CHAPTER 10

Summary and discussion
SUMMARY AND DISCUSSION

There is an urgent need for reliable biomarkers to increase efficacy and reduce unnecessary toxicity and costs of antibody-based therapy in cancer. Antibody imaging using positron emission tomography (PET) with \(^{89}\text{Zr}\)-labeled mAbs provides a potential imaging biomarker by assessment of target engagement of therapeutic mAbs.

The aim of this thesis was to develop \(^{89}\text{Zr}\)-immuno-PET as a clinical tool to guide antibody-based therapy. Feasibility, technical and biological validation of \(^{89}\text{Zr}\)-immuno-PET were investigated as essential steps towards application in drug development and routine clinical practice.

Part I Feasibility of \(^{89}\text{Zr}\)-immuno-PET

\(^{89}\text{Zr}\)-labeled mAbs are safe to administer

Chapter 2 describes the first clinical \(^{89}\text{Zr}\)-immuno-PET study. This study was performed in twenty patients with squamous cell carcinoma of the head and neck (HNSCC). Patients were at high risk of having neck lymph node metastases and therefore scheduled to undergo neck dissection (with or without resection of the primary tumor). All patients received 75 MBq of \(^{89}\text{Zr}\)-labeled chimeric monoclonal antibody (cmAb) U36 (10 mg) and immuno-PET scans were obtained up to 6 days post injection (p.i.).

Chapter 2 describes the safety of administration of \(^{89}\text{Zr}\)-cmAb U36. The procedure was well tolerated in all patients; no serious or drug-related adverse events were reported. Two patients developed a human-anti-chimeric antigen (HACA) response, related to the protein part of the \(^{89}\text{Zr}\)-labeled mAb conjugate, not to the chelate.

Administration of \(^{89}\text{Zr}\)-labeled mAbs was also well tolerated in the other clinical studies described in this thesis. No adverse events related to the radiotracer were reported for \(^{89}\text{Zr}\)-rituximab in patients with diffuse large B cell lymphoma (Chapter 7) and \(^{89}\text{Zr}\)-antiCD44 in patients with CD44-expressing solid tumors (Chapter 8). In addition, the first 15 clinical trials with \(^{89}\text{Zr}\)-immuno-PET in oncology (published between 2006 and 2016) showed no safety issues (Chapter 4).
The radiation exposure due to $^{89}$Zr-immuno-PET is $\sim$0.6 mSv/MBq

In Chapter 2, biodistribution and radiation dose of $^{89}$Zr-cmAb U36 were investigated in the cohort of 20 patients with head and neck cancer. The normal organ with the highest absorbed dose was the liver (mean dose: 1.25±0.27 mSv/MBq in men and 1.35±0.21 mSv/MBq in women, due to clearance and catabolism of antibodies via the liver), thereafter followed by kidneys, thyroid, lungs and spleen. The mean absorbed red marrow dose was 0.07±0.02 mSv/MBq and 0.09±0.01 mSv/MBq in men and women, respectively. Measured excretion via the urinary tract was less than 3% during the first 3 days p.i.. The mean effective dose was 0.53±0.03 mSv/MBq in men and 0.66±0.03 mSv/MBq in women.

Similar values for the mean effective dose have been reported in the literature for $^{89}$Zr-cetuximab (0.61 mSv/MBq) (1) and $^{89}$Zr-trastuzumab (0.48 mSv/MBq) (2).

Based on these studies, a typical $^{89}$Zr-immuno-PET study, performed with an injected dose of 37 MBq, results in an effective dose of 22.2 mSv (plus 3mSv for each low dose CT scan). The radiation exposure due to $^{89}$Zr-immuno-PET is relatively high (compared to 4.8 mSv for $^{18}$F-FDG-PET, $\sim$13.3 mSv for a diagnostic CT-scan of the neck, thorax and abdomen (depending on the protocol), 0.04 mSv for a chest X-ray, 0.05 mSv for a transatlantic flight) (3). The average lifetime risk of dying from cancer due to radiation exposure of 1 mSv is estimated at 1 in 20.000 for a 40-year old person (4). However, this risk should be seen in perspective for patients who already have a form of cancer. In general, the radiation safety principle ‘as low as reasonably achievable (ALARA)’ should be applied (5).

Tumor uptake can be visualized with $^{89}$Zr-immuno-PET

Chapter 3 describes the performance of immuno-PET with $^{89}$Zr-cmAb U36 for the same cohort of twenty patients with HNSCC as in Chapter 2. The target antigen of cmAb U36, CD44v6, is abundantly expressed in HNSCC.

Prior to surgery, all patients were evaluated by computed tomography (CT) and/or magnetic resonance imaging (MRI) and $^{89}$Zr-immuno-PET. Imaging results were compared with histopathological findings per neck side (left or right), as well as per lymph node level (6 levels per side). All primary tumors were visualized on $^{89}$Zr-immuno-PET (n=17). Lymph node metastases were identified in 18 of 25 positive levels (sensitivity 72%) and in 11 of 15 positive sides (sensitivity 73%). For CT/MRI, sensitivity per level and per side was 60% and 73%, respectively. $^{89}$Zr-immuno-PET corresponded with pathology in 112 of 121 operated levels.
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(accuracy 93%) and in 19 of 25 sides (accuracy 76%). Two false-positive findings (two levels) were obtained with $^{89}$Zr-immuno-PET, without explanation. Seven tumor-involved lymph node levels were missed by $^{89}$Zr-immuno-PET. These tumor-involved lymph nodes were relatively small (<1x1.5cm), and contained just a small proportion of tumor tissue (~50% tumor infiltration). For CT/MRI, accuracy per level and per sided were 90% (109/121) and 80% (20/25), respectively. Six out of 7 tumor-involved lymph node levels that had been missed by $^{89}$Zr-immuno-PET, were also missed by CT and/or MRI. In conclusion, these results indicate that the diagnostic imaging performance of $^{89}$Zr-immuno-PET was similar to CT/MRI for the detection of HNSCC lymph node metastases.

In daily clinical practice, CT and MRI are already established diagnostic imaging modalities. This study shows that visual detection of tumor uptake of $^{89}$Zr-cmAb U36, a novel imaging technique, is feasible. Next to diagnostic implications, these achievements might open avenues for guiding the development and application of therapeutic antibodies.

Tumor uptake and blood pool activity can be quantified with $^{89}$Zr-immuno-PET

In Chapter 2, feasibility of quantification with immuno-PET with $^{89}$Zr-cmAb U36 is described. PET-derived quantification of radioactivity concentrations in the left ventricle of the heart showed good agreement with radioactivity concentrations measured in venous blood samples (difference equals 0.2% ± 16.7% [mean ± SD]), except for heavyweight patients (>100kg). For tumors, good agreement was found between PET-derived quantification at 6 days p.i. and measurement of radioactivity concentrations in surgical biopsies obtained at 7 days p.i., with slightly lower values for PET (mean deviation -8.4% ± 34.5%).

Clinical $^{89}$Zr-immuno-PET studies in oncology provide relevant and sustainable results

In Chapter 4, we provide a review summarizing the results from the first 15 clinical trials with $^{89}$Zr-immuno-PET in oncology published between 2006 and 2016. These trials have contributed towards the development of $^{89}$Zr-immuno-PET as an imaging biomarker by showing correlation between uptake of $^{89}$Zr-labeled mAbs on PET and target expression levels in biopsies.

The ZEPHIR study is an example how $^{89}$Zr-immuno-PET, combined with early response assessment by $^{18}$F-FDG-PET, can be used to predict response to antibody-based therapy, in this case with the antibody-drug conjugate,
trastuzumab-emtansine (T-DM1). In this study in patients with HER2-positive metastatic breast cancer, tumor detection and staging was performed with conventional imaging (\(^{18}\text{F}-\text{FDG-PET}\)) and in addition, tumor targeting was assessed with \(^{89}\text{Zr}\)-trastuzumab-PET (6). After 3 cycles of treatment with trastuzumab-emtansine (T-DM1), early response was assessed with conventional imaging (\(^{18}\text{F}-\text{FDG-PET}\)). This is a promising design for future application of \(^{89}\text{Zr}\)-immuno-PET as a clinical tool to guide antibody-based therapy.

“All that is gold does not glitter”

Based on this review of initial clinical trials with \(^{89}\text{Zr}\)-immuno-PET, further development of \(^{89}\text{Zr}\)-immuno-PET is required to allow assessment of target engagement. Two requirements for each \(^{89}\text{Zr}\)-labeled mAb were identified to realize its full potential. One requirement is that the biodistribution of the \(^{89}\text{Zr}\)-labeled mAb (imaging dose) reflects the biodistribution of the drug during treatment (therapeutic dose). Another requirement is that PET should be capable to assess the specific, antigen-mediated, tumor uptake of the \(^{89}\text{Zr}\)-MAb. Currently, there are no standardized criteria to define positive uptake on \(^{89}\text{Zr}\)-immuno-PET. This may be improved by quantitative analysis of tumor uptake on \(^{89}\text{Zr}\)-immuno-PET. Therefore, imaging procedures, including data analysis and quantitative measurements of tumor uptake should be standardized and validated for future application of \(^{89}\text{Zr}\)-immuno-PET.

Part II Validation of \(^{89}\text{Zr}\)-immuno-PET

For each new measurement instrument, knowledge of measurement variability is required for correct interpretation of the results. For \(^{18}\text{F}-\text{FDG-PET}\), measurement variability for tumor uptake measured with SUV is approximately 10% (7). \(^{89}\text{Zr}\)-immuno-PET is challenged by the low injected dose and low positron abundance of \(^{89}\text{Zr}\), leading to a relative low signal-to-noise ratio. These factors will result in increased measurement variability for \(^{89}\text{Zr}\)-immuno-PET compared to \(^{18}\text{F}-\text{FDG-PET}\).

Therefore, we investigated two sources of measurement variability for \(^{89}\text{Zr}\)-immuno-PET: noise-induced variability (Chapter 5) and interobserver reproducibility of tumor uptake quantification (Chapter 6).
Measurement variability due to noise is significant in $^{89}\text{Zr}$-immuno-PET

Chapter 5 evaluates noise-induced variability of $^{89}\text{Zr}$-immuno-PET for quantification of uptake in normal tissues and tumors. Per original scan, raw PET data was split in two equal parts and reconstructed into two count-reduced images (each representing 50% of the original injected dose). Noise-induced variability (expressed as the within-subject coefficient of variation (CoV)) for $^{89}\text{Zr}$-antiCD20, $^{89}\text{Zr}$-antiEGFR and $^{89}\text{Zr}$-antiCD44 was ~3% for large organs (brain, liver, lung, kidney, spleen) and ~20% for tumors. For tumor quantification, this is a significant source of measurement variability.

Interobserver reproducibility of tumor quantification for $^{89}\text{Zr}$-immuno-PET is excellent

Before tumor uptake quantification with $^{89}\text{Zr}$-immuno-PET can be evaluated in large clinical trials, multicenter reproducibility has to be assessed. In Chapter 6, interobserver reproducibility of tumor uptake quantification for $^{89}\text{Zr}$-immuno-PET was determined, using the same software and standard operating procedure in two centers (VUMC and UMCG). Three observers manually delineated tumor volumes of interest (VOI) ($n=103$) for $^{89}\text{Zr}$-antiCD20, $^{89}\text{Zr}$-antiEGFR and $^{89}\text{Zr}$-antiHER2. Maximum, peak and mean standardized uptake values (SUV$_{\text{max}}$, SUV$_{\text{peak}}$ and SUV$_{\text{mean}}$) were used to quantify tumor uptake.

Interobserver reproducibility (median CoV) was excellent for SUV$_{\text{max}}$ and SUV$_{\text{peak}}$ (0% and 0%). For SUV$_{\text{mean}}$, measurement error due to interobserver variability in tumor uptake quantification was 7%. Even for SUV$_{\text{max}}$, there were cases where the three observers did not obtain exact the same value (26/103). This was due to insufficient contrast for manual delineation, resulting in delineation of a different structure (4/103) or location of the voxel with the maximum intensity at the border of the VOI (16/103). These tumor lesions cannot reliably be quantified and should therefore be excluded. Standardization by application of eligibility criteria for VOI quantification (e.g. VOI are deemed ineligible when the voxel with the maximum uptake was located at the edge of the VOI) is recommended to optimize interobserver reproducibility.

For clinical application, it is not only necessary to determine measurement variability, but also to assess reliability. Reliability is defined as ‘the degree to which measurement is free from measurement error’ (8). Reliability in our datasets was good (ICC > 0.8; Chapter 5 and 6). It is important to realize that reliability depends on the range in measurements (for example tumor uptake) and this is not directly generalizable between different datasets.
Tumor uptake of $^{89}$Zr-rituximab-PET was correlated to CD20 expression in biopsies

As mentioned in the introduction, treatment of patients with B cell non-Hodgkin lymphoma includes rituximab, an anti-CD20 mAb. Insufficient tumor targeting might cause therapy failure in relapsed/refractory disease. In Chapter 7, we investigated the performance of $^{89}$Zr-rituximab-PET for assessment of CD20 targeting. CD20 expression in tumor biopsies was assessed by immunohistochemistry (IHC) in six patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). $^{89}$Zr-rituximab-PET scans were acquired and tumor uptake was assessed for the corresponding tumor lesions.

Tumor uptake on $^{89}$Zr-immuno-PET was concordant with IHC in 5 patients: in one patient no tumor uptake was observed on immuno-PET with absence of CD20 expression in the tumor biopsy, in the other four patients tumor uptake was concordant with CD20-positive biopsies. Intense tumor uptake of $^{89}$Zr-rituximab on PET ($\text{SUV}_{\text{peak}} = 12.8$) corresponded with uniformly positive CD20 expression on IHC in one patient. Moderate tumor uptake of $^{89}$Zr-rituximab (range $\text{SUV}_{\text{peak}} = 3.2$-5.4) corresponded with positive CD20 expression on IHC in three patients. In one patient tumor uptake of $^{89}$Zr-rituximab was observed (SUV$_{\text{peak}} = 3.8$), while the biopsy was CD20-negative, indicating either a false-positive immuno-PET finding or heterogeneous target expression/sampling error of the biopsy. Therefore, to understand the cause of this discordant finding further analysis of the imaging signal is required, as the total PET signal consists the sum of non-specific and target-mediated, specific uptake.

Overall, these results indicate the potential of $^{89}$Zr-rituximab-PET as an imaging biomarker for CD20 expression. Subsequently, the value of PET imaging with $^{89}$Zr-rituximab to predict response to therapy has to be determined.

$^{89}$Zr-immuno-PET can be used to assess antigen-mediated uptake in normal tissues

Especially in early stages of drug development, it is of interest to identify which therapeutic mAb has high potential to provide selective treatment by targeting the tumor, without affecting normal tissues. A non-invasive technique to investigate and predict antigen-mediated uptake in normal tissues is expected to improve drug development strategies. Antigen-mediated, specific uptake is expected to be dose-dependent. If the target antigen is present on normal tissues, dose-dependent uptake is expected (this is also referred to as the antigen sink).
In Chapter 8, we investigated application of $^{89}$Zr-immuno-PET as a clinical tool to assess antigen-mediated uptake in normal tissues in a phase I dose escalation study, using the anti-CD44 antibody RG7356 as an example. Thirteen patients with CD44-expressing solid tumors received $^{89}$Zr-labeled RG7356 after a variable dose of unlabeled antibody (0 to 675 mg). Tracer uptake in normal tissues (liver, spleen, kidney, lung, bone marrow and brain, blood pool) was used to calculate the area under the time antibody concentration curve (AUC).

Within the dose range of 1 to 450 mg tissue-to-blood AUC ratios decreased for the spleen, liver, bone marrow, lung and kidney, indicating dose-dependent uptake. This observation indicates target antigen expression in normal tissues, limiting the use of RG7356 for targeting toxic payloads to the tumor (e.g. antibody-drug conjugate approaches). This study demonstrates how immuno-PET in a dose escalation study provides a non-invasive technique to quantify dose-dependent uptake in normal tissues, indicating specific, target-mediated uptake. No focal tumor uptake was observed in the lowest dose cohorts (1-200 mg), suggesting insufficient supply of mAb for tumor targeting. In all patients receiving ≥ 450 mg (n=7) tumor uptake of the antibody was observed, suggesting antigen-mediated uptake. However, a different study design using two administrations of the tracer per patient (with a variable dose of unlabeled antibody), would be better suited to determine dose-dependency for tumors. Recently, an example of such a study design was reported to assess antigen-mediated specific tumor uptake for a $^{89}$Zr-labeled antiHER3 mAb (9).

$^{89}$Zr-immuno-PET can be used to assess non-specific uptake in normal tissues Currently, it is common practice to report the result of $^{89}$Zr-immuno-PET studies as SUV. However, this value represents the total PET signal and may contain a significant non-antigen mediated contribution. Quantification of non-specific uptake in normal tissues is the first critical step towards quantification of target-engagement in normal tissues and tumor with $^{89}$Zr-immuno-PET. This non-specific contribution in normal tissues is expected to be similar for a non-binding mAb and for mAbs without target expression in the respective tissue. Non-specific uptake is reversible (e.g. blood volume) or irreversible (due to $^{89}$Zr-residualization after mAb degradation).

In Chapter 9, non-specific uptake in normal tissues without known target expression was assessed for four $^{89}$Zr-labeled intact IgG1 antibodies ($^{89}$Zr-antiCD20, $^{89}$Zr-antiEGFR, $^{89}$Zr-antiPSMA and $^{89}$Zr-antiHER2). Patlak graphical
evaluation of transfer constants was used to estimate the reversible ($V_t$) and irreversible ($K_i$) contributions to the total measured uptake for the kidney, liver, lung and spleen. At least 3 scans at equilibrium state (≥ 1 day p.i.) are required to assess the quality of the fit. Baseline values were calculated per tissue combining all mAbs without target expression. The transfer constants obtained were interpreted in terms of the physiological components of antibody biodistribution. A literature search was performed to obtain predicted values for these physiological components for a non-binding intact IgG1 mAb.

We found that non-specific, reversible uptake was similar to the predicted value for a non-binding mAb (10). Non-specific, irreversible uptake corresponded with the predicted value for the fractional catabolic rate of IgG. In case of target engagement, we expect to observe an increased $K_i$ compared to the baseline value. Expression of PSMA was reported for the kidney and therefore target engagement of $^{89}$Zr-antiPSMA is expected in this tissue. For $^{89}$Zr-antiPSMA, a four-fold higher $K_i$ was observed for the kidney, indicating target engagement.

Usually, $^{89}$Zr-immuno-PET scans are analyzed at a single time point, representing the sum of all physiological components of antibody distribution, being either target specific or non-specific. This study showed how the various physiological components of antibody distribution contribute to the measured SUV. For example, in the kidney a SUV of ~2.5 was measured for $^{89}$Zr-antiPSMA at 1 to 7 days p.i.. Non-specific uptake accounted for a SUV of ~1.6 (66%) at 1 day p.i. and decreased to ~0.6 (22%) at 7 days p.i.. This observation indicates how the contribution of non-specific uptake decreases over time.

"It is sometimes a good idea to develop a new measurement instrument"
This study shows that non-specific uptake of mAbs for tissues without target expression can be quantified using $^{89}$Zr-immuno-PET at multiple time points. These results form a crucial base for measurement of target-engagement by therapeutic antibodies in-vivo with $^{89}$Zr-immuno-PET. For future studies, a pilot phase including at least 3 scans ≥ 1 day p.i., is required recommended to assess non-specific uptake as a function of time, to optimize study design for detection of target engagement.
FUTURE PERSPECTIVES

In this thesis, we found that $^{89}\text{Zr}$-immuno-PET is safe and feasible. An important advantage of $^{89}\text{Zr}$-immuno-PET is that whole-body information can be obtained non-invasively and quantitatively. Recently, progress has been made to facilitate improved chemical procedures (11) and by providing recommendations to obtain quantitative accuracy and harmonized image quality for $^{89}\text{Zr}$-immuno-PET in a multicenter setting (12, 13). $^{89}\text{Zr}$-immuno-PET studies have been collected in an online accessible warehouse of molecular imaging data with the aim to increase and exchange knowledge on whole body drug distribution (14). The first $^{89}\text{Zr}$-immuno-PET studies with immune checkpoint inhibitors, antibody drug conjugates and bispecific antibodies show promising results (15-17).

Disadvantages of $^{89}\text{Zr}$-immuno-PET are the radiation exposure, scan time required and the complexity of logistics. The studies on measurement variability of $^{89}\text{Zr}$-immuno-PET for tumor quantification described in this thesis indicate that noise is a significant contribution. We studied validity of $^{89}\text{Zr}$-immuno-PET and observed correlations between tumor uptake on $^{89}\text{Zr}$-immuno-PET and underlying biology. However, potential false-positive findings indicate the need for quantification. Therefore, we developed methods using dose-dependency and multiple time point scans to assess target-mediated uptake for normal tissues as a crucial step.

Future studies should focus on the following aspects:

1. Improvement of precision by reduction of noise
   New technical developments to optimize sensitivity are expected to result in shorter scan time, higher resolution and increased precision. In 2018, the first total-body PET/CT scanner was introduced (18,19). Opposed to current PET/CT scanners that use a ring that allows only 10-15% of the body within the field of view at one time, the total-body PET/CT scanner uses detector rings that cover the entire body. This system allows almost maximal detection of radiation emitted, resulting in increased signal-to-noise ratio in the images (18). This can become a game changer in the application of $^{89}\text{Zr}$-immuno-PET. Shorter scan time/reduction of administered radioactivity will allow to perform test-retest studies to assess repeatability of $^{89}\text{Zr}$-immuno-PET. Repeatability studies are usually performed for technical validation. However, until
now this type of study design has been limited by the relative high radiation exposure of \(^{89}\)Zr-immuno-PET.

In addition, reduction of radiation exposure will allow application of \(^{89}\)Zr-immuno-PET for indications beyond oncology, for example in auto-immune diseases where mAb-based therapy is also used (20). Finally, increase in sensitivity is expected to allow molecular imaging of other slow-kinetic drugs (e.g. nanoparticles) and cell imaging.

2. Further biological and clinical validation (including cost effectiveness)

Before \(^{89}\)Zr-immuno-PET can be applied in large scale clinical trials or in daily clinical practice, the link with underlying biology and clinical outcome should be confirmed. We observed a potential false-positive finding for \(^{89}\)Zr-rituximab in relapsed/refractory non-Hodgkin lymphoma (Chapter 7) and two false-positive findings for \(^{89}\)Zr-cmAb U36 in head and neck cancer (Chapter 3). Visual assessment of \(^{89}\)Zr-immuno-PET is used to localize non-physiological accumulation of the radiotracer, indicating target-mediated uptake. Visual assessment provides a qualitative biomarker, assuming that target-mediated, specific uptake increases over time, and dominates the total PET signal at late time points (e.g. 3-6 days p.i.) when tumor uptake is visible.

Future studies are required to develop a method for quantification of target-engagement in tumors. However, tumor characteristics are more complex and more variable (within and between patients) compared to normal tissues. Therefore, tumors with and without target expression can be studied to investigate non-specific uptake in tumors. Although tumor biopsies are often used as reference, immunohistochemistry may not be a true gold standard for target engagement of mAbs. Biopsies have several limitations, for example sampling error due to heterogeneity in target expression. In addition, detection of target expression by IHC does not provide information on accessibility of the target in-vivo (whether the therapeutic mAb has reached the target). Future work to relate quantification of \(^{89}\)Zr-labeled mAbs to PBPK modeling is expected to provide more insight in how the PET signal is linked to the underlying biology. This information is required to define which measure (visual, SUV, Ki) is suitable for assessment of target engagement. The type of measure (e.g. single time point, or multiple time point) has impact on study design for further clinical validation studies and cost-effectiveness.
Provided that all requirements are met, we envision that $^{89}$Zr-immuno-PET can be used in the near future for the following clinical applications:

- “whole-body in-vivo immunohistochemistry” for individualized treatment
- measurement of target engagement in tumor and normal tissues to guide drug development

The latest developments in mAb-based treatment of cancer include many new drugs that have now reached the clinic: antibody-drug conjugates, bispecific antibodies, immune checkpoint inhibitors and chimeric antigen receptor (CAR)-T cells (21). Different mechanisms have been explored to increase the efficacy of traditional mAbs (e.g. use of a toxic payload (ADC) or by triggering the immune system (e.g. activating T-cells to kill the malignant cells). These treatment approaches have in common that their effects are all target-antigen mediated. Therefore, we need to shine a light on whether these drugs reach the disease. This is essential information to better understand their efficacy and toxicity and to learn how to dose appropriately. The timing is crucial to accompany these expensive novel targeted therapies with $^{89}$Zr-immuno-PET as biomarker for target engagement, especially as society struggles to find a way towards affordable and accessible healthcare.

**CONCLUSION**

This thesis describes the development of $^{89}$Zr-immuno-PET as a clinical tool to guide antibody-based treatment in cancer. Initial clinical studies of $^{89}$Zr-immuno-PET in oncology show feasibility, including safety. Technical validation indicates that multi-center interobserver reproducibility of tumor uptake quantification was excellent, although measurement variability due to noise was substantial. Biological validation studies show that $^{89}$Zr-immuno-PET is able to measure the underlying biology (correlation with target expression, dose-dependency and assessment of non-specific uptake). Future work should be aimed at reduction of measurement variability using improved PET-CT scanners, quantification of specific uptake in tumor and clinical validation (e.g. prediction of response to antibody-based treatment). If these requirements are met, $^{89}$Zr-immuno-PET can be used as a clinical tool to guide patient and drug selection for antibody-based treatment in cancer.
REFERENCES