CLINICAL SCIENCE

# DESIGN OF FEASIBILITY STUDY FOR THE ESTABLISHMENT OF PRODUCTION OF ZIRCONIUM-89 RADIOISOTOPE AND IMPLEMENTATION OF $^{89}$ZR-RADIOPHARMACEUTICALS IN CLINICAL PRACTICE IN THE REPUBLIC OF NORTH MACEDONIA

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## Abstract

In the last decade, the application of radiopharmaceuticals based on zirconium-89 ($^{89}$Zr) radiometal has increased in both preclinical and clinical studies. The most frequently used $^{89}$Zr-radiopharmaceutical is $^{89}$Zr-trastuzumab used in the management of patients with breast cancer. Breast cancer is the most common cancer among women in North Macedonia and the most common cause of death from malignant neoplasms in this population; therefore, the introduction of new nuclear medicine procedures in these patients might improve the management of this disease. However, the introduction of radioisotope and radiopharmaceutical production requires significant investments, both manpower and financial. The purpose of this work is to present the design conceptualization of a feasibility study for the establishment of production of zirconium-89 radioisotope and implementation of $^{89}$Zr-radiopharmaceuticals in clinical practice in the Republic of North Macedonia and to present the initial results from the first phases of the study. This feasibility study is designed to include preliminary analysis, market research, technical feasibility analysis, economic analysis, review and analysis of all data and feasibility conclusion. The evaluation of the data from the analyses conducted in all study phases is needed to identify the favourable and unfavourable factors and circumstances in order to make a final assessment of the feasibility of establishing the zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals production and implementation of $^{89}$Zr-trastuzumab use in nuclear medicine practice.

КЛИНИЧКИ ИСПИТУВАЊА

# ДИЗАЈН НА ФИЗИБИЛИТИ СТУДИЈА ЗА ВОСПОСТАВУВАЊЕ НА ПРОИЗВОДСТВО НА ZIRCONIUM-89 РАДИОИЗОТОП И ИМПЛЕМЕНТАЦИЈА НА $^{89}$ZR-РАДИОФАРМАЦЕВТИЦИ ВО КЛИНИЧКАТА ПРАКСА ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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## Извадок

Во последната деценија, радиофармацевтските препарати што содржат zirconium-89 ($^{89}$Zr) радиоизотоп имаат зголемена примена како во претклиничките, така и во клиничките студии. Најчесто користен $^{89}$Zr-радиофармацевтик е $^{89}$Zr-trastuzumab кој се применува во насока на планирање на терапија на пациенти со рак на дојка. Ракот на дојката е најчестиот карцином кај жените во Северна Македонија и најчеста причина за смрт од малигни неоплазми кај оваа популација, затоа воведувањето нови дијагностички процедури во нуклеарната медицина може да придонесе за подобро планирање на терапијата кај овие пациенти. Сепак, воспоставувањето на производство на радиоизотопи и радиофармацевтици бара значителни инвестиции, финансиски и кадровски. Целта на овој труд е да го претстави дизајнот на физибилити студијата за воспоставување на производство на zirconium-89 радиоизотоп и имплементација на $^{89}$Zr-радиофармацевтици во клиничката пракса во Република Северна Македонија, како и да ги претстави резултатите од почетните фази на студијата. Оваа физибилити студија е дизајнирана така што вклучува прелиминарна анализа, истражување на пазарот, анализа на техничка изводливост, економска анализа, преглед и анализа на сите податоци и заклучок за физибилност. Евалуацијата на податоците од анализите во рамки на сите фази на студијата е потребна за да се идентификуваат поволните и неповолните фактори и околности за да се донесе конечна проценка на физибилноста за воспоставување на производство на zirconium-89 радиоизотоп и $^{89}$Zr-радиофармацевтици и воведување на $^{89}$Zr-trastuzumab во нуклеарно-медицинската пракса.

## Introduction

Radiopharmaceutical preparations or radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose to diagnose, stage a disease, monitor treatment, or provide therapy.[1,2]

Regarding the radiopharmaceuticals used for positron emission tomography (PET) imaging, the application of radiometals in nuclear medicine worldwide is progressing steadily. Short-lived radiometals are suitable for combination with ligands that exhibit rapid pharmacokinetics (e.g., small molecules or peptides), while long-lived radiometals are suitable for visualizing slow biological processes, such as antibody biodistribution (immuno-PET).[3]

Zirconium-89 is one of the radiometals that in the last decade has been increasingly used in both preclinical and clinical studies.[3,4] The zirconium-89 half-life of 78.4 h corresponds to the biological half-life of monoclonal antibodies, making this radioisotope suitable for immuno-PET imaging.[3-5] Immuno-PET combines the sensitivity of PET with the specificity of antibodies. The use of $^{89}$Zr is promising for monitoring antibody-based cancer therapies and a number of studies have been conducted to investigate the feasibility of $^{89}$Zr immuno-PET imaging for predicting the efficacy of radioimmunotherapy and antibody therapies, imaging target expression, detecting target-expressing tumors, and monitoring of anti-cancer chemotherapies.[4] There are literature data on more than 90 clinical studies, of which already completed studies involve more than 20 antibodies labelled with $^{89}$Zr.[6]

A common method for obtaining zirconium-89 radioisotope is by irradiating solid target material with accelerated protons in medical cyclotrons, typically using energies of 10–18 MeV.Due to the easy availability of the target material in natural form, $^{89}$Y(p, n)$^{89}$Zr is considered to be the best nuclear reaction for the production of $^{89}$Zr in medical cyclotrons.[5,7-9]

Having in mind all the above, the potential of $^{89}$Zr-radiopharmaceuticals to expand the possibilities in terms of cancer management and research development in North Macedonia, as well as the fact that the only cyclotron in the country is within the University Institute of Positron Emission Tomography (UI PET), the idea of preparing a feasibility study for the establishment of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals production in this institute is rational.

The cyclotron at UI PET, GE PET trace 800 16.5 MeV, according to its technical characteristics belongs to the group of cyclotrons, which can produce the radioisotope $^{89}$Zr. UI PET is the only site for producing PET radioisotopes and radiopharmaceuticals in the country and also it is a centre for molecular diagnostics where 2,000 oncology patients are scanned annually.

This study aims to present the design of the feasibility study for the establishment of zirconium-89 radioisotope production and the implementation of $^{89}$Zr-radiopharmaceuticals in clinical practice in the Republic of North Macedonia and to present the initial results from the first phases of the study. The design is conceived

originally and structured taking into consideration several aspects. The results of the feasibility study will provide an objective insight into all aspects of the feasibility of this proposed idea, as well as a conclusion regarding the impact that radiopharmaceuticals based on this radioisotope may have on making clinical decisions in the management of the malignancies in the country.

## Materials and Methods

The feasibility study to establish the production of zirconium-89 radioisotope and $^{89}$Zr- radiopharmaceuticals is designed to cover the following phases:

- preliminary analysis;
- market research;
- technical feasibility analysis;
- economic analysis (financial analysis and pharmacoeconomic analysis);
- review and analysis of all data;
- conclusion on feasibility.

### *Preliminary analysis*

The preliminary analysis includes:

- review of statistical data regarding malignant diseases in North Macedonia;
- review of clinical applications data of $^{89}$Zr-radiopharmaceuticals.

The review of malignant disease statistics is performed by literary search of reference databases, international (Global Cancer Observatory) and domestic (Mortality Register and Cancer Register of Institute of Public Health).[10-12] These databases display statistics of malignant diseases, such as total new cases per year, most common cancers among new cases - sex distribution, and mortality from malignant diseases in Macedonia (mortality rate and primary localization).

The review of the application of $^{89}$Zr-radiopharmaceuticals in clinical trials is based on a literature search, that is, a reference database for clinical trials. (ClinicalTrials.gov, a Web-based resource maintained by the U.S. National Library of Medicine).[6]

### *Market research*

Within this step, searches are conducted regarding:

- the distribution of medical cyclotrons in Europe;
- zirconium-89 radioisotope production sites in Europe;
- zirconium-89 radioisotope price, and
- the potential possibilities for placement of the produced radioisotopes at a cost-effective price.

The information on the distribution of medical cyclotrons is obtained from the International Atomic Energy Agency (IAEA) Cyclotron Distribution Database.[13] The research on the production sites of zirconium-89 radioisotope in Europe is based on a literature search of studies published in scientific journals, data on the production of these radioisotopes presented at professional symposia and congresses, as well as media available data from radioisotope manufacturers. The zirconium-89 radioisotope price information is based on data obtained from

manufacturers. The research of the potential possibilities for placement of the produced radioisotope at a cost-effective price is based on the obtained data on the needs and possibilities for use for clinical purposes in our country and the region.

### *Technical feasibility analysis*

The estimation of technical feasibility is based on the analysis of the technical capacities of UI PET in terms of space and equipment necessary for the implementation of the production of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals. As part of this phase of the feasibility study, it is also verified whether additional equipment/apparatus is needed to realize the production.

### *Economic analysis*

The assessment of economic feasibility is conducted in two phases and includes financial analysis and pharmacoeconomic analysis. Firstly, the costs are defined (direct and indirect), and then they are calculated according to data obtained by a literature search, as well as data from UI PET.

For performing pharmacoeconomic analyses, data collected by a literature search of clinical trials conducted with these radiopharmaceuticals have been applied. In order to cover the initial clinical data and to simulate the patterns of real practice, meta-analysis is applied which is a systematic method for finding, evaluating and combining the results of different scientific studies.[14] A cost-effectiveness analysis is performed, which is a systematic method that compares two or more alternative treatments by measuring the cost of money (MKD) and the health outcomes over the years, based on the utility results presented in the literature. The cost-benefit analysis compares the net production costs of both preparations with the benefits arising from their use expressed in monetary terms.[15-17] Depending on the literature data obtained during the research, the two analyses can be combined.

### *Review and analysis of all data*

The processing of the results of analyses is one of the phases of the feasibility study, during which the data from all previously conducted analyses are evaluated: preliminary analysis, market research, technical feasibility analysis and economic analysis.

### *Conclusion on feasibility*

After conducting all the analyses, as well as after reviewing all the obtained data, a conclusion is made about the feasibility of the proposed idea, i.e., whether the process of establishing production of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals in UI PET is feasible.

## Results

Given that the feasibility study is ongoing, this paper presents the results of the analyses already done, the preliminary analysis and the market research (distribution of medical cyclotrons in Europe and zirconium-89 radioisotope production sites in Europe).

*Preliminary analysis*

- Malignant diseases on a national level

Neoplasms are the second leading cause of death in Macedonia, after circulatory system diseases. In 2020, 24.25 % of deaths in the population aged 1 to 64 years and 12.68 % of deaths in the population over 64 years were due to malignant diseases.[11]

In the period from 2011 to 2020, the average mortality rate from malignant neoplasms in both sexes was 180 per 100,000 population. For the same ten-year period, the average mortality rate from malignant neoplasms in men was 215 and in women 146 per 100,000 population. From 2011 to 2020, the most common cause of death from malignant neoplasms in men was malignant neoplasm of the bronchi and lungs (average mortality rate 63.9 per 100,000 men), and in the same period, the most common cause of death from malignant neoplasms in women was malignant breast neoplasm (average mortality rate 29.07 per 100,000 women).[12]

In the period from 2011 to 2020, there were an average of 6,808 new cases of cancer per year or 328 cases per 100,000 inhabitants. About 87.8 % of cancer cases were among the population over the age of 50, of which 19.3 % were between the ages of 50 and 60 years. The most common cancer diagnoses in the period of ten years (2011-2020) in the entire population were malignant neoplasms of the bronchi and lungs with 13.12 % of the total reported cases, followed by malignant neoplasms of the breast, other malignant neoplasms of the skin, colon, stomach, prostate, liver and intrahepatic bile ducts, rectum, bladder, corpus uteri etc. In the male population, the most common cancers in the period of 2011- 2020 were malignant neoplasms of the bronchi and lungs with 18.80 % of the total reported cases, followed by malignant neoplasms of the prostate, other malignant neoplasms of the skin, stomach, colon, bladder, liver and intrahepatic bile ducts, rectum, larynx, pancreas, etc. In the same ten years period, the most common cancers in females were malignant neoplasms of the breast with 25.29 % of the total reported cases, followed by non-melanoma malignancies of the skin, malignant neoplasms of corpus uteri, bronchi and lungs, colon, cervix uteri, stomach, ovaries, rectum, liver and intrahepatic bile ducts, etc.[12]

According to the Global Cancer Observatory database, among 7,632 new cases of cancer in 2020, the five most common cancers in both sexes, with the exception of non-melanoma skin cancer, were cancers of the lung (14.9 %), breast (12.9 %), colorectum (12.4 %), prostate (10.3 %), corpus uteri (4.8 %). Among women, the most common new cases in 2020 were cancers of the breast (29.2 %), colorectum (14.4 %), corpus uteri (10.9 %), lung (7.2 %), cervix uteri (3.3 %), and in men, the most common were cancers of the lung (21 %), prostate (18.5 %), colorectum (10.9 %), bladder (7.0 %), stomach (5.2 %). Regarding the mortality rate from malignant diseases in 2020, the first ten malignancies were cancers of the lung (23.3 %), breast (7.5 %), prostate (7.1 %), stomach (6.6 %), pancreas (6.4 %), colon (6.0 %), brain, central nervous system (6.0 %), rectum (5.8 %), liver (4.4 %), and bladder (3.1 %).[10]

- $^{89}$Zr-radiopharmaceuticals in clinical trials

According to ClinicalTrials.gov, as of May 9, 2021, there have been a total of 93 clinical trials involving $^{89}$Zr-radiopharmaceuticals, of which 48 studies have status completed, terminated, or unknown. Most clinical studies were conducted in the Netherlands (28 studies), followed by the United States (16 studies), Belgium and China with 2 studies each, and one clinical study each in Australia, Sweden, Denmark, Korea, France and Spain.[6]

$^{89}$Zr-radiopharmaceuticals used in these clinical trials were $^{89}$Zr-bevacizumab (9 studies), $^{89}$Zr-trastuzumab (6 studies), $^{89}$Zr-Df-IAB2M (3 studies), $^{89}$Zr-cetuximab (3 studies), $^{89}$Zr-pembrolizumab, $^{89}$Zr-J591, $^{89}$Zr-panitumumab, $^{89}$Zr-girentuximab, $^{89}$Zr-DFO-pertuzumab each in 2 clinical trials and $^{89}$Zr-Df-IAB22M2C, $^{89}$Zr-KN035, $^{89}$Zr-MMOT0530A, $^{89}$Zr-AMG211, $^{89}$Zr-ABT806, $^{89}$Zr-daratumumab, $^{89}$Zr-Cripec Docetaxel, $^{89}$Zr-GC1008, $^{89}$Zr-durvalumab, $^{89}$Zr-GSK3128349, $^{89}$Zr-GSK2849330, $^{89}$Zr-BI754111, $^{89}$Zr-GSK2398852, $^{89}$Zr-RO5429083, $^{89}$Zr-TAK-164, 89Zr-nanocoll, $^{89}$Zr-DS-8895a, $^{89}$Zr-RO5479599 each in one clinical study.[6]

*Market research*

- Distribution of medical cyclotrons in Europe

A total of 1,266 cyclotrons are registered in the International Atomic Energy Agency (IAEA) cyclotron database, of which 356 are located in Europe, Turkey and the Russian Federation (including its Asian part). In Europe, the largest number of cyclotrons is in Italy - 45 cyclotrons, followed by Germany - 43, France - 32, the United Kingdom - 28, Spain - 21, the Netherlands - 13, Belgium - 13, Denmark - 10, etc. There are 59 cyclotrons on the entire territory of the Russian Federation, and 20 in Turkey. As for the Balkan Peninsula, Bulgaria and Romania have 4 cyclotrons each, Greece two and North Macedonia and Croatia have one cyclotron each.[13]

- Zirconium-89 radioisotope production sites in Europe

In the Netherlands, there is GMP (Good Manufacturing Practice)-compliant production of $^{89}$Zr for the research community. Research in-house productions are registered in Germany, Great Britain, Italy, Turkey, Belgium and Russia.

*Technical feasibility analysis*

The cyclotron at UI PET, PETtrace 16.5 MeV GE Healthcare Cyclotron, according to its technical characteristics is convenient for the production of $^{89}$Zr radioisotope. There are commercially available $^{89}$Zr purification and labelling modules which compatibility with existing UI PET systems is being evaluated.

## Discussion

A feasibility study is an analysis of the viability, that is, the sustainability of a given idea. The feasibility study aims to objectively and rationally reveal the strengths and weaknesses of the proposed venture, the opportunities and threats present in the environment, the necessary resources to realize the idea and finally the prospects for success. The

feasibility study assesses the project's potential for success; therefore, perceived objectivity is an important factor in the credibility of the study. For this reason, feasibility studies should be conducted with an objective, unbiased approach to provide information on which decisions can be based. The goals of feasibility studies are to thoroughly understand all aspects of a given project, concept or plan; to identify any potential problems that may arise during the implementation of the project; to determine whether, after considering all the important factors, the project is feasible that is, worth undertaking. Feasibility analysis covers several aspects of feasibility: technical, economic, financial, regulatory, operational, temporal, etc. The aspects covered in the study, i.e., the design of the feasibility study itself are based on the characteristics of the project/idea that is proposed.[18] A preliminary analysis is also often performed to determine if the project/idea concept is justified.

However, the current literature is very scarce regarding comprehensive feasibility studies in the field of radiopharmacy. There are literature data for some radiopharmaceuticals regarding the analysis of technical feasibility for their production, but there are no data about feasibility studies that also analyze the effect of their potential implementation in routine clinical practice and further research. As a result of technological development, the designing and development of new radiopharmaceuticals are progressing rapidly, with a continuous expansion of perspectives regarding their use. For developing countries, their introduction into healthcare practice is a challenge, and therefore an objective assessment is needed that takes into account not only the economic aspect but also the clinical impact and development of research potential.

This feasibility study for the establishment of the production of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals is designed originally and it includes preliminary analysis, market research, technical feasibility analysis, economic analysis (financial and pharmacoeconomic), review and analysis of all data and feasibility conclusion.

The preliminary analysis aims to assess whether there is a field for the application of $^{89}$Zr-radiopharmaceuticals in our country and for that purpose it includes a review of statistical data regarding malignant diseases on a national level and a review of clinical applications data of $^{89}$Zr-radiopharmaceuticals.

The market research is conducted in order to define the geographical impact of the market. The market competitiveness and the transport cost are factors that affect the price of the product - radioisotope. This is especially important considering the nature of radioactive preparations, i.e., their short shelf life. The longer geographic distance of the production site to the site of use hugely contributes to a higher price of the radioactive product. As the results show, there is no $^{89}$Zr production in the Balkan countries.

The technical feasibility analysis focuses on the technical resources available to the organization implementing the proposed idea and includes an assessment of the hardware, software and other technical requirements of the proposed sys-

tem. In the framework of this feasibility study, the technical feasibility analysis is being performed to determine whether the production process of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals in UI PET is technically feasible in terms of space and equipment.

The financial analysis, as the first phase of the economic feasibility analysis, is carried out to determine the initial investment for the establishment of zirconium-89 radioisotope production; financial investments (costs) in the process of production of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals as well as the price of the product (radioisotope and radiopharmaceutical products).

The pharmacoeconomic analysis, as the second phase of the economic analysis, aims to assess the justification for the implementation of $^{89}$Zr-radiopharmaceuticals in clinical practice. The subject of the pharmacoeconomic analysis is $^{89}$Zr-trastuzumab, a radioimmunoconjugate containing the recombinant humanized monoclonal antibody trastuzumab radiolabeled with zirconium-89. $^{89}$Zr-trastuzumab was selected as the subject of pharmacoeconomic analysis on the basis of the preliminary analysis results. As per statistics related to malignant diseases, breast cancer is the most common cancer among women in Macedonia and the most common cause of death from malignant neoplasms in this population. On the other hand, $^{89}$Zr-trastuzumab is one of the most common $^{89}$Zr-radiopharmaceuticals in clinical trials.

$^{89}$Zr-trastuzumab binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2), enabling visualization and quantification of HER2-expressing tumour cells, by positron-emission tomography.[4,19] According to the literature data, PET imaging with $^{89}$Zr-trastuzumab supports clinical decision-making in patients with breast cancer when HER2 status cannot be determined by standard workup.[20,21] $^{89}$Zr-trastuzumab has the potential to characterize the HER2 status of the complete tumour burden in patients with breast cancer, thus obviating repeat or multiple tissue sampling to assess intrapatient heterogeneity of HER2 status.[22] HER2-PET imaging with $^{89}$Zr-trastuzumab shows excellent tumour tracer uptake and can be used to detect HER2-positive breast cancer metastases and quantify $^{89}$Zr-trastuzumab uptake, non-invasively.[23] PET scanning after administration of $^{89}$Zr-trastuzumab at appropriate doses allows visualization and quantification of uptake in HER2-positive lesions in patients with metastatic breast cancer.[19]

After completion of all the feasibility analyses, a review of all the data is needed in order to identify favourable and unfavourable factors and circumstances (internal and/or external), that is, to determine the favourable opportunities and/or limitations for the implementation of the proposed idea, as well as the benefits of eventual realization. In the end, after data evaluation, a conclusion on feasibility is made.

## Conclusion

When designing feasibility studies, the aspects important for the realization of a given idea should first be evaluated and consequently, based

on them, the necessary analyses should be defined. We have designed a feasibility study for the establishment of production of zirconium-89 radioisotope and $^{89}$Zr-radiopharmaceuticals that covers the elements of feasibility related to the technical and financial aspects of the production process, research potentials, but also includes an assessment of the clinical impact of the eventual implementation of $^{89}$Zr-radiopharmaceuticals in the management of patients with malignant diseases in the Republic of North Macedonia.

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