Reflections on the Demand for PSMA- and SSTR-Targeted Radiopharmaceutical Therapies: Why We Were Wrong (and Why We Will Be Right Eventually)

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Following the Food and Drug Administration's approval of Lutathera and Pluvicto in 2018 and 2022, respectively, we predicted that 120,000 and 30,000 radiopharmaceutical therapy (RPT) cycles would soon be administered annually in the United States to treat prostate cancer (PC) and neuroendocrine tumors (NETs). From this, we deduced the number of theranostic centers that would be required to meet this demand under various on-site capacity scenarios (*1*).

Our forecast was based on annual PC mortality data (*2*) adjusted for screen failure in about 15% of all patients by VISION criteria (*3*) and by treatment nonresponse in about 50% of recipients. We considered that around 40,000 individuals with end-stage disease minus 6,000 screen failures (15%) would annually be potential treatment candidates. We also assumed that the 50% of nonresponders would discontinue treatment after 2 cycles, whereas the responders would complete the 4–6 scheduled cycles. Thus, we estimated that 34,000 patients would need a total of approximately 120,000 treatment cycles/y (Table 1). Understandably, these numbers were grounded on common sense estimates rather than on sophisticated analyses derived from PC epidemiology (*2*).

We also considered recent NET demographics. The annual age-adjusted incidence of NETs per 100,000 persons has steadily increased, with the most recent Surveillance, Epidemiology, and End Results data indicating an increase from 4.90 in 2,000 to 8.19 in 2018 (*4*). Current estimates indicate about 12,000–15,000 new cases annually. These numbers will likely increase as diagnostic awareness and tools are more widely available. A key issue in terms of disease load is that the often-indolent nature of the disease is associated with a significant prevalence currently considered as approximately 170,000 cases in the United States. The prevalence of NETs has increased from 0.0038% in 1998 to 0.060% in 2017, thus the number of patients that require treatment annually can be predicted to increase in parallel. Indeed, the aggregate disease burden of NET as a gastrointestinal cancer is only exceeded by that of colon cancer (*5*). At diagnosis, approximately 40% of patients exhibited regional and distant disease, which is not amenable to surgical cure. Overall, only about 20% of newly diagnosed tumors undergo curative surgery, and the majority (~80%) will experience recurrence and slowly progressive disease. A substantial group is therefore likely to enter consideration for further therapy. We "conservatively" estimated that approximately 7,500 patients with NETs per year might benefit from therapy with ^{177}Lu-DOTATATE (Table 1) (*1*).

A review of real-life data revealed that our predictions were inaccurate. Novartis distributed close to 9,500 cycles of Pluvicto in the third quarter of 2024 which was a more than 50% increase from 6,000 cycles in Q3 of 2023. A total of around 35,000 doses have been distributed in 2024. This comprised treatment discontinuation in approximately 50% of patients and an average of 3.5 cycles/patient. Approximately 11,000 patients started or completed Pluvicto treatment in 2024. Thus, we overestimated the number of PC patients treated with Pluvicto by a factor of more than 3 (Table 1).

More than 3,500 Lutathera doses were distributed in Q3 of 2024, an increase of approximately 20% from Q3 2023. Close to 12,000 treatment cycles were given in fiscal year 2024, and most patients likely completed all 4 standard treatment cycles (as the disease course is much more extended than in the end-stage PC population). Thus, we can assume that around 3,000 patients were treated with Lutathera in 2024. We therefore overestimated the number of NET patients treated with Lutathera by more than 100% (Table 1).

WHY WERE OUR PREDICTIONS WRONG?

Agent Production

Initial problems with Pluvicto rollout dampened the enthusiasm and confidence in this new treatment (*6*). These problems have been overcome, and Novartis' supply of Pluvicto has been reliable and robust. Yet, the supply problem created uncertainty and a more subdued market environment with concerns raised about the sustainability of prostate-specific membrane antigen (PSMA)–targeted RPT.

Evidence Proving Advantage

The absence of clear evidence for a difference in overall survival in comparison to chemotherapy or other treatments can often be explained by trial design that includes cross-over, occasioned by some reluctance to apply RPT (*3*,*7*–*10*).

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TABLE 1
Initial Predictions and Actuals

RPT agent	Predicted (*1*)		Approximate actuals in 2024	
	Patients per year	Cycles per year	Patients in 2024	Cycles in 2024
^{177}Lu-DOTATATE	7,500	30,000 (4 cycles/patient)	3,000	12,000
^{177}Lu-PSMA	34,000	120,000 (2–6 cycles/patient)	11,000	35,000
Total	41,500	150,000	14,000	47,000

Slow Rate of Adoption

Changes in practice patterns take time, especially if technologies or approaches are involved that are not commonly used in medical practice. As shown for commonly prescribed classes of drugs, physician preferences rather than specific patient factors often account for time to adoption (*11*). Lutathera was the pioneering radiopharmaceutical approved for large-scale oncologic applications; however, its widespread adoption by oncologists was gradual and faced skepticism because of its radioactive nature. In contrast, the adoption of Pluvicto is complex but has progressed more swiftly, leveraging the insights gained during the implementation of Lutathera.

Fear of Losing Patients

Nuclear medicine is not yet a key PC patient management partner of uro-oncologists. Nuclear medicine communication with referring physicians needs to improve to alleviate fears of losing patients to other services. Such financial considerations may affect referral patterns.

Utility of Usage

Compared with chemotherapy, multiple additional steps are needed to place an RPT order. Thus, there is a learning curve for referring physician offices. Radioactive drugs have a short shelf life. Indications are currently limited to patients who previously underwent a taxane-based chemotherapy attempt. However, even first-line taxane nonresponders frequently switch to a second-line taxane treatment (cabazitaxel), a standard of care practice pattern. Despite its superior tolerability and effectiveness on quality of life, nonresponding patients are only infrequently offered a switch to Pluvicto early during chemotherapy failure.

General Aversion to Radiation-Based Therapy

Radiophobia affects both patients and referring physicians, as the concept that any level of radiation is dangerous has permeated large sectors of the healthy and patient populations. This pervasive notion has led to the misperception that toxic effects resulting from the cumulative impact of various treatments can be interpreted exclusively in terms of RPT toxicity. Educational efforts for providers and patients to emphasize and explain a high benefit-to-risk ratio will be helpful to discredit false beliefs (*12*). Novartis has started direct television marketing to patients with metastatic castration-resistant PC (mCRPC). Yet our current efforts remain insufficient. There is an unmet need to inform and educate patient advocacy groups about the efficacy, favorable side effect profile, and improved quality of life of many patients undergoing PSMA and somatostatin receptor (SSTR)–targeted RPT. As has been pointed out for RPT, there tends to be an overemphasis with consequent overstated anxiety based on undue focus on rare complications such as myelosuppression, myelodysplastic syndromes, and renal toxicity, all of which compare favorably with those associated with chemotherapy (*12*). We should seek to ensure that the divide between proradiation and antiradiation groups is resolved by education and constructive dialogue.

Optimizing Patient Management

Insufficient communication among the nuclear medicine and uro-oncology teams, leading to loss of trust, and concerns about less-than-optimal patient management by theranostic nuclear medicine experts is another concern.

Paving the Path of Progress

RPTs were pioneered by nuclear medicine specialists in Europe. Following a trajectory like that observed in Europe during the 2010s, U.S. oncologists experienced a parallel process after 2018, characterized by initial resistance, subsequent skepticism regarding efficacy, concerns about toxicity, and a gradual shift toward cautious optimism. This evolution culminated in significant engagement from pharmaceutical companies, leading to the inclusion of peptide receptor radionuclide therapy (PRRT) in numerous studies, including those sponsored by pharma, National Cancer Institute alliance groups, foundations, and investigator-initiated trials.

Redefining the Treatment Decision-Making Process

The implementation of RPT necessitates a collaborative approach in which nuclear medicine physicians (the authorized users) serve as integral members of the tumor board. Their role extends beyond merely administering the treatment; they contribute their specialized knowledge to the decision-making process. In instances where nuclear medicine physicians (or radiation oncologists) limit their involvement to administration, oncologists may find themselves isolated in their treatment choices, often opting for alternative therapies before considering radiopharmaceutical options.

Learning to Sequence for Success

The landscape of medicine has evolved to prioritize evidence-based practices, particularly in the context of high-cost pharmaceuticals. Over the past 2 decades, the treatment options for NETs have expanded significantly from a limited array of surgical interventions, somatostatin analogs, and chemotherapy to a rapidly growing selection of drugs. However, current guidelines do not provide specific recommendations regarding treatment sequencing. To attain this degree of specificity in recommendations, it is necessary to undertake multiple randomized phase 2 and 3 trials, which not only are expensive but also rely on funding or sponsoring from the pharmaceutical industry. The NETTER-2 trial (*5*), along with the anticipated results from the COMPOSE trial (*13*), is expected to guide oncologists in opting for PRRT as a first- or second-line treatment option, rather than reserving it for late-stage or last-resort scenarios.

WHAT DO OUR REVISED PREDICTIONS LOOK LIKE?

Although market growth has thus far been modest, significant growth acceleration can be predicted as additional patient populations will be treated with PSMA- and SSTR-targeted RPTs. The results of the phase 3 PSMAfore trial in which 468 castration-resistant, taxane-naïve patients were randomized to ^{177}Lu-PSMA-617 versus a change of an androgen receptor pathway inhibitor (ARPI) were recently published. Cross-over from ARPI change to ^{177}Lu-PSMA-617 was allowed after the primary endpoint of the study, radiographic progression, was confirmed (*8*). ^{177}Lu-PSMA-617 prolonged progression-free survival (11.6 vs. 5.59 mo; hazard ratio, 0.49 [95% CI, 0.39–0.61]; $P < 0.0001$), elicited a more profound prostate-specific antigen response (51% vs. 17%), had a more favorable side effect profile, and prolonged the time to first skeletal event. However, there was no difference in overall survival between the ^{177}Lu-PSMA-617 and ARPI change group. This likely was because of the ethically required cross-over option from ARPI change to ^{177}Lu-PSMA-617 (hazard ratio, 0.98; 57% of patients in the ARPI change group crossed over).

An interim analysis of the 2:1 randomized SPLASH study in patients with progressive mCRPC on ARPI and with PSMA-avid PET disease was recently presented (*9*). The primary endpoint was radiographic progression-free survival. Complete response rate (9.3% vs. 0%), best overall response (38% vs. 12%), and median radiographic progression-free survival (9.5 vs. 6 mo; hazard ratio, 0.71 [95% CI, 0.55–0.92]; $P = 0.0088$) favored ^{177}Lu-PNT2002 ([^{177}Lu]-PSMA-I&T). Due to the cross-over design, there was no difference in overall survival between groups (1.11 [range, 0.73–1.69]; $P = 0.615$).

The ECLIPSE trial also demonstrated a statistically significant and clinically meaningful improvement in the median radiographic progression-free survival of patients with PSMA-positive mCRPC previously treated with ARPI after treatment with up to 6 doses of 200 mCi (7.4 GBq) of ^{177}Lu-PSMA-I&T compared with a change in ARPI (*10*).

Although overall survival benefits are not firmly established, these data strongly suggest that an expansion of the mCRPC population to include chemotherapy-naïve patients is likely. Modeling the flow of patients through various clinical PC stages, Scher et al. estimated the incidence of mCRPC at 42,970 patients in 2020 (*14*). Accounting for screen failure in about 15% of all patients by VISION criteria (*3*) and assuming treatment nonresponse in about 50%, around 36,000 would be eligible for receiving a total of 126,000 PSMA-targeted treatment cycles. In other words, our prior prediction (*1*) remains essentially unchanged even after including chemotherapy-naïve mCRPC patients (Table 2).

The recently published NETTER-2 trial revealed that Lutathera plus long-acting release octreotide reduced the risk of progressive disease by 72% when compared with high-dose octreotide long-acting release alone in newly diagnosed patients with grade 2 or 3 advanced gastroenteropancreatic NETs that are SSTR-positive (*5*). Based on these results, Lutathera could or should be placed as a first-line NET treatment with sales exceeding $1 billion/y (*5*). Oncologists usually adopt a conservative strategy. Although the annual NET incidence ranges from 12,000 to 19,000, resulting in an estimated patient pool of approximately 9,600 to 15,000 (when we exclude resectable tumors), in the absence of progression, oncologists generally refrain from the initiation of any treatment other than somatostatin analogs (Table 2).

TABLE 2
Revised Predictions

RPT agent	Patients per year	Cycles per year
^{177}Lu-DOTATATE	9,600–15,000	38,400–60,000 (4 cycles/patient)
^{177}Lu-PSMA	36,000	126,000 (2–6 cycles/patient)
Total	41,500	Up to 186,000

CONCLUSION

Based on the above studies in patients with castration-resistant, chemotherapy-naïve PC, PSMA-targeted RPT use is expected to grow substantially following new Food and Drug Administration–approved indications. Even more substantial market growth can be expected if additional pivotal phase 3 clinical trials in PC patients with even earlier-stage disease show RPT superiority (*15*,*16*). Outreach to and close collaboration with the uro-oncology community will further facilitate the acceptance and widespread adoption of RPT.

There will be an increase in PRRT use in NETs. However, providing a specific figure is complex because of various factors (sample limitations, evolving histopathology techniques, lack of widespread availability of sophisticated diagnostic tools) that transcend elementary epidemiological considerations alone. The NETTER-2 trial used somatostatin analogs as comparator arm, which is considered a minimal benchmark for grade 3 NETs. In such instances, chemotherapy currently remains the preferred treatment option. If the COMPOSE trial produces favorable outcomes, it could potentially shift this established viewpoint. Efforts to promote the favorable RPT risk-to-benefit profile need to be intensified, especially in terms of better defining the optimal time point for effective intervention with PRRT. Focused and objective discussion and education need to be implemented to diminish the prevalent radioaversion climate to facilitate judicious implementation of the most effective therapy and its correct sequencing rather than decisions based on practice patterns.

Thus, our predictions were off as we initially underestimated the philosophical and interdisciplinary barriers to RPT adoption. Yet, we are confident that we will be correct in the end. We did not consider PSMA addition data for the current prediction. If these will be reviewed favorably by the Food and Drug Administration, patients with hormone-sensitive disease could be included and expand Pluvicto eligibility dramatically (*17*).

Let us not forget the wise words of Seneca, "*Non est ad astra mollis e terris via*" (There is no easy way from the earth to the stars).

DISCLOSURE

Johannes Czernin serves on the Scientific Advisory Boards of SOFIE Biosciences and Aktis oncology and is a founder of SOFIE Biosciences and Trethera Therapeutics. Lisa Bodei served as a nonremunerated consultant for Novartis, Ipsen, ITM, Iba, Great Point Partners, Point Biopharma, RayzeBio, Abdera, Fusion, Converge, Solve Tx, Amgen, and Wren Laboratories. She also received institutional research support from Novartis. Irvin Modlin is Medical and Scientific Advisor to Clifton Life Sciences. Jeremie Calais reports grants from support to his institution from Lantheus, Novartis, and POINT Biopharma. He also reports

consulting activities (advisory boards, speaker, blinded reader) for Advanced Accelerator Applications, Amgen, Astellas, Bayer, Blue Earth Diagnostics Inc., Curium Pharma, Coretag, DS Pharma, Fibrogen, GE HealthCare, Isoray, IBA RadioPharma, Janssen Pharmaceuticals, Monrol, Lightpoint Medical, Lantheus, Novartis, Nucleus Radiopharma, Pfizer, POINT Biopharma, Progenics, Radiomedix, Radiopharm Theranostics, Sanofi, Siemens-Varian, SOFIE, and Telix Pharmaceuticals, outside of the submitted work. No other potential conflict of interest relevant to this article was reported.

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