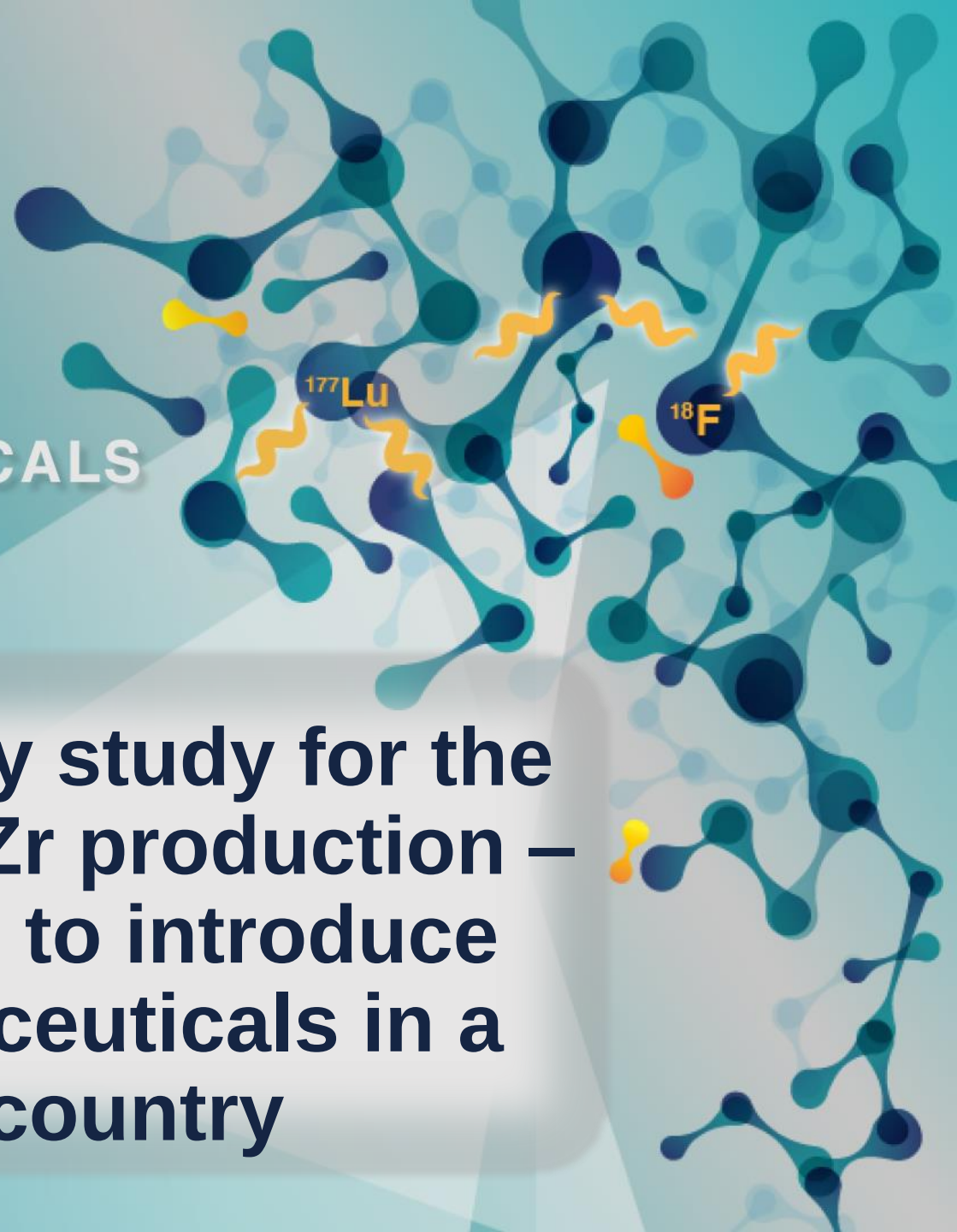
INTERNATIONAL SYMPOSIUM
ON TRENDS IN RADIOPHARMACEUTICALS

#ISTR2023

IAEA Headquarters, Austria

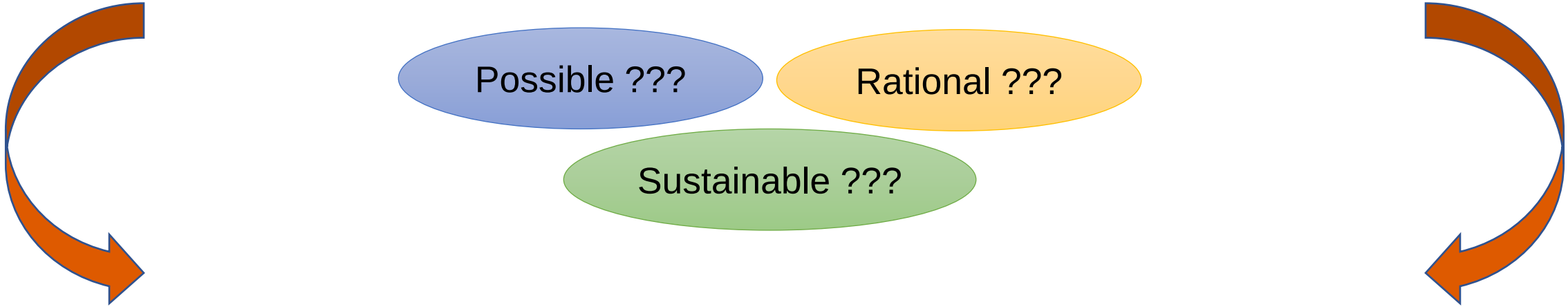
17 – 21 April 2023



Design of feasibility study for the establishment of ^{89}Zr production – tailored approach to introduce new radiopharmaceuticals in a developing country

IAEA
International Atomic Energy Agency

Establishing radiopharmaceutical production in a developing country is challenging, mainly in the economical aspect.



A feasibility study provides an objective insight into many aspects of the feasibility of the idea of introducing new radiopharmaceutical.

North Macedonia

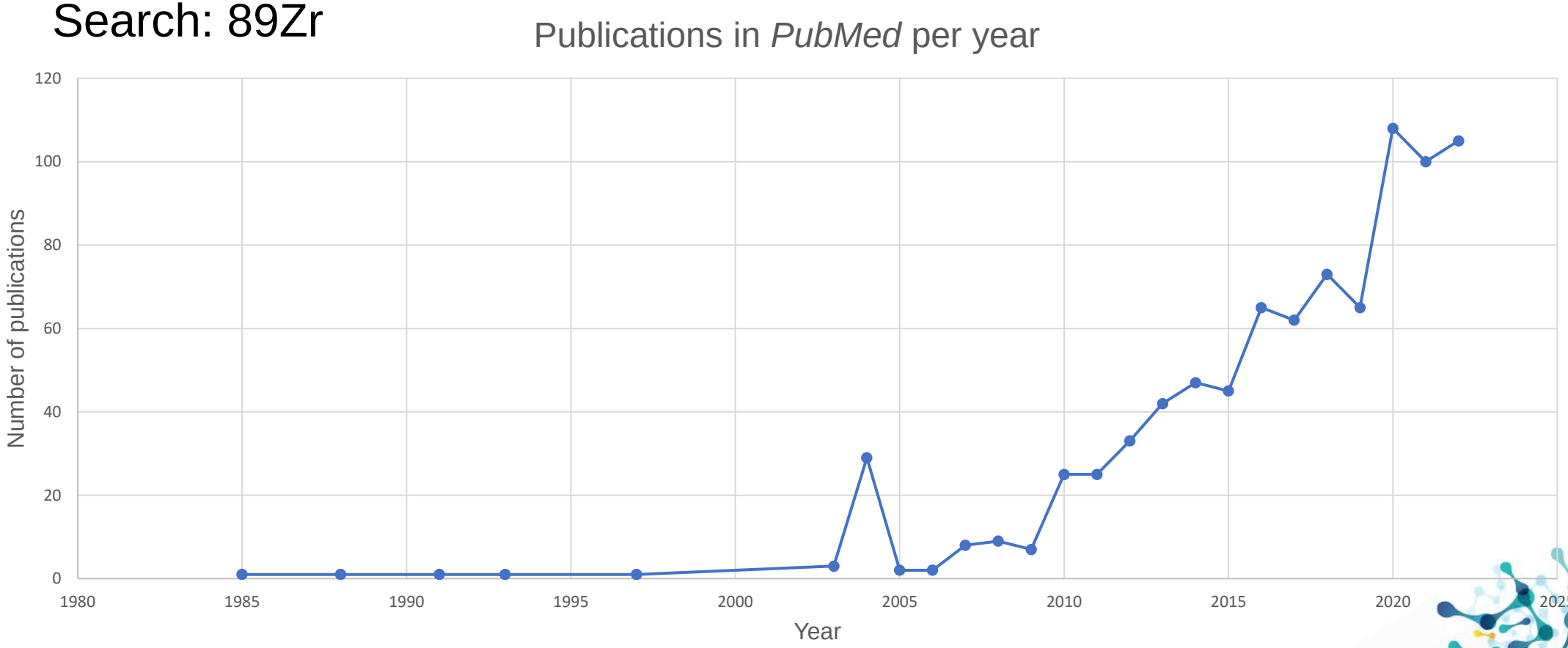
- **Developing country in Southeastern Europe**
- **Centralized production – 1 facility for the production of PET radioisotopes and radiopharmaceuticals (University Institute of PET)**

Feasibility study for the establishment of production of zirconium-89 radioisotope and implementation of ^{89}Zr-radiopharmaceuticals in clinical practice

- Ongoing study

ZIRCONIUM-89
– EMERGING PET RADIOMETAL

Search: 89Zr



Zirconium-89

Zirconium-89 half-life of 78.4 h corresponds to the biological half-life of monoclonal antibodies.

- **Half-life 78.4 h**
- **Immuno-PET radionuclide**
- **Labelling of antibodies, nanoparticles, proteins, peptides, and cells**

DESIGN OF FEASIBILITY STUDY

- PRELIMINARY ANALYSIS
- MARKET RESEARCH
- TECHNICAL FEASIBILITY ANALYSIS
- ECONOMIC ANALYSIS
- REVIEW AND ANALYSIS OF ALL DATA
- FEASIBILITY CONCLUSION

1 PRELIMINARY ANALYSIS

Objective: To assess whether the clinical application of ^{89}Zr-radiopharmaceuticals in the country is possible and justified.

1-1 Review of statistical data regarding malignant diseases in North Macedonia (frequency and mortality)

- Reference databases: international (Global Cancer Observatory) and domestic (Mortality Register and Cancer Register of Institute of Public Health)

1-2 Review of clinical applications data of ^{89}Zr-radiopharmaceuticals

- Reference database for clinical trials (ClinicalTrials.gov)

1-1 Review of statistical data regarding malignant diseases in North Macedonia

Neoplasms (C00-D48) are the ***second leading cause of death*** in Macedonia, after circulatory system diseases.

Deaths in 2020 due to malignant diseases	
1 – 64 years	> 64 years
24.25 %	12.68 %

Mortality Register, Institute of Public Health, 2021

2011-2020
The most common cause of death from malignant neoplasms:

average mortality rate in both sexes
180 per 100,000 population

Males: **bronchi and lungs cancer**

average mortality rate 63.9 per 100,000 men

Females: **breast cancer**

average mortality rate 29.07 per 100,000 women

Cancer Register, Institute of Public Health, 2021

10 most common primary cancer sites (N.Macedonia), 2011 - 2020

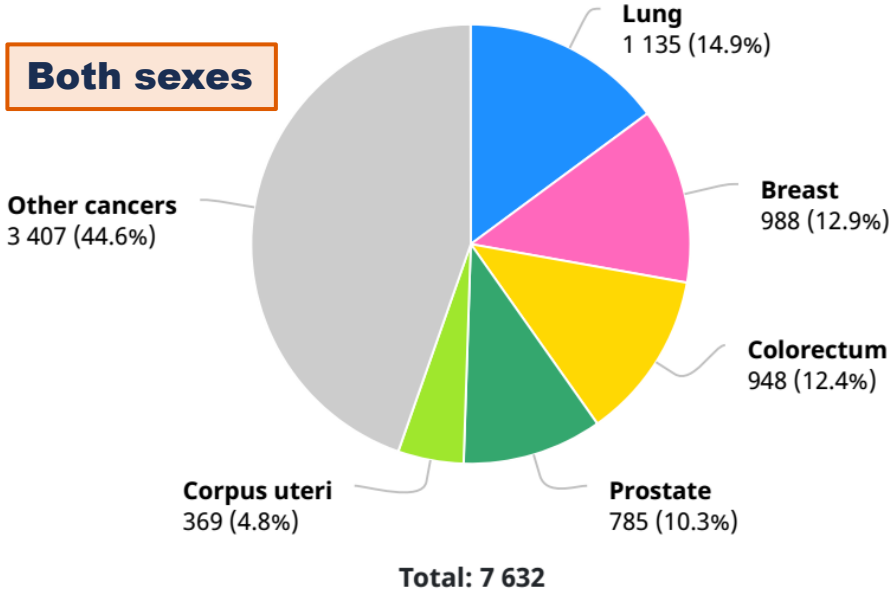
Total			Males			Females		
Code	**Primary sites**	**%**	**Code**	**Primary sites**	**%**	**Code**	**Primary sites**	**%**
C34	Bronchus and lung	13.12	C34	Bronchus and lung	18.80	C50	Breast	25.29
C50	Breast	11.59	C61	Prostate	9.77	C44	Other of skin	7.38
C44	Other of skin	8.22	C44	Other of skin	8.90	C54	Corpus uteri	7.30
C18	Colon	6.10	C16	Stomach	7.50	C34	Bronchus and lung	6.16
C16	Stomach	6.06	C18	Colon	6.50	C18	Colon	5.61
C61	Prostate	5.38	C67	Bladder	5.67	C53	Cervix uteri	5.16
C22	Liver and intrahepatic bile ducts	4.20	C22	Liver and intrahepatic bile ducts	5.08	C16	Stomach	4.30
C20	Rectum	4.00	C20	Rectum	4.38	C56	Ovary	3.83
C67	Bladder	3.93	C32	Larynx	3.85	C20	Rectum	3.53
C54	Corpus uteri	3.28	C25	Pancreas	3.10	C22	Liver and intrahepatic bile ducts	3.11
	Other	34.13		Other	26.44		Other	28.33

1-1 Review of statistical data regarding malignant diseases in North Macedonia

Number of new cases in 2020

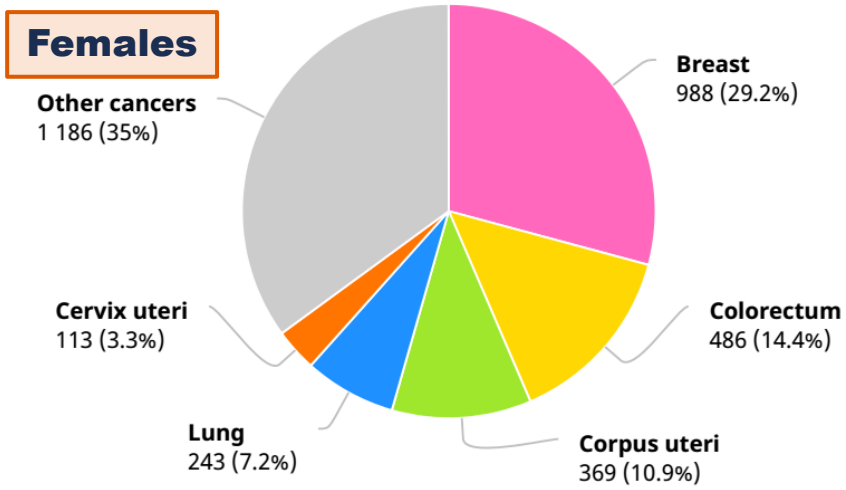
Global Cancer Observatory, 2021

Both sexes



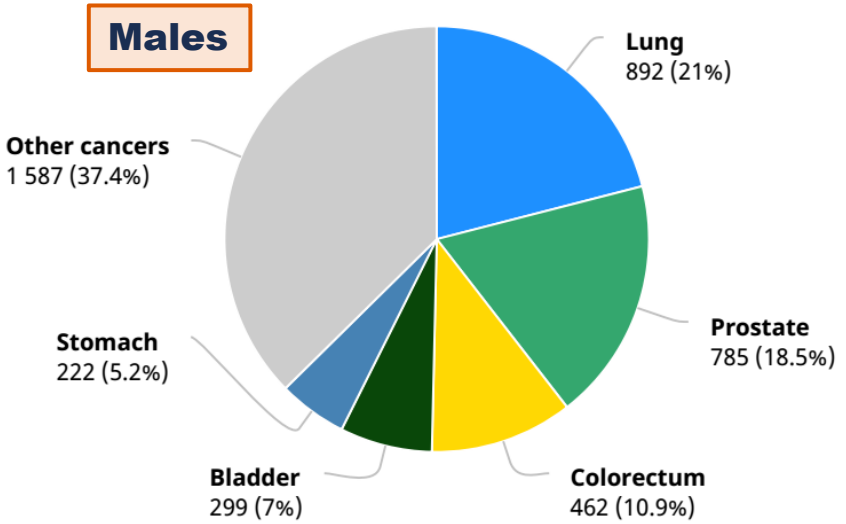
Total: 7 632

Females



Total: 3 385

Males



Total: 4 247

1-2 Review of clinical applications data of ^{89}Zr-radiopharmaceuticals

- **Clinical trials in total** (until 09.05.2021): 93
- **Status - completed, terminated, unknown**: 48
- **Countries**: Netherlands – 28, USA – 16, Belgium – 2, China – 2, Australia – 1, Sweden – 1, Denmark – 1, Korea – 1, France – 1, Spain – 1
- **Radiopharmaceuticals**: **^{89}Zr-bevacizumab** (**9**), **^{89}Zr-trastuzumab** (**6**), ^{89}Zr-Df-IAB2M (**3**), ^{89}Zr- Cetuximab (**3**), ^{89}Zr-Pembrolizumab (**2**), ^{89}Zr-J591 (**2**), ^{89}Zr-panitumumab (**2**), ^{89}Zr-Girentuximab (**2**), ^{89}Zr-DFO-pertuzumab (**2**), ^{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-BI 754111, ^{89}Zr-GSK2398852, ^{89}Zr-RO5429083, ^{89}Zr-TAK-164, ^{89}Zr-nanocoll, ^{89}Zr-DS-8895a, ^{89}Zr-RO5479599

УИ·ПЕТ

NIH U.S. National Library of Medicine
ClinicalTrials.gov

2 MARKET RESEARCH

Objective: To define the geographical impact of the market.

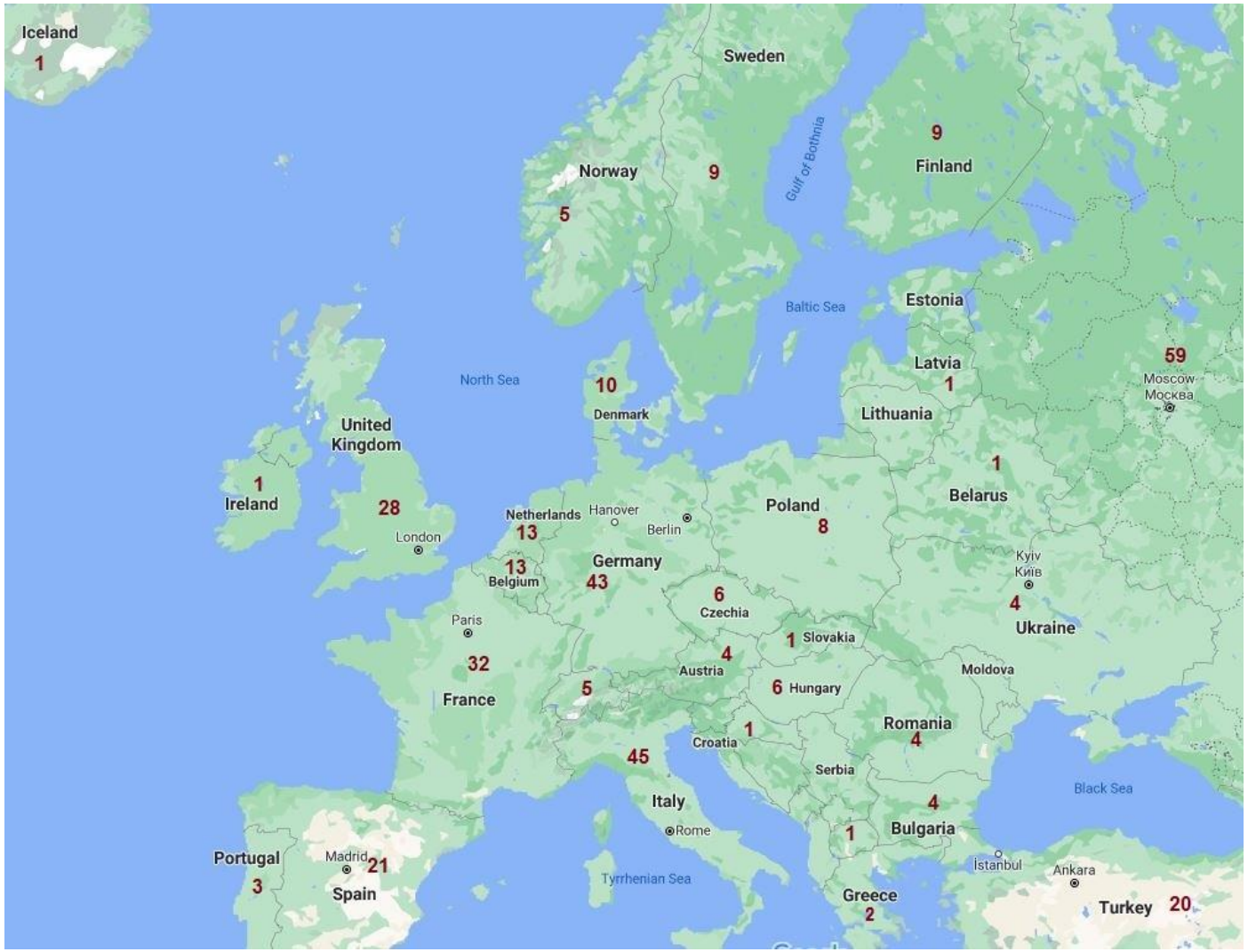
2-1 Distribution of medical cyclotrons in Europe

IAEA Cyclotron Distribution Database

2-2 Zirconium-89 production sites in Europe

Literary search

2-1 Distribution of medical cyclotrons in Europe



Worldwide:
1266

Europe + Turkey +
Russian Federation
(including its Asian part):
356

https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx (December 2022)

2-2 Zirconium-89 production sites in Europe

Netherlands (GMP compliant production of ^{89}Zr for the research community)

France

Turkey

Germany

Italy

Romania

United Kingdom

Belgium

Portugal

Russia

Poland

No zirconium-89 production on the Balkan Peninsula

3 TECHNICAL FEASIBILITY ANALYSIS

Ongoing

- Analysis of the technical capacities of the production site (University Institute of Positron Emission Tomography) in terms of space and equipment necessary for the realisation of the production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals.

Objective: To determine what type of additional equipment/apparatus is required.

3 TECHNICAL FEASIBILITY ANALYSIS

Zirconium-89 radioisotope

Production mode: cyclotron | **$^{89}Y(p,n)^{89}Zr$**

UI PET technical capacities: → 3 production and 2 QC laboratories

↓

Cyclotron PETtrace 860
- Beam energy 16.5 MeV
- Maximum current 100 uA on dual beam
- Possibility for the additional embedding of solid targets

3 TECHNICAL FEASIBILITY ANALYSIS

Zirconium-89 radioisotope

Production mode: cyclotron | **$^{89}Y(p,n)^{89}Zr$**

UI PET technical capacities: → 3 production and 2 QC laboratories

Cyclotron PETtrace 860
- Beam energy 16.5 MeV
- Maximum current 100 uA on dual beam
- Possibility for the additional embedding of solid targets

4 ECONOMIC ANALYSIS

Economic feasibility assessment

1. ***Financial analysis***
2. ***Pharmacoeconomic analysis***

4-1 FINANCIAL ANALYSIS

Methodology: Defining and calculating the costs (direct and indirect)
- data from literature search and from UI PET (production process simulation).

Objective: 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).

4 ECONOMIC ANALYSIS

4-2 PHARMACOECONOMIC ANALYSIS

Methodology: ***Cost-effectiveness analysis***

Objective: To assess the justification for the implementation of ^{89}Zr-radiopharmaceuticals in clinical practice.

Subject of the pharmacoeconomic analysis – **^{89}Zr-trastuzumab**.

Selection on the basis of the results of ***the preliminary analysis***:

→ ^{89}Zr-trastuzumab is one of the most common ^{89}Zr-radiopharmaceuticals in clinical trials;

→ on the national level, breast cancer is the most common malignancy and the most common cause of death from cancers in the female population.

4 ECONOMIC ANALYSIS

4-2 PHARMACOECONOMIC ANALYSIS

^{89}Zr-trastuzumab

Visualisation and quantification of HER2 status

⇩

An individualised approach to breast cancer management

5 REVIEW AND ANALYSIS OF ALL DATA

Evaluation of data

Factors

Circumstances

Limitations

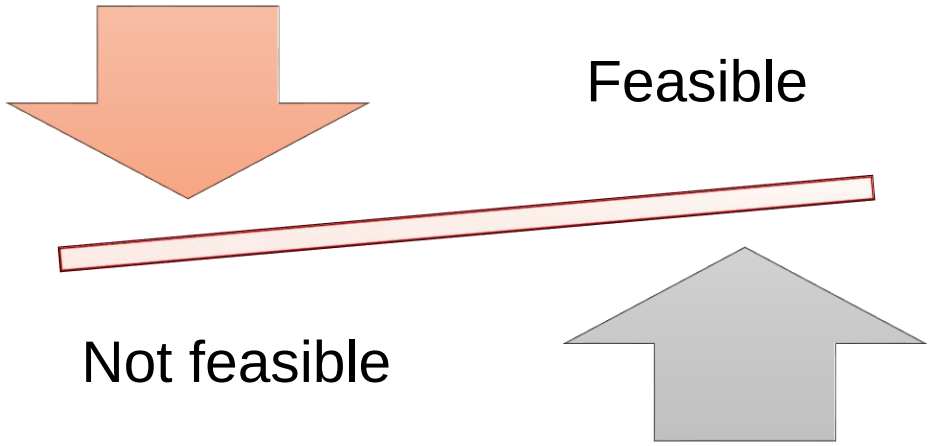
Opportunities

Risks

Benefits

6 FEASIBILITY CONCLUSION

Decision on whether the process of establishing the production of zirconium-89 radioisotope and ^{89}Zr-radiopharmaceuticals at the University Institute of Positron Emission Tomography is feasible.



Imperative - to expand the possibilities in terms of cancer management and research development in North Macedonia

“Invention is the most important product of man's creative brain. The ultimate purpose is the complete mastery of mind over the material world, the harnessing of human nature to human needs.”

Nikola Tesla

“Regardless of the beauty of the science involved in the development of the radiotracer, the ultimate goal is not the science, but the ability to improve the quality of life.”

Prof. Susan Z. Lever

THANK YOU VERY MUCH FOR YOUR ATTENTION!

University Institute of PET
Skopje, North Macedonia

Design of feasibility study for the establishment of ^{89}Zr production – tailored approach to introduce new radiopharmaceuticals in a developing country

Katerina Kolevska*, Maja Chochevska,
Marija Atanasova Lazareva,
Maja Velichkovska, Filip Jolevski,
Bistra Angelovska, Ana Ugrinska

* E-mail:
kolevskakaterina@gmail.com
katerina.kolevska@ugd.edu.mk