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Tackling the Last Mile: A major component to successfully establish radioligand therapy

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Running title: Tackling the Last Mile

The term “last mile” originates from the telecommunication industry describing the difficulty of connecting the end customer to the main telecommunication networks (*1*). Successfully tackling the last mile is associated with economic success in a number of different industries in addition to telecommunications, in particular within the supply chain and logistics industry. Translating this concept to the anticipated expansion of radioligand therapy automatically shifts the focus to the delivery of the therapy to the patients. The first difficult 25 miles of the marathon have been run by discovering and developing new therapies, investigating them in well-designed clinical trials, and gaining government approval. The last mile is to successfully delivery the therapy to patients.

With two promising radioligand therapies recently approved by the Food and Drug Administration – Lutathera (^{177}Lu-Dotatate) and Pluvicto (^{177}Lu-PSMA-617) – the stage is set for a radioligand therapy renaissance. Especially with the abundance of convincing clinical data in support of Pluvicto (*2–5*), leading to a huge buzz. However, early lessons were learned from Lutathera after the Food and Drug Administration approval in 2018. There was an initial steep rise in demand, but sales plateaued far earlier than expected, never fully reaching the anticipated

revenue potential. One can infer as to why this occurred. First, there were not enough hospitals prepared to offer Lutathera. Next, with neuroendocrine tumors being a specialized disease often treated in dedicated centers, sometimes these neuroendocrine tumor centers do not have nuclear medicine departments organized to deliver this new therapy. Additionally, overall, there are low numbers of neuroendocrine tumors with approximately 12,000 patients diagnosed each year in the United States (*6*). When starting with a relatively low number of patients, and adding not having enough centers to provide Lutathera treatment, economies of scale, or an average cost decrease as output increases, was not allowed to occur. Will the story be different for Pluvicto? One advantage is that prostate cancer is more common with over 260,000 new cases per year in the United States (*7*). But how can we make sure that all patients can be reached and that the last mile does not prevent sustainable success of radioligand therapy?

Securing patient access clearly depends on scaling up the delivery of radioligand therapy to many more clinical institutions capable of administering the therapy. Conservative estimates predict that 70-280 theranostic centers will be needed in the US to treat neuroendocrine and prostate cancer alone, depending on how many treatments are performed per day per site (*8*). In addition, with more studies underway to investigate the utility of radioligand therapy as earlier line therapy and in other cancers, even more centers may be required. The five key factors of successfully implementing radioligand therapy include 1) drug supply, 2) infrastructure and regulatory requirements (radioactive material program license etc.), 3) staff (including authorized users), 4) reimbursement and 5) patients (referred). The first pillar, drug supply, is not without challenges. Production can be affected by a number of issues including Lutetium-177 shortages due to reactor shutdowns, inability to meet increasing governmental requirements, and site contamination. While the pharmaceutical companies handle the first pillar, our field, nuclear

medicine, has to pay attention to the remaining pillars. In order to identify eligible patients, experts in radioligand therapy should be present in multi-disciplinary tumor boards, form reliable collaborations and patient referral pathways, and ensure that patients then return to the primary leading physician for further follow-up care. To ensure that there is enough staff to provide care to the patients, nurses, technologists, pharmacists, medical doctors, medical physicists, and more professionals will require specialty training. To guarantee a high-quality training for all subspecialities involved, curricula need to be established and to some degree standardized. Another important aspect is to overcome financial disincentives for patient referring collaborators by potentially considering revenue share options.

Infrastructure investment (including infusion chairs, shielding, waste management systems etc.), as well as reimbursement, require the buy in of major stakeholders such as payers, hospital administration, and government organizations (requiring coordinated lobbying on behalf of patient interests). Reimbursement needs to include not only payment for the drug, but also payment for all associated procedures such as administration, dosimetry and imaging required for patient selection. Without a clear pathway to pay off the investment into new infrastructure, the required ramp up of theranostic centers will not be successful. Advocacy, collaboration, consistency and hard work is needed to build these five strong pillars. Recent joint European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging and International Atomic Energy Agency efforts have been initiated to ignite the establishment of theranostic centers, but this is only the beginning (*9*).

After reviewing the essential pillars for radioligand therapy delivery, what are the concrete necessary action items that need to be completed? Each center needs to create an individual viable business plan including strategies for infrastructure development, staff preparation, and

creation of revenue with reimbursements. Regulatory framework must be locally established such as licensing, proper storage, and waste management and disposal. Contracts need to be established with the availability of vendors on site for assistance. Educational sessions ought to be organized to inform nuclear medicine staff, referring clinicians, and patients about the new therapies. Patient acceptance is also an important part of success and with education, this should be attainable due to high patient convivence (intravenous therapy) and low side effects.

For those who are not yet convinced of the importance of the last mile, let's turn to the logistics giant Deutsche Post DHL Group for an example. The company encompasses a vast portfolio of logistics services and is thereby suited to analyze the significance of last mile businesses in terms of barriers to entry and financial attractiveness. Deutsche Post DHL Group's services range from international door-to-door express services, domestic and international parcel networks, over (door/port-to-port/door) international air, sea and ground freight forwarding, down to warehousing and customer-dedicated domestic transport. The group's published financial figures (*10*) consistently suggest higher returns for business models including last mile activities. In 2021, the activities with less of a focus on the last mile generated between 5.1% and 5.7% earnings before interest and taxes (EBIT) margin, whereas the divisions including distributed last mile services generated up to 17.4% EBIT margin in the same year.

Whereas "successfully tackling" the last mile goes along with significant economic upside in the logistics industry it is a prerequisite to turn theranostics into a major oncological therapy option. However, distributing specific therapies with limited shelf-life around the globe in a secure and traceable way is considered the most challenging task in this industry, often performed by highly specialized niche players.

The renaissance of theranostics brings along one of the most exciting times in our field. Apart from the clinical effectiveness and the regulatory approval, successfully establishing the winning pillars of radioligand therapy's last mile will determine the sustainable success of theranostics.

Disclosures:
Dr. Herrmann reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, personal fees from Aktis Oncology, personal fees from Theragnostics, personal fees from Pharma15, personal fees from Debiopharm, personal fees from AstraZeneca, personal fees from Janssen, outside the submitted work. Dr. Pomykala reports personal fees from ABX outside the submitted work. Mr. Würker is an employee of DHL not involved in the delivery of radiopharmaceuticals.

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