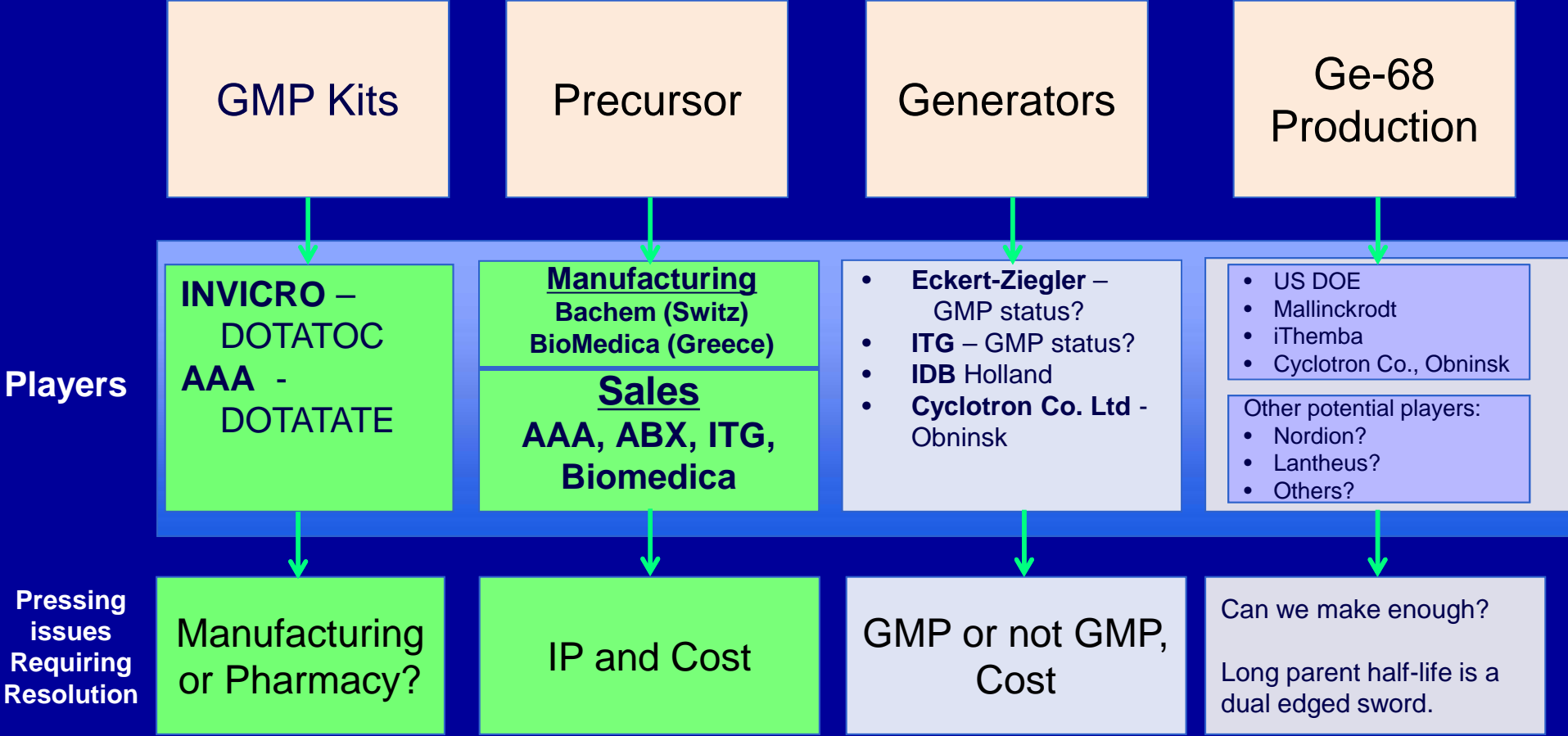
Cost Recovery

- FDA believes that in most cases the cost of an investigational drug in a clinical trial intended to support a marketing application is an ordinary cost of doing business.
- The purpose of permitting charging for an investigational drug in a clinical trial is to permit a sponsor to recover the costs of making certain drugs when clinical trials could not be conducted without charging because the cost of the drug.
- A sponsor authorized to charge for its drug in a clinical trial can only recover its direct costs.

Charging for imaging is outside the purview of FDA

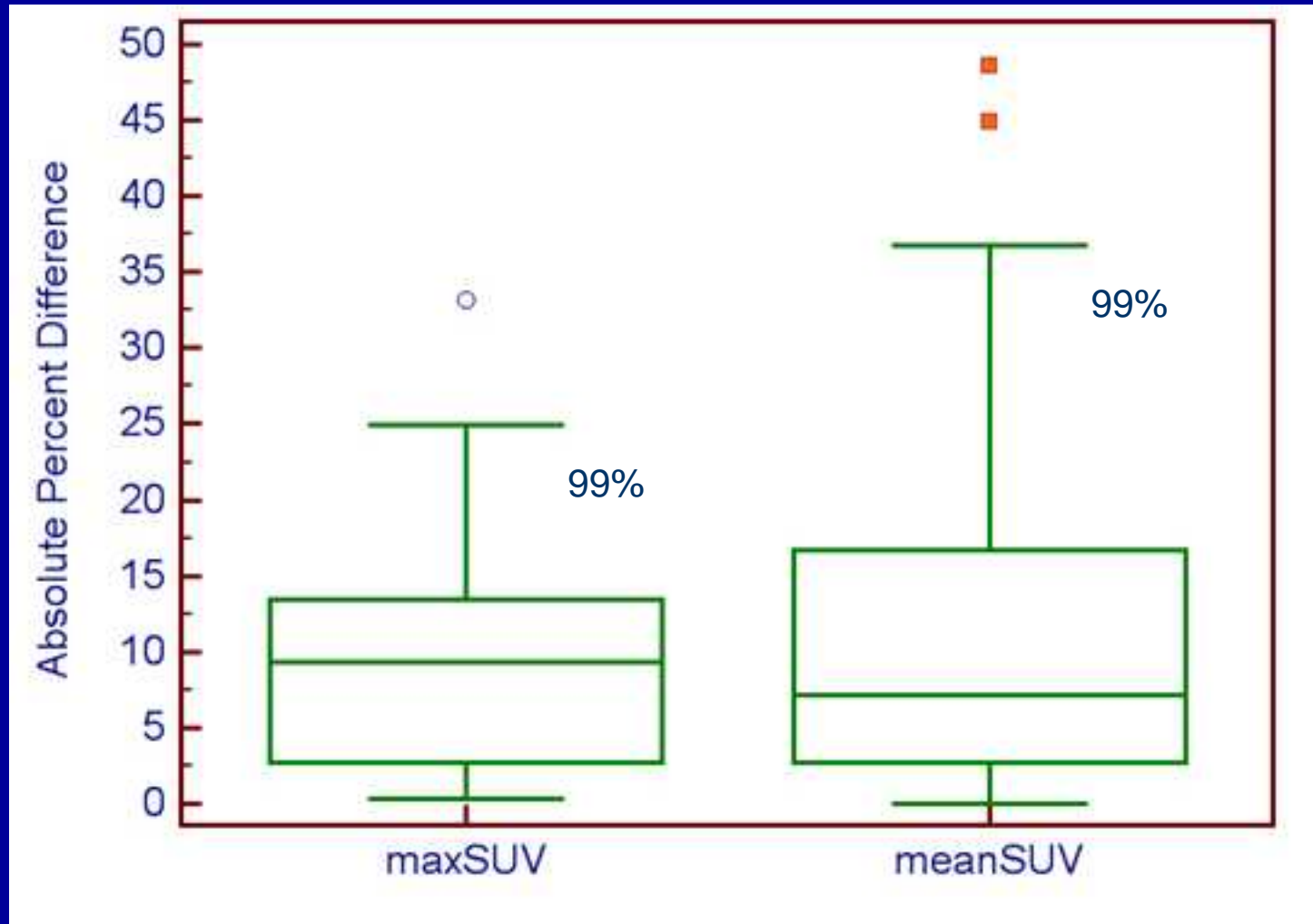
| IP Situation | | | |
|--------------|------------|-------|------------|
| | IP Europe | IP US | IP Canada |
| DOTATOC | 2015 | 2014 | 2014 |
| DOTATATE | 2014 | 2015 | 2015 |
| DOTANOC | Off Patent | 2022 | Off Patent |

The Big Picture

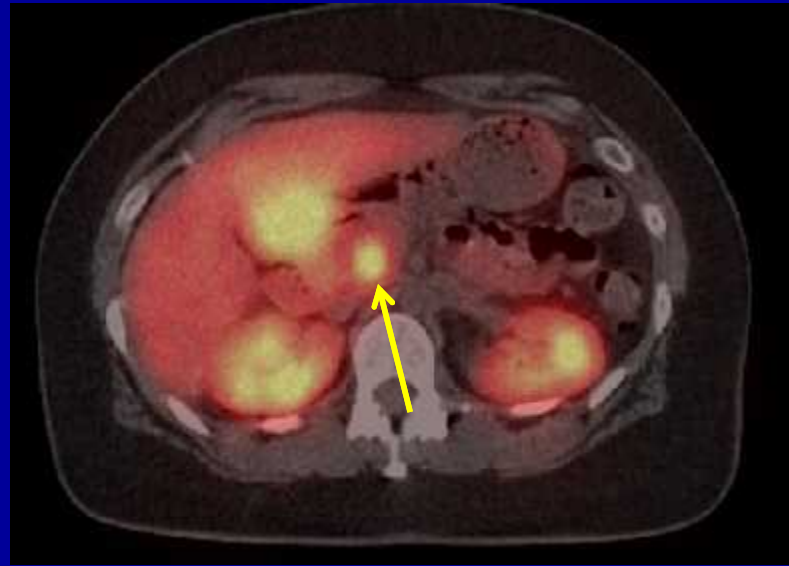


Other Considerations: Distribution (Cardinal, IBA, PETNET), Patients, NET oncologists.*

Y Menda, LL Boles Ponto, M Schultz, GKD Zamba, GL Watkins, DL Bushnell,
MT Madsen, JJ Sunderland, MM Graham, TM O' Dorisio, MS O' Dorisio.
Repeatability of Ga-68 DOTATOC PET Imaging in Neuroendocrine Tumors.
Pancreas. 2013 v42:937-43.



Unknown Primary with Metastatic NET to Liver and Bones, Negative Octreoscan and CT for Primary



Scan Results (N=127)

Diagnosis of NET

- Ga-68 DOTATOC positive in only 3/27 patients presenting with symptoms / labs suggestive of elevated serotonin without diagnosis of NET (2 false positive, 1 unconfirmed)

Unknown Primary

- Ga-68 DOTATOC identified primary tumor in 16/25 pts with metastatic disease, 11 true positive. 2 false positive 3 unconfirmed. 9 false negative.

Initial staging & Restaging (75)

Funding is provided via a Cost-Recovery IND

Presentations from Industry and Academia

1. Ronald Walker, Vanderbilt University, Nashville, TN
2. Andre Iagaru, Stanford, Palo Alto, Ca
3. Sherly Mosessian, UCLA, Los Angeles, Ca
4. Jim Fletcher, Indiana University, Indianapolis
5. Harshad Kulkarni, Zentralklinik, Bad Berka, Germany
6. Ebrahim Delpassand, Excel Diagnostics, Houston, Tx
7. Dirk Becker, Eckert & Ziegler, Germany
8. Izabela Tworowska, Radiomedix, Houston, Tx
9. Maurizio Mariani, Advanced Accelerator Applications, France



^{68}Ga -DOTATATE PET/CT

Vanderbilt Experience

Ronald C Walker MD, Jeff Clanton RPh BCNP,
Eric Liu MD, Dominique Delbeke, MD PhD
Nashville, TN

^{68}Ga -DOTATATE PET/CT - Vanderbilt



- IND 111972
- [clinicaltrials.gov NCT01396382](https://clinicaltrials.gov/ct2/show/study/NCT01396382)

Table 1: Neuroendocrine tumor types (n=97):

| Primary Tumor Type | Number of Patients |
|---|--------------------|
| Lung | 7 |
| Stomach/prox duodenum/pancreas | 22 |
| Mid-gut | 44 |
| Hindgut/rectal | 3 |
| Other | 5 |
| Metastatic disease from unknown primary | 16 |

^{68}Ga -DOTATATE PET/CT - Vanderbilt



- Safety, efficacy and non-inferiority study
- Toxicity (serial EKG, CMP, vital signs) before and after scans – no significant toxicity observed
- Compared to conventional imaging (CT, MRI, ^{111}In -Octreotide) for impact on care
- Independent readings for reproducibility
- Impact: none, minor (e.g. change in existing treatment plan) or major (e.g. change to new treatment plan)

^{68}Ga -DOTATATE PET/CT - Vanderbilt

Impact on Care vs. all CI:

- No impact: 55 (56.7%)
- Impact: 42 (43.3%)
- Minor impact: 10 (10.3%) – most commonly a change in surgical plan
- Major impact: 32 (33.0%) – most commonly to refer patients to PRRT or to convert patients to a surgical plan.
- Number of patients referred to PRRT as a result of ^{68}Ga DOTATATE: 15 (15.5%)
- Number of patients where PRRT referral was cancelled (due to poor uptake): 2 (2.1%)
- Number of patients referred for PRRT with positive ^{68}Ga DOTATATE and negative ^{111}In Octreotide: 5 (5.2%)

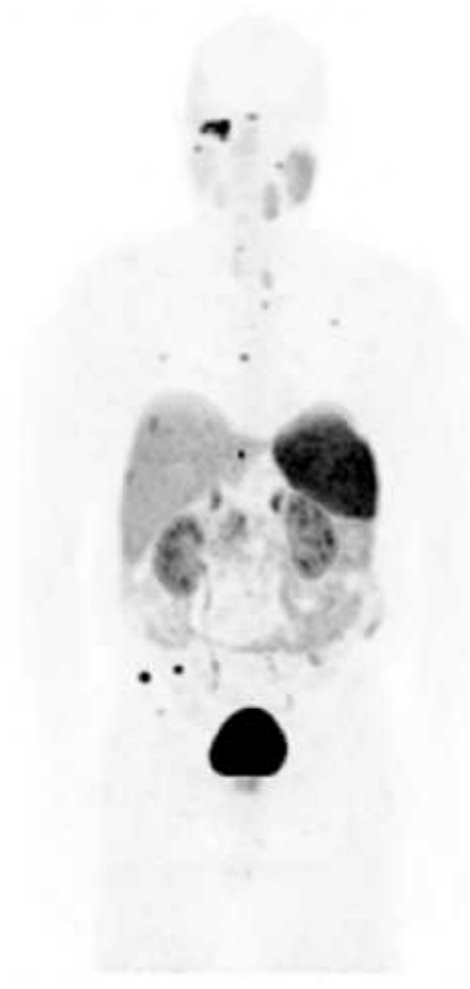


^{68}Ga DOTA TATE PET: Current Status at Stanford

- 33 patients enrolled to-date since Jan 2014
- IND approved as EAP for 200 participants
- Cost recovery mechanism in place
- Cannot bill patients directly per local IRB
- Cannot bill MediCare/MediCal
- Professional fee waived
- Did not see a decrease in the price of precursor yet
- Almost completely replaced ^{111}In Octreoscan[®]
- Roughly $\frac{3}{4}$ of claims reimbursed by insurance



^{111}In Octreoscan[®]



^{68}Ga DOTA TATE

- Changes in management in 15 of the 20 patients who had ^{111}In -Octreoscan[®]
- Will apply for funding to do ^{68}Ga DOTA TATE PET/MRI

UCLA- ^{68}Ga -DOTATATE PET/CT studies



Clinical

- Johannes Czernin M.D.
- Martin Auerbach M.D.
- Ken Herrmann M.D.

Manufacturing

- Sam Sadeghi Ph.D
(Director of cyclotron and radiochemistry facility)

Regulatory

- Sherly Mosessian Ph.D
- Shaojun Zhu M.S.



Regulatory summary

1. **UCLA IND (Reference to Vanderbilt IND)**
 - 12/18/12: IND was approved with cost recovery.
 - By March, 2014, 100 patients were imaged.
 - FDA did not grant request to increase number of patients beyond 100 as part of a Phase I IND

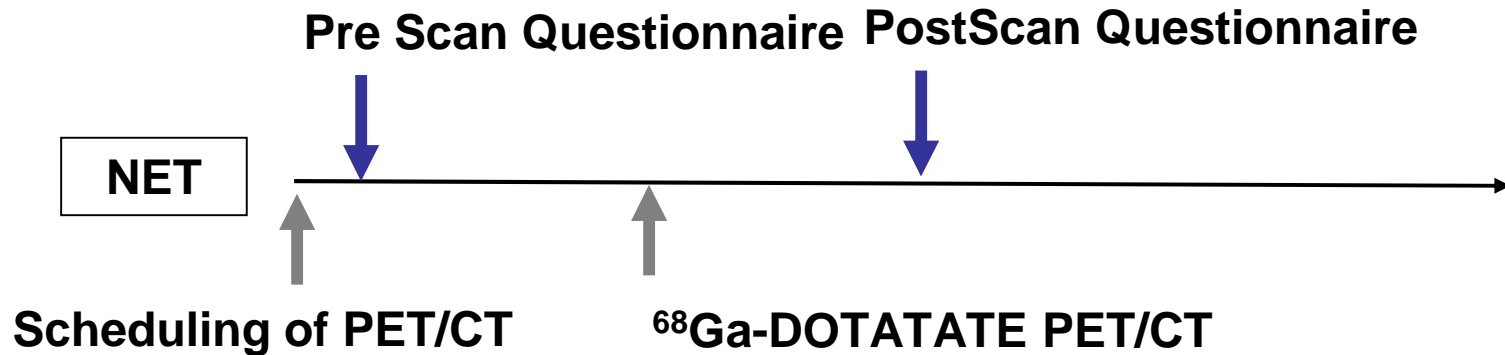
2. **UCLA Expanded Access IND (Content similar to Stanford Expanded Access IND)**
 - 05/01/14: UCLA Expanded Access IND was approved with cost recovery to enroll 300 patients.
 - Currently in the process of finalizing IRB amendment approval and enrolling human subjects.



Study Aim/Design



- NOPR like design to determine the impact of ^{68}Ga -DOTATATE PET/CT on the management of patients with NETs



| Pre Scan Questionnaire | Post Scan Questionnaire |
|----------------------------|-------------------------|
| Staging/Restaging | Post Scan M1 Suspicion |
| Prior Therapy | Change of M1 Suspicion |
| Tumor Location/Grade/Stage | New Metastases? |
| M1 Suspicion | Intended Treatment |
| Intended Treatment | Treatment Changes? |

Management changes

- ▶ Major management changes: 28%

| Major change type | N (% change) |
|--------------------------------|-----------------|
| Away from surgery | 7 / 61 (11.5 %) |
| To surgery | 8 / 61 (13.1%) |
| From treatment to no treatment | 1 / 61 |
| From no treatment to treatment | 1 / 61 |

- ▶ Overall management changes: 31 / 61 (51%)

First year Experience with ^{68}Ga DOTA-NOC

James W. Fletcher, Mark Green, Mark Tann, Mary Maluccio,
Carla Mathias, Gary Hutchins

Department of Radiology and Imaging Sciences
Indiana University School of Medicine
Indiana/Purdue University in Indianapolis



Indiana University Health



SCHOOL OF MEDICINE
INDIANA UNIVERSITY

^{68}Ga DOTA-NOC

- Expanded Access IND # 117,255
- Source of ^{68}Ga has been Eckert-Ziegler generator
- Initial estimate of 30 patients per year over 4-years
- Actual enrollment Year 1 → 39 patients



Preparation

- All doses met specified release criteria
- Doses averaged 4.7 ± 0.6 mCi
- Production time: elution \rightarrow dose release: 46 ± 5 minutes
(usually 44 minutes, but three doses delayed by need to re-filter or to repeat endotoxin test because device issue)
- Radiochemical purity: $98.2 \pm 0.7\%$
- Virtually no ^{68}Ge breakthrough $3 \times 10^{-7} \%$



Indications:

1. Patients with neuroendocrine cancers who are potentially candidates for treatment by multivisceral transplant.
2. Patients in whom a liver mass has been upon biopsy found to be a neuroendocrine tumor (presumably metastatic), and whose treatment requires detection of the unknown primary tumor and/or definition of the extent of disease.
3. Patients in whom prior, clinically indicated, ^{111}In -Octreoscan SPECT has failed to address the clinical diagnostic need, and for whom the superior resolution and target/background contrast of a ^{68}Ga -DOTA-NOC PET/CT study is clinically judged to be in the patient's best interest for advancing decisions about their



Patient INdications

- Use of ^{68}Ga -DOTA-NOC PET/CT to locate a primary lesion in patients with liver metastases and an unknown primary → 5 patients
 - 2 had disease in liver but no evidence of primary site
 - Lack of occult primary led to change in surgical management in 1
 - 3 had previously unknown occult primaries located by study (2 pancreas, 1 small bowel)
 - Both PNET patients went on to get systemic treatment which was a change in management



Patient INdications

- **Use of ^{68}Ga -DOTA-NOC PET/CT to determine eligibility for multivisceral transplant → 10 patients**
 - Six (6) patients had evidence of previously unknown disease outside the abdomen, making them ineligible for multivisceral transplant under our current eligibility criteria.
 - Two (2) patients had occult asymptomatic bone metastases
 - Four (4) patients had disease in the lungs or extra-abdominal lymph node basins (i.e. mediastinum)



Patient INdications

- **Thirteen (13) patients underwent ^{68}Ga -DOTA-NOC PET/CT to evaluate extent of disease for one of several reasons**
- Five (5) patients had considerably greater disease burden than expected.
- Three (3) patients had disease burden as predicted, or less than predicted.
- Two (2) patients had recurrent disease detected by ^{68}Ga -DOTA-NOC PET/CT, and a change in management based on that result.
- Three (3) patients had negative ^{68}Ga -DOTA-NOC PET/CT scans, prompting a change in management and evaluation of other causes of presenting symptoms.



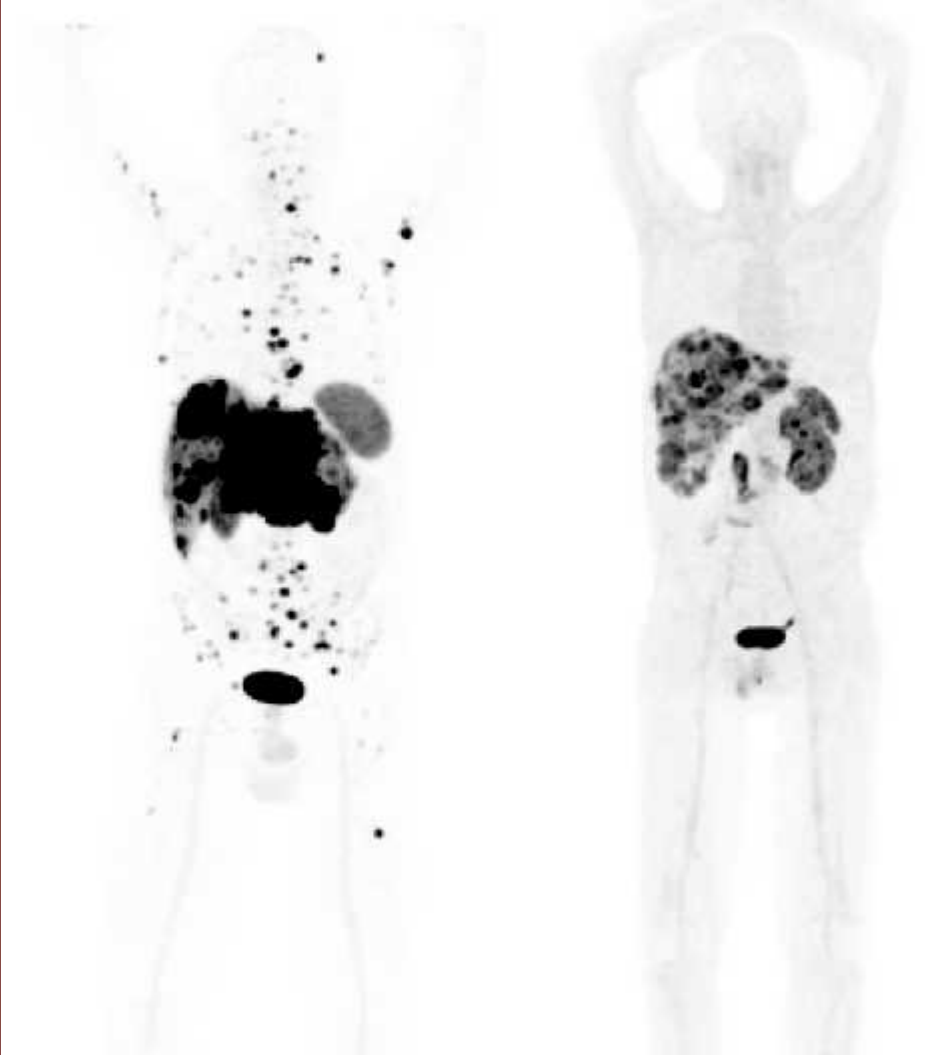
Summary

- No adverse reactions with exception of transient 2-5 minute nausea in ~50% of patients
- No adverse events
- No drop outs
- High quality images that provided information that exceeded what was available from conventional imaging (^{111}In -Octreotide, contrast enhanced CT)



Sample Images

- Images obtained approximately 1-hour after injection on Siemens mCT device. Typically with contrast enhancement of CT (Isoview 370).
- 3-minutes per bed position.



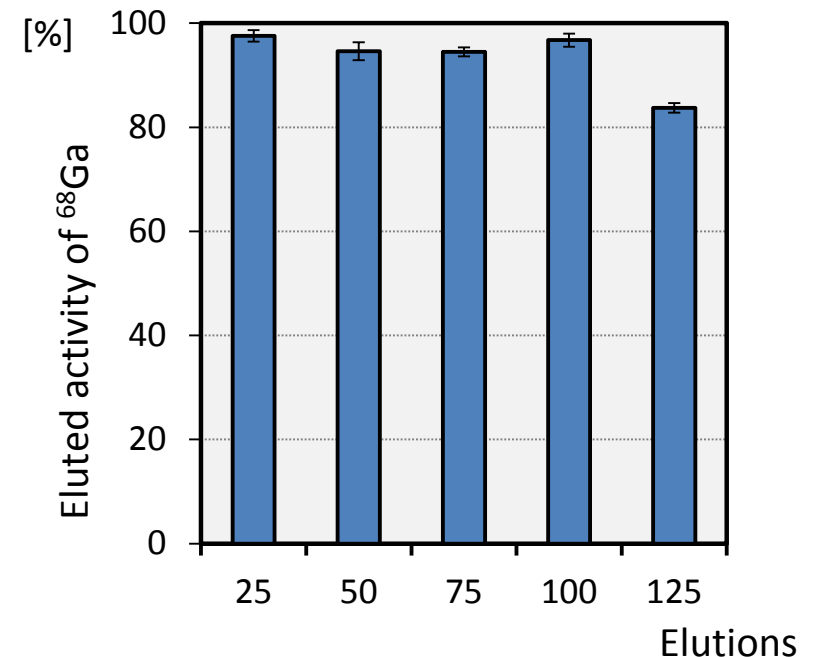
Indiana University Health



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Update on ^{68}Ga -DOTATATE (GalioMedix™) and $^{68}\text{Ge}/^{68}\text{Ga}$ generators (ITG GmbH)

- RadioMedix Inc. – Phase I/II IND application (IND 117289)
(Compounding, radiolabeling, QC validation, IND submission)
- Prepared ~ 110 doses
- 1-2 doses of ^{68}Ga –DOTATATE per day
(PET/CT imaging: 1-3 patients)
- $^{68}\text{Ge}/^{68}\text{Ga}$ generator ITG GmbH (30 mCi); 50mCi
- Consistent and reliable elution profiles;
Elution yield >80% on calibration date and
during shelf life of generators



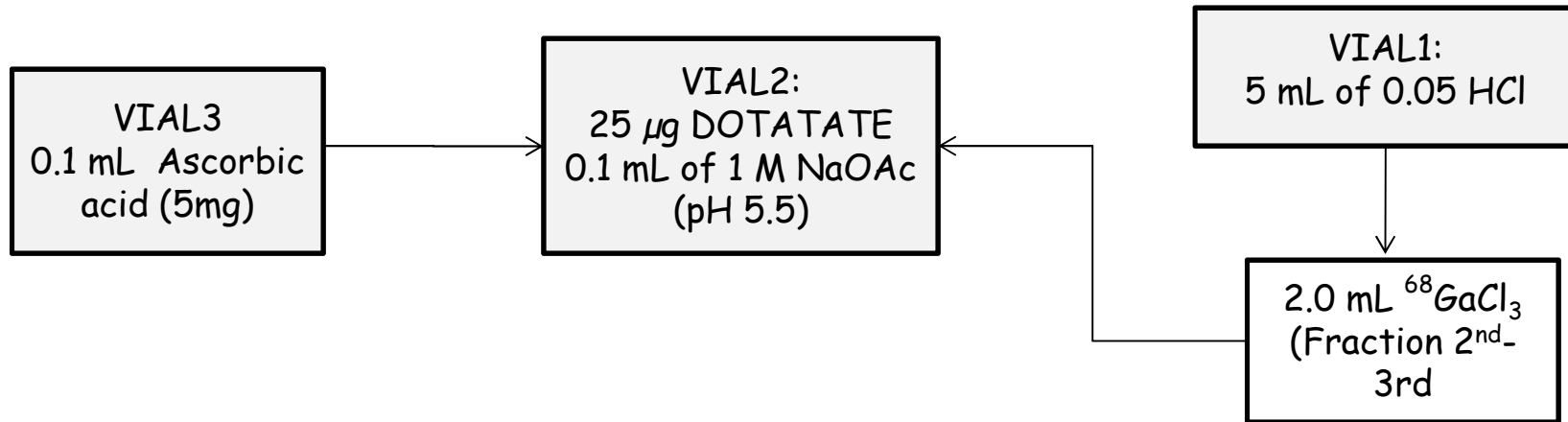
ITG GmbH $^{68}\text{Ge}/^{68}\text{Ga}$ generators:

Novel GMP-grade generators with shelf life of 12 months or 250 elutions
DMF authorization – final stage

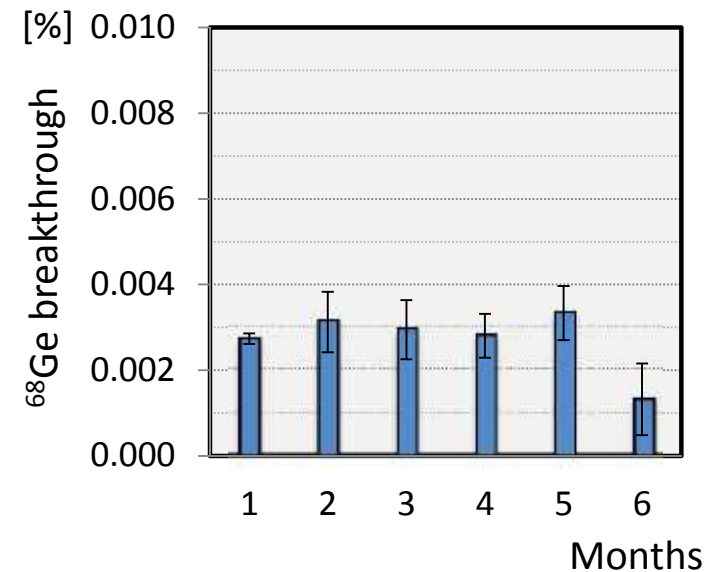


Simplified protocol for the dose preparation using ITG $^{68}\text{Ge}/^{68}\text{Ga}$ generators

- No need for pre-purification /pre-concentration of ^{68}Ga using ion exchange resin
- No need for purification of the final dose



| Required specification | Observed parameters |
|---------------------------------|--|
| Dose: 4 – 16 mCi | $7.34 \pm 3.4\text{mCi}$ |
| RCP > 95% as determined by iTLC | $98.998 \pm 1.1\%^*$ |
| Ge-68 content <0.01% | $0.00265 \pm 2.05\text{E-}03 \%$ |



RadioMedix Inc. - Distribution and compounding services

RadioMedix Inc. - ITG GmbH (Germany) Business Partnership

- US Exclusive distribution rights for the ITG GmbH products:

$^{68}\text{Ge}/^{68}\text{Ga}$ generators

IQS ^{68}Ga Fluidic labeling module

DOTATOC

$\text{Ac}^{225}/\text{Bi}^{213}$ generators

and $\text{W}^{188}/\text{Re}^{188}$ generators

- ^{68}Ga program using ITG GmbH generators has been initiated in US clinical centers and networks of radiopharmacies
- Offer leasing plan for $^{68}\text{Ge}/^{68}\text{Ga}$ generators (6, 12, 18 months)

RadioMedix Inc.

- Provide support and on –site training
- Compound and distribute the DOTATOC kits

Izabela Tworowska itworowska@radiomedix.com

Wednesday, June 11th-Radiopharmacy, Abstract 612



Kit for the preparation of ^{68}Ga -labeling of sst analog peptides





A sterile, lyophilised, easy-to-use kit approach for the preparation of ^{68}Ga -labeling of sst analog peptides

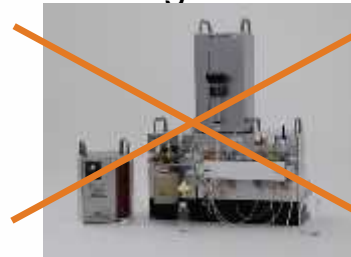
- One of the barriers to more widespread use of Ga-68 PET is the absence of sterile, lyophilised easy-to-use kits for the direct preparation of ^{68}Ga drugs.
- Currently the preparation of ^{68}Ga -radiopharmaceuticals implies articulate synthesis procedure and/or the use of synthesis modules which need **fully-equipped cGMP radiopharmacy**.
- **Extensive quality controls** of a product resulting from an extemporaneous production process are also required.
- Both the synthesis set-up and the relevant quality controls are currently under the responsibility of the individual clinical centres.
- Conversely, kit-type production allows a simple ^{68}Ga -labeling procedure based on **direct reconstitution** of a pre-formulated GMP kit, **not requiring cGMP manufacturing processing of the eluate or additional filtration or purification steps**.
- Kit-type production of ^{68}Ga -radiopharmaceutical **would definitively make ^{68}Ga the PET analogue of $^{99\text{m}}\text{Tc}$** .

No need for cGMP, radiochemistry modules and extensive QC

Kit approach: production of ^{68}Ga -DOTATATE or ^{68}Ga -DOTATOC injectable solution by reconstitution of a pre-formulated GMP kit adding directly the eluate from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator without the need of any automatic module (only an heating block is required)

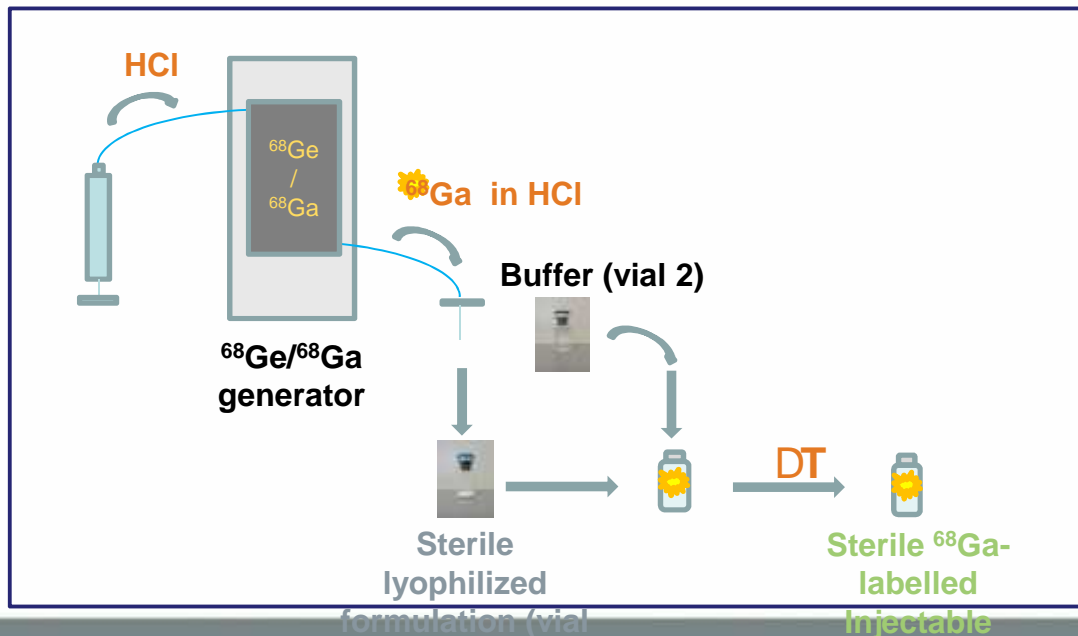


Straightforward and standardized reconstitution procedure



- ~~Not standardized procedure~~
- ~~Onerous equipment costs (module and analytical instruments) in cGMP environment~~
- ~~Need for expert staff~~
- ~~Extensive QC~~

Reduced QC tests to be performed locally



| Test | Specifications |
|--------------------------------------|----------------|
| pH | 3.2 – 3.8 |
| Radiochemical Purity (ITLC) Rf 0-0.1 | % peak with 3% |

Standardized pharmaceutical product with controlled quality and wide availability for PET localization of primary and/or metastatic lesions of GEP-NETs



^{68}Ga kits are now freely available for clinical trials

- The kit-based approach developed by AAA for the preparation of ^{68}Ga -Dotatate and ^{68}Ga -Dotatoc satisfies the necessity of a standardized pharmaceutical product with controlled quality and wide availability.
- AAA is actively pursuing development of the kits in **both USA and Europe** for the diagnosis and the management of GEP-NETs.
- The ^{68}Ga -Dotatate kit is the ideal companion diagnostic agent of AAA Lutathera[®], currently in Phase III (Netter I study) for the treatment of mid-gut carcinoid, with which it shares the same chemical features.
- The pharmaceutical development of both kits is completed.
- Following the activation of the relevant INDs, the **kit can be made available for free** for Investigator Driven Studies of relevant interest.

Update:

Generator now approved

Status Quo ^{68}Ga :
Registration of the Eckert & Ziegler
GMP $^{68}\text{Ge}/^{68}\text{Ga}$ -Generator in the EU



SNMMI 2014
CTN Meeting

St. Louis, MO, USA
June 9th 2014

Dr. Dirk W. Becker
Eckert & Ziegler Radiopharma GmbH
Berlin, Germany

Update June 19th 2014:
Generator is approved
in several European
Countries

Ge⁶⁸/Ga⁶⁸ Generators supplied by Eckert & Ziegler



Cyclotron
Obninsk, Russia



E&Z IGG100



EZR pharm. Grade

Chemical grade only

GMP

Update June 19th 2014: Generator is approved for registration in several European Countries

GMP certificate of the Eckert & Ziegler Ge⁶⁸/Ga⁶⁸ Generator

GMP certificate was issued in June 2012

Landesamt für Gesundheit und Soziales



Zertifikat-Nr./Certificate no: 2012/01/Eckert & Ziegler Radiopharma

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Part 1

Issued following an inspection in accordance with Art. 111 (5) of Directive 2001/83/EC or Art. 15 of Directive 2001/20/EC

The competent authority of GERMANY confirms the following:

The manufacturer

Eckert & Ziegler Radiopharma GmbH

Site address

**Robert-Rössle-Straße 10
13125 Berlin**

has been inspected under the national inspection programme in connection with **manufacturing authorisation no. 5373/Eckert & Ziegler Radiopharma/I** in accordance with Art. 40 of Directive 2001/83/EC or Art. 13 of Directive 2001/20/EC transposed in the following national legislation:

*Sect 13 para 1 Arzneimittelgesetz
(German Drug Law)*

Part 2

A) Human Medicinal Products

1 MANUFACTURING OPERATIONS

1.1 Sterile products

1.1 Aseptically prepared
(list of dosage forms)

1.1.1.6 other aseptically prepared products:
Radionuclide-Generators

1.6 Quality Control testing

1.6.3 Chemical/Physical

Any restrictions or clarifying remarks related to the scope of this certificate for part 2 A) Human Medicinal Products:

To 1.1.1.6:

⁶⁸Ge/⁶⁸Ga-Generators with active substance ⁶⁸Ge/⁶⁸Ga-chloride for radiolabelling of precursors for diagnosis with Positron-Emission-Tomography

- The GMP grade generator is distributed by EZR only
- It was developed between 2008 and 2011.
- The production site is located north of Berlin, Germany
- **UPDATE June 19th 2014:**
The GMP grade $^{68}\text{Ge}/^{68}\text{Ga}$ -generator is now approved for registration in several European Countries. MA will be issued and DMF in the US will be filed



Why and How to Register a Radionuclide Generator as a Drug?

- According to EU Directive 2001/83/EC, Ch. I, Art. 6.2 before placing a radionuclide generator on the market a marketing authorization has to be issued by the competent authorities of that member state. (mandatory)
- According to the German Medicinal Products Act, 1. Ch., Sect 4, Art. 8 are radionuclide generator considered as radiopharmaceuticals and therefore need to be registered (mandatory)
- According to the Guideline on Radiopharmaceuticals EMEA/CHMP/QWP/306970/2007, Ch. 4.1: the mother and the daughter radionuclides in a radionuclide generator, both are to be considered as active ingredients (mandatory)
- In the Pharm. Eu. there is a monograph about “Gallium (Ga68) solution for radiolabelling” (2013/2464)