J of Nuclear Medicine Technology, first published online February 2, 2018 as doi:10.2967/jnmt.117.205021

PET Radiopharmaceuticals: What's new, what's reimbursed, and what's next?

Bonnie N. Clarke

Society of Nuclear Medicine and Molecular Imaging, Reston, Virginia

Correspondence to:

Bonnie N. Clarke
Director, Research and Discovery

Phone: 703.667.5120
Fax: 703.667.5135
e-mail: bclarke@snmmi.org

PET Radiopharmaceuticals: What's new, what's reimbursed, and what's next?

The field of molecular imaging – the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems – is undergoing a period of growth and expansion. Of the ten Food and Drug Administration (FDA)-approved positron emission tomography imaging agents, six have been approved in the past five years. This explosion of approvals may be attributed to release of FDA 21 CFR part 212 Current Good Manufacturing Practice for Positron Emission Tomography Drugs on December 10, 2009. Part 212 provides clear expectations and guidelines for FDA approval of radiopharmaceuticals.

Radiopharmaceutical – NDA* sponsor	Original approval date
Fluoride F-18 (sodium Fluoride F-18) (GE)	2/24/1972
Cardiogen-82® rubidium Rb 82 generator (Bracco)	12/29/1989
Fludeoxyglucose F18 (Downstate Clinic)	8/19/1994 (epileptic foci only)
Fludeoxyglucose F18 (Weill Cornell)	8/5/2004 (glucose metabolism)
Ammonia N13 (Feinstein)	8/23/2007
Amyvid™ Florbetapir F18 (Avid Radiopharmaceuticals)	4/6/2012
Choline C 11(Mayo Clinic)	9/12/2012
Vizamyl™ Flutametamol F18 (GE Healthcare)	10/25/2013
Neuraceq™ Florbetaben F18(Piramal)	3/19/2014
Axumin® fluciclovine F18 (Blue Earth Diagnostics)	5/27/2016
NETSpot® Ga 68 dotatate (AAA)	6/1/2016

Table 1. FDA approved positron emission tomography (PET) agents. Note: Nomenclature follows FDA approved label. *From* http://accessdata.fda.gov
*New Drug Application

Of the most recently approved agents, Amyvid, Vizamyl, and Neuraceq – all proprietary agents with intellectual property or patents – underwent a 'typical' development pathway. Each molecule was owned by a corporate entity, namely Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly and Company), GE Healthcare, and Piramal Imaging, respectively, who guided the development of the agents through prospective Phase 1, 2, and 3 studies, including an imaging correlation to post-mortem confirmation of beta-amyloid neuritic plaques (the plaques that are thought to cause Alzheimer's disease). Mayo Clinic's ^{11}C-choline, Blue Earth Diagnostic's (BED) Axumin, and Advanced Accelerator Application's (AAA) NETSPOT, however, all took alternate routes to FDA approval.

In September 2012, FDA approved ^{11}C-choline with the indication of: ^{11}C-choline injection is a radioactive diagnostic agent for positron emission tomography (PET) imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized

tomography (CT), or magnetic resonance imaging. In these patients, ^{11}C-choline PET imaging may help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation. Suspected prostate recurrence is based upon elevated blood prostate specific antigen (PSA) levels following initial therapy. A limitation of use specifically noted on the drug label was that ^{11}C-choline PET imaging is not a replacement for histologic verification of recurrent prostate cancer.
At the time of the approval, ^{11}C-choline was a technological breakthrough in prostate cancer imaging and therapy, allowing detection of sites of recurrence, and subsequently, more effective treatment strategies to be employed months earlier than conventional imaging. Unlike the beta-amyloid agents which underwent multiple prospective studies, the safety and effectiveness of ^{11}C-choline was documented with a systematic review of five published studies involving a total of 98 patients. FDA noted that there was a substantial body of human studies with ^{11}C-choline that showed utility in other cancer types as well. Except for minor skin inflammation at the injection site, no adverse events were reported. (*1*)

The approval of choline by FDA represented a paradigm shift in radiopharmaceutical drug development. This was apparent with the approval of new agents, namely Axumin and NETSPOT, within one week of each other in May and June 2016. Fluciclovine was developed at Emory University by Mark Goodman, PhD, professor of radiology and imaging scientist Emory University School of Medicine. The first paper on the compound was published in 1999. Emory patented the compound, licensed it to Japan's Nihon Mediphysics, and Dr. Goodman continued his research for several years. In 2008, GE Healthcare licensed the technology before spinning it off to the newly-formed BED in 2014. (*2*) Of note, SNMMI's Clinical Trials Network (CTN) was collaborating with GE Healthcare on the agent and had secured a grant from Movember to conduct a Phase 3 study prior to the transfer to BED. Because of this history, both Emory University and CTN played a role in the filing of the NDA. Axumin, or fluciclovine (formerly known as FACBC), was approved on the basis of two studies. The data was submitted from four clinical sites in the US, Italy, and Norway and analyzed prospectively by UK-based Blue Earth Diagnostics. The first study was a comparison of fluciclovine scans to histopathology data in 105 men; the second was a comparison to ^{11}C-choline scans in 96 patients. Both studies supported the indication for imaging with Axumin in men with prostate cancer with elevated PSA levels following prior treatment. (*3*)

The first scans with ^{68}Ga-labelled somatostatin receptors (ssrt) were done in Europe as early as 1999. (*4*) Literally thousands of articles on the human use of ^{68}Ga-DOTATATE had been published since that time, including many saying that this was a safe and effective method of imaging neuroendocrine tumors (NETs). (*5*) Because of the success of ^{68}Ga-ssrt imaging in Europe and Australia, physicians in the US wanted to study the agents. The CTN started a Gallium Users Group in 2012 to help US institutions conduct ^{68}Ga-DOTATATE and -DOTATOC studies. CTN developed standardized release criteria for the imaging agents, protocols, imaging manuals, a template investigational new drug application (IND), and information on gallium generators so that universities had a toolkit to get expanded access trials up and running. By 2014, the number of sites imaging with ^{68}Ga-ssrts increased from two to twelve, offering NET patients in the US a scan that otherwise would have required a trip to Europe.

NETs are an orphan disease which FDA defines as a disease with a prevalence of 200,000 or less. By definition, prevalence is the number of cases in the population at a given time, or, simply how widespread a disease is (everyone with NET irrespective of when they were diagnosed). Incidence, by comparison, is the rate of occurrence of new cases and gives one information about the risk of contracting a disease (how many people were diagnosed in a particular year). Thus, NETSPOT received orphan drug designation and received priority review status. Orphan drugs are handled by the FDA's Office of Orphan Product Development (OOPD) and have a slightly different pathway to approval, including the waiving of the Prescription Drug User Fee Act (PDUFA) fee, currently close to $2 million, to file the NDA. Three studies established the safety and effectiveness of NETSpot; a comparison of ^{68}Ga-DOTATATE to CT and/or MRI, a histopathology or clinical follow-up comparison, and an evaluation of patients with NET recurrence. (*6*)

In the approval of these three agents, FDA accepted an analysis of imaging data that was collected outside of the confines of a company-sponsored Phase 3 trial. This points to the importance of these agents in helping determine effective treatment strategies in serious diseases.

Using the New Radiopharmaceuticals

In 2012, the Mayo Clinic was the only site approved to use ^{11}C-choline. Since that time several other institutions – University of Texas MD Anderson, Washington University School of Medicine in St. Louis, and Zevacor - have received FDA approval following submission of abbreviated NDAs (ANDAs). Zevacor produced choline at their Decatur, Illinois facility with plans to expand to additional sites. (Zevacor was acquired by Sofie Biosciences in May 2017). With a half-life of 20 minutes for ^{11}C, distribution is extremely limited. Administration differs from FDG in that patients do not need to fast. The 10-20 mCi dose is injected in a bolus intravenous injection while the patient is on the scanner bed and imaging begins immediately after the injection. Localized uptake of ^{11}C-choline in a site suspicious for prostate cancer recurrence is determined by comparison of the anatomical relationship of concentrated radioactivity to the neighboring tissue background (exclusive of radioactivity physiologically accumulated in the pancreas, liver, spleen, kidney and colon).

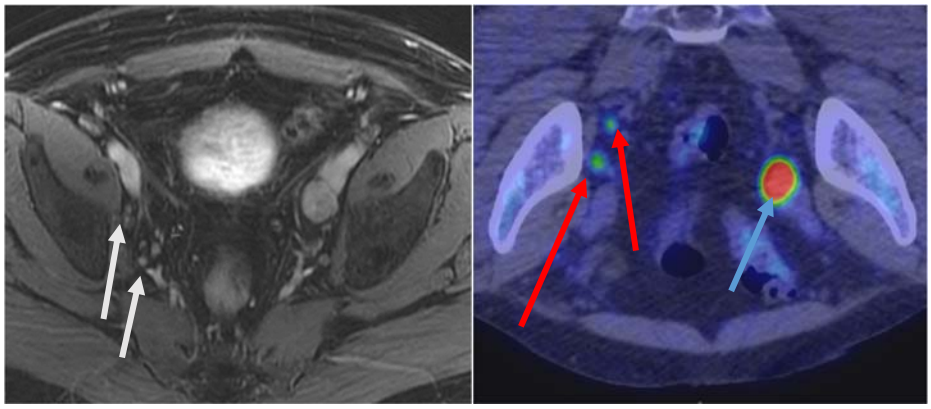
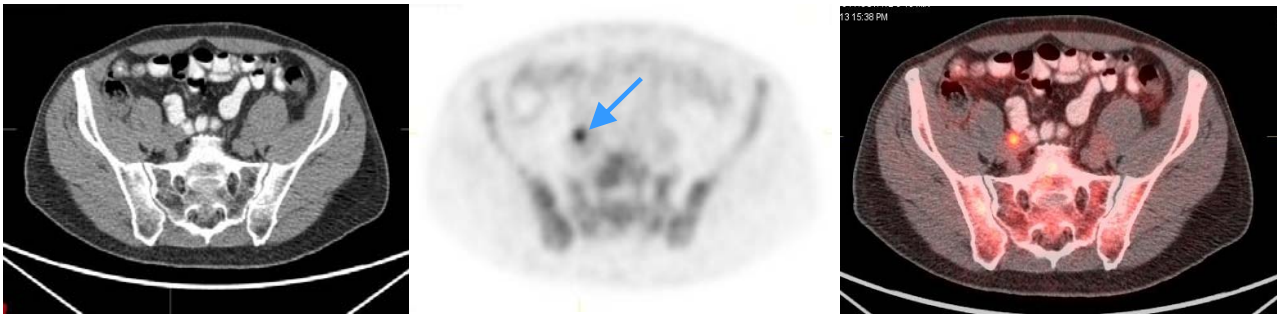


Figure 1. MRI (left) and choline PET/CT (right) in a patient with prostate cancer recurrence (PSA 3.3) show an enlarged left external iliac lymph node with choline uptake (blue arrow) and small right external iliac and internal iliac lymph nodes (grey arrows) with choline uptake (orange arrows). The small right nodes are only considered abnormal on choline PET/CT. PET showed more extensive disease than MRI. After treatment, all nodal disease (circle) shows resolution (left image) and the PSA is < 0.01. Courtesy of Mayo Clinic.

Blue Earth Diagnostic's Axumin, labelled with ^{18}F (half-life =110 minutes), is manufactured and distributed in the US by an ever-expanding number of PETNET Solutions radiopharmacies. Fluciclovine is an amino acid; it works in prostate and other cancer imaging because amino acids are key nutrients for tumor growth so the fluciclovine is incorporated into the tumor cells. (*7*) In preparation for a fluciclovine scan, patients should avoid significant exercise for at least one day prior to PET imaging (to avoid amino acid uptake in muscle) and should not eat or drink for at least 4 hours prior to drug administration. Patients are dosed on the scanner bed with 10 mCi by intravenous bolus injection. Uptake time is 3 to 5 minutes, with a target of 4 minutes. Imaging should start over the pelvis with a least 3 minutes per bed position, the scan time for the first two bed positions can be increased if desired. Localization of prostate cancer recurrence in sites typical for prostate cancer is based on fluciclovine uptake in comparison to tissue background. For lesions less than 1 cm in diameter, focal uptake greater than blood pool should be consider suspicious for prostate cancer. For larger lesions, uptake equal to or greater than bone marrow is considered suspicious for prostate cancer recurrence. To be qualified to order and read Axumin scans, physicians must successfully complete the CTN-developed Axumin Image Interpretation Training presentation and exam located at http://www.snmmi.org/Research/Content.aspx?ItemNumber=10689&navItemNumber=6820.



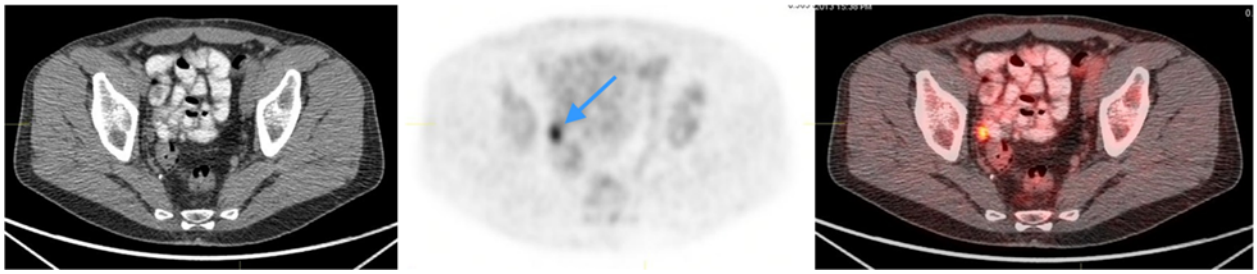


Figure 2: CT, fluciclovine PET, and PET/CT fused (left to right) in a patient with prostate cancer presenting with rising PSA (2.31 ng/mL) post-EBRT and brachytherapy. MR was negative for extra-prostatic disease. Images show positive sub-cm right common iliac and obturator nodes (blue arrows); malignant on laparoscopic dissection.

AAA's NETSPOT, ^{68}Ga-DOTATATE, has a half-life of 68 minutes and is distributed in the US in unit dose form by Cardinal Health and United Pharmacy Partners (UPPI, LLC). Sites that have their own germanium 68/gallium 68 generator (^{68}Ge/^{68}Ga), namely the Eckert & Ziegler (E&Z) GalliaPharma® generator, can order lyophilized kits from AAA and prepare NETSPOT onsite. (Of note, only the Good Manufacturing Practice (GMP)-grade E&Z generator GalliaPharma is approved for use with the kits.) Patients are advised to drink sufficient amounts of water to ensure adequate hydration prior to dosing with DOTATATE, no other special preparation is required. There is controversy over the temporary discontinuation of 'cold' octreotide therapy before the scan. For patients on long-acting therapy (Sandostatin or LAR/Somatuline), the scan should be scheduled at the end of the treatment cycle (e.g., 4 weeks after last injection). For short-acting Sandostatin, schedule the scan 12 or more hours after the last administration. Recommended dose of radioactivity is 2MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq or 5.4 mCi. The uptake time is 40 to 90 minutes with a goal of 60 minutes. The typical field of view is mid-thigh to top of head, with the direction of imaging being caudal to cranial with 3 to 4 minute/bed position suggested, depending on scanner model and body habitus of the patient. If a diagnostic CT scan is requested as part of PET/CT, the CT protocol appropriate for the body region(s) requested should be used. Intraluminal gastrointestinal contrast media may be used, but positive oral contrast such as barium should be avoided as it may cause attenuation correction defects. (*8*) ^{68}Ga-DOTATATE binds to all somatostatin receptor type 2-expressing cells including the pituitary, thyroid, liver, adrenal glands, spleen, pancreas, bowel and urinary system. A complete NETSPOT Image Interpretation Training course, developed by CTN, is available on the SNMMI website at http://www.snmmi.org/Research/Content.aspx?ItemNumber=10689&navItemNumber=6820

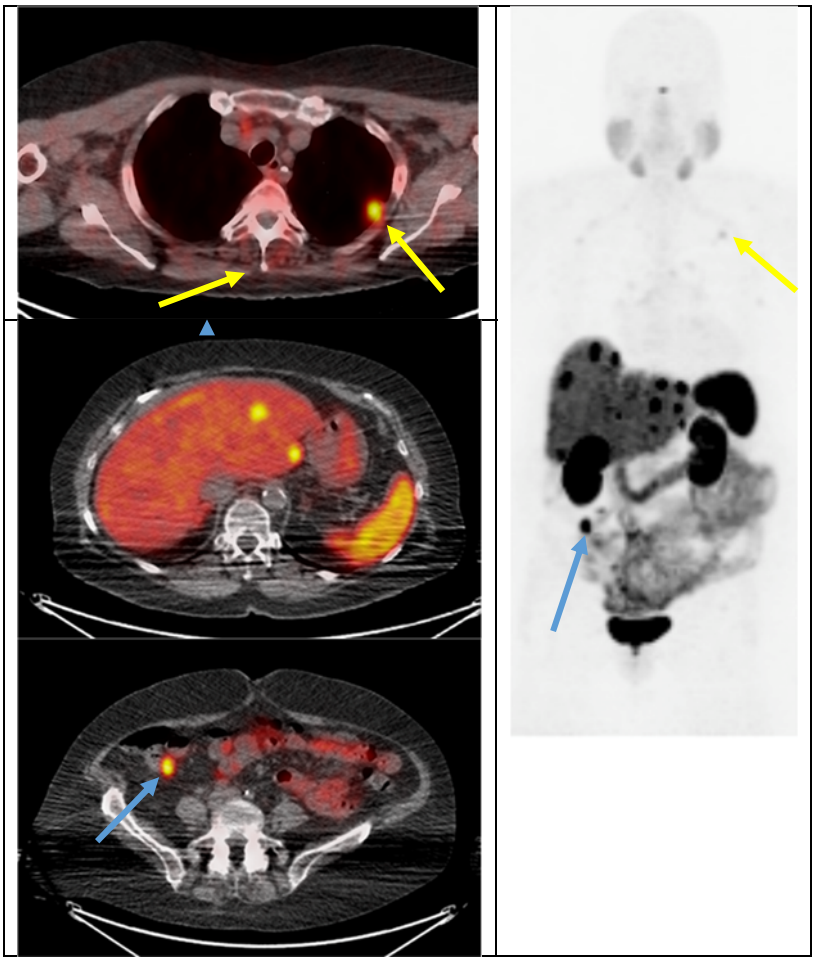


Figure 3: 73-year-old woman with a history of metastatic NET. Lung and lymph node metastases (yellow arrows), multiple liver metastases, and terminal ileum primary tumor (blue arrows). *Courtesy UCSF*.

Currently, The Centers for Medicare and Medicaid Services (CMS) reimburse these agents. ^{11}C-choline is reimbursed at $5,700 per study dose up to 20 mCi. ^{18}F-fluciclovine is reimbursed at $389.55 per 1 mCi administered. ^{68}Ga-DOTATATE is reimbursed at $66.74 per 0.1 mCi administered. (*9*) Coverage by private payors varies; SNMMI continues to work for consistent reimbursement for these and all radiopharmaceuticals.

What's Next?

Lantheus, in partnership with GE Healthcare, is starting a 522-patient international trial to evaluate the diagnostic efficacy of ^{18}F-flurpirdaz injection PET myocardial perfusion imaging in the detection of coronary artery disease. This would be the second phase three trial for flurpiridaz on its path to regulatory approval and commercialization.

Perhaps the hottest topic in molecular imaging is theranostics, a combination of a diagnostic and a therapeutic agent, such as ^{68}Ga- and ^{177}Lu-DOTATATE. The phase 3 randomized,

controlled NETTER-1 trial showed the remarkable efficacy of lutetium-177 DOTATATE (brand name Lutathera®) for the treatment of patients with advanced midgut neuroendocrine tumors. The study demonstrated markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR. (*10*) FDA provided the date of January 26, 2018 for the approval of the NDA. (*11*) The other theranostic combination dominating journals is ^{68}Ga- and ^{177}Lu-PSMA (prostate-specific membrane antigen) for prostate cancer imaging and therapy. In Europe, PSMA has been labeled with alpha-emitting actinium-225 and used to treat castration-resistant prostate cancer with promising anti-tumor activity. (*12*) Another promising prostate cancer theranostic pair that bears mentioning are the bombesin analogs, ^{68}Ga- and ^{177}Lu-RM2. Pentixafor, labeled with ^{m99}Tc or ^{68}Ga, binds avidly to CXC chemokine type 4 (CXCR4) receptors, upregulated in a number of cancers, most notably multiple myeloma. The therapeutic analog pentixather, labeled with either α- or β-emitting particles, has shown promising activity against both hematologic malignancies and solid tumors. (*13*) While none of these imaging or therapy agents are FDA-approved, all are being studied in the US and abroad.

These promising personalized, precision medicine combinations are garnering attention outside of the nuclear medicine world. Swiss drug maker Novartis is buying AAA for $3.9 billion to strengthen its oncology portfolio with Lutathera and other theranostic agents in the pipeline. (*14*) Endocyte, an Indiana-based biopharmaceutical company, announced their acquisition of exclusive worldwide licensing rights to PSMA-617, a therapeutic ligand for prostate cancer when labelled with ^{177}Lu. Endocyte estimates that radiotherapy for prostate cancer offers a $1 billion market opportunity. (*15*) These drugs represent the tip of the iceberg, as the number of ligands, therapeutic isotopes combinations, and targets continues to grow. As a community, we will need to work together to effectively employ and advance the utilization of these promising theranostic agents.

(*1*) FDA Approves ^{11}C-Choline for PET in Prostate Cancer, *J Nucl Med* 2012
(*2*) FDA approves Emory-developed prostate cancer imaging probe, June 1, 2016. http://news.emory.edu/stories/2016/06/fluciclovine_fda_approval/
(*3*) FDA approves new diagnostic imaging agent to detect recurrent prostate cancer, May 27, 2016. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503920.htm
(*4*) Hofman, M., Maecke, H., Börner, A. et al.; Biokinetics and imaging with the somatostatin receptor PET radioligand 68Ga-DOTATOC: preliminary data. *Eur J Nucl Med* (2001). https://doi.org/10.1007/s002590100639
(*5*) Deppen, S, et al.; 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. *J Nucl Med* 2016.
(*6*) FDA approves new diagnostic imaging agent to detect rare neuroendocrine tumors, June 1, 2016. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504524.htm
(*7*) Wang, Q, et al.; Targeting ASCT2-mediated glutamine uptake blocks prostate cancer growth and tumor development. *J Pathol*. 2015.
(*8*) Antoch G, Freudenberg LS, Egelhof T, et al. Focal tracer uptake: a potential artifact in contrast-enhanced dual-modality PET/CT scans. *J Nucl Med* 2002.
(*9*) SNMMI Medicare Hospital Outpatient Prospective Payment System, November 2, 2017. http://snmmi.files.cms-plus.com/docs/hpra/Non_Searchable_Folder/SNMMI_HOPPS_2017F_2018F.pdf
(*10*) Strosberg J, El-Haddad G, Wolin E, et al. NETTER-1 Trial Investigators. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017.
(*11*) Advanced Accelerator Applications Announces New Prescription Drug User Fee Act (PDUFA) date of January 26, 2018, for Lutetium Lu 177 Dotatate (Lutathera®), August 28, 2017. http://www.adacap.com/wp-content/uploads/2017/08/2017-08-28-Press-Release-AAA-FDA-New-Lutathera-PDUFA-Date-FINAL-ENG-2.pdf
(*12*)Kratochwil C, Bruchertseifer F, et al. Targeted α-Therapy of Metastatic Castration-Resistant Prostate Cancer wit 225Ac-PSMA-617: Dosimetry Estimate and Empiric Dose Finding. *J Nucl Med* 2017.
(*13)*Annemiek ME, Walenkamp CL, et al. CXCR4 Ligands: The Next Big Hit? *J Nucl Med* 2017.
(*14*) Novartis announces the planned acquisition of Advanced Accelerator Applications to strengthen oncology portfolio. October 30, 2017. https://www.novartis.com/news/media-releases/novartis-announces-planned-acquisition-advanced-accelerator-applications
(*15*) Endocyte announces exclusive worldwide license of phase 3 ready PSMA-targeted radioligand therapy for development in prostate cancer. October 2, 2017. http://investor.endocyte.com/releasedetail.cfm?ReleaseID=1042317