Landscape of early-phase oncology studies in the Netherlands

The Netherlands has been a natural favourite for conducting clinical research, with the Dutch healthcare system ranking among the best in Europe, the high level of education of investigators, large number of key opinion leaders, high quality Standard of Care (SOC) as well as the specialist centres in place that enable collection of reliable data. As an oncology dedicated contract research organisation, specialising in early-phase oncology drug development, SMS-oncology's expertise mirrors the contemporary landscape for clinical cancer drug research within its home base in the Netherlands.

Biopharmaceutical industry

As a nation with a long trading history, the Netherlands is famous for being a country of entrepreneurial mentality. As the government and school education encourages start-ups and innovation, nearly 12% of the Dutch working population is self-employed. The life sciences & health industry is one of the top sectors in the country, with a leading growth rate of 25% from 2010–2016. With 455 biopharmaceutical companies – a doubling in the past 10 years –, 85 hospitals, eight University Medical Centers (UMCs) and eight science parks, the Netherlands is one the most concentrated life science & health ecosystems in the world.

Science Parks and UMCs in NL

Thanks to an open culture and flexible mindset, small/midsize biotech has boomed, contributing to 95% of all biopharma firms. Almost a quarter of these companies are dedicated to oncology, with 110 products being cancer therapies. Hitherto, collaboration between research, university biomedical center and biopharmaceutical companies allowed the Netherlands to nest the most innovative oncology drugs in the past decade: CAR-T leads (Kite Pharma), immunotherapy and antibody giants (Genmab and Merus), cancer immunotherapy innovators (previously Organon, now MSD-Merck) and more.

Infrastructure and centres of excellence

The strategic location of the Netherlands in terms of access to Europe and other areas of the world via its train system and airports is further acknowledged through the move of the European Medicines Agency (EMA). This relocation is expected to bring the Netherlands into the spotlight, attracting more biopharmaceutical industry to the country in order to build close relations with EMA.

The Netherlands offers an outstanding R&D infrastructure, where start-ups can flourish and contribute to innovative medicines. Being the nerve centre for oncology research innovation, life science parks connect prominent university medical center, scientists and biotech companies, permitting a collaborative atmosphere and faster evolution to better treatments. Amsterdam (120 biotech companies in biotech, IT and technology), Utrecht (108 companies in life science & health, sustainability and healthy urban living), Leiden Science Parks (106 biotech companies in drug development and medtech or services in both), Pivot Park (56 companies in contract research, product development and pharma services) and Zernike Campus Groningen (150 science and engineering companies) are the main hubs for development of new cancer medicines. Science parks are strategically located in close proximity to UMCs.

As UMCs and peripheral hospitals are located within the reach of cities – and hence of patients – all together forming an attractive network of clusters for clinical studies, within a small radius. UMCs also take responsibility for the training and education of investigators and staff who are expected to deal with high-quality trials. The recent advances in oncology drug development and increasing complexity of clinical oncology studies continue to challenge clinical research professionals. Qualified investigators and study teams, along with well integrated electronic health systems, are crucial for the conduct and success of early-phase oncology studies. The academic center of excellence in the Netherlands serve this aspect to a satisfactory level and are well equipped to handle more technical studies. This is also reflected in study completion rates all being above 80% in top institutes[1].

Although on a European level, the top 10 sponsors for oncology trials are global pharmaceutical companies, in the Netherlands, studies in academic centres of excellence dominate the clinical study landscape, indicating a healthy innovation streamline from bench to bedside: The Netherland Cancer Institute (NKI),

Top 10 Sponsors in clinical trials

Antoni van Leeuwenhoek Hospital, Erasmus Medical Center, Vrije Universiteit Amsterdam (VU) and Academic Medical Center (AMC) are among the top 10 sponsors for the number of early-phase oncology clinical trials[1].

Another strength of the Netherlands is the increasingly growing public-private partnerships (PPPs) that bring together entrepreneurs, government and non-profit organisations (NGOs). A new addition to the 200 PPPs is the oncology-specialised Oncode Institute, uniting over 40 of the most outstanding research groups to foster scientific discoveries for next-generation therapies.

Disease epidemiology and clinical studies

The Netherlands is at the forefront of clinical drug research. Within a changing global clinical drug research environment with an increasing number of competitive countries, it is therefore essential to have insights into the strengths and weaknesses of the Netherlands as a clinical drug research country.

Ranking 12th in the world, the Netherlands has a high rate of cancer incidence, partly due to increased diagnosis and awareness, with one out of three deaths due to cancer in men (35%) and one in four deaths in women (28%)[2]. Lung cancer, accounting for 8% of deaths, is the third-leading cause of deaths behind heart disease and Alzheimer's and other dementia.

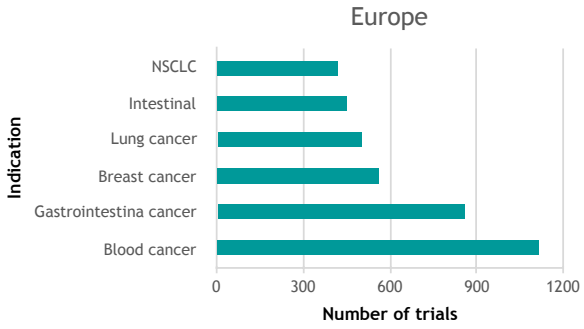
For Dutch men, the three most common cancers are:	For Dutch women, the three most common cancers are:
• Prostate cancer • Skin cancer • Colorectal cancer	• Breast cancer • Skin cancer • Colorectal cancer

Overall, this compares to the distribution of cancer cases worldwide, except for lung cancer. Lung cancer is the leading cancer type by incidence and mortality worldwide[3].

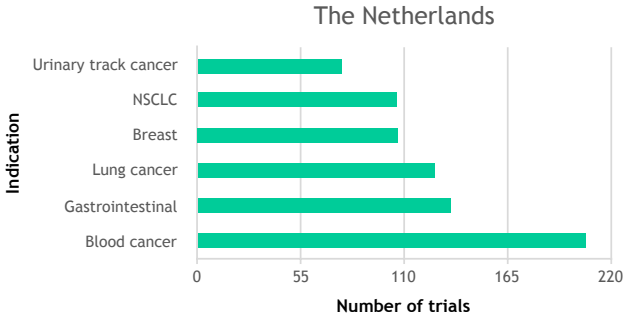
The Netherlands has a very active clinical landscape, with over 2000 clinical trials ongoing or planned. The majority of trials are ongoing in oncology with around 800 trials, followed by trials in the area of neurology and cardiology, with around 290 and 220 each, respectively.

In the field of oncology, there is an almost equal distribution of ongoing trials in the Netherlands of phase I, II and III. This is slightly different compared to ongoing trials in Europe overall; here the majority of oncology trials are in phase III, followed by phase I and then phase II trials. In the USA, oncology trials are mainly in phase II followed by phase I and then a relatively low number of phase III trials. This data reflects an active clinical landscape of oncology trials in the Netherlands, supported by an innovative drug development sector[1].

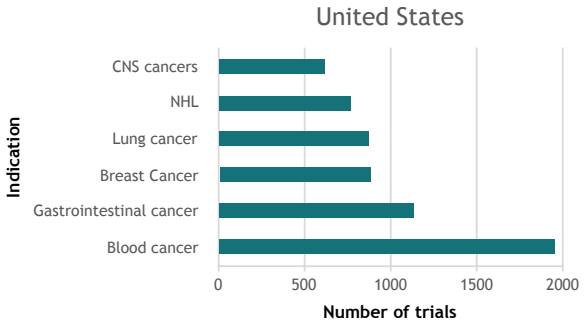
Immuno-oncology, as a novel therapy area in oncology, also contributes to the Dutch oncology trials landscape. There are almost equal numbers of trials ongoing for immuno-oncology for phase I, II and III. Interestingly, around 50% of phase I trials are immuno-oncology trials, of which the majority is trials with combination therapies. Europe-wide, ongoing immuno-oncology trials are either in phase I or II, and less in phase III. Also here, combination therapy trials represent the majority of phase I and phase II trials. The Netherlands compares to the US immuno-oncology landscape in the phase I and phase II trial distribution. Here, approximately 10% of the number of ongoing phase I and phase II trials in the USA are the ongoing number in Netherlands. Interestingly, the number of ongoing phase III trials is around 40% of the number of these immuno-oncology trials in the US[1].



Tumor indications most studied in EU



Tumor indications most studied in NL



Tumor indications most studied in US

The main cancer indications for ongoing trials are:

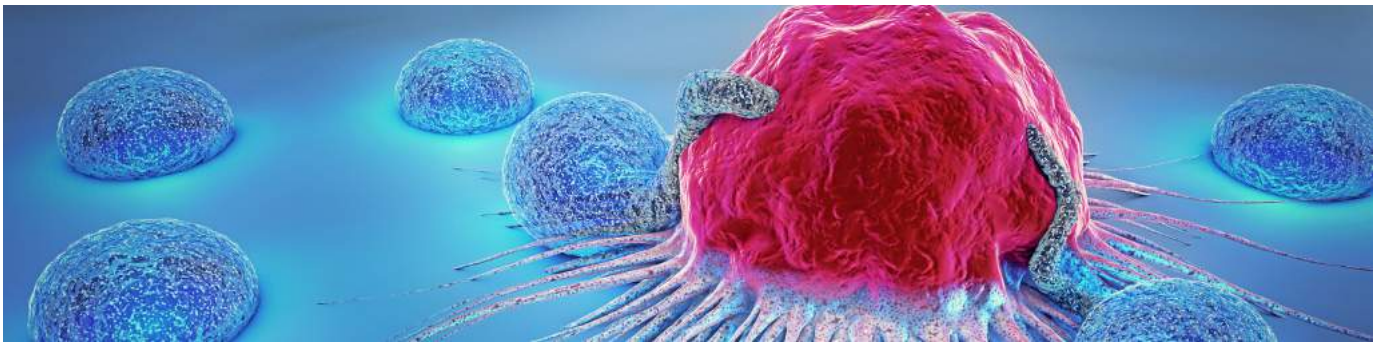
- Blood cancers
- Gastrointestinal tumours
- Lung cancer
- Breast cancers
- Urinary cancers

The main cancer indications for ongoing trials in the EU are:

- Blood cancers
- Gastrointestinal tumours
- Breast cancer
- Lung cancer
- Intestinal cancers

The focus of ongoing oncology trials in the Netherlands on blood cancers can be explained by a tremendous unmet medical need to improve current therapies and offer innovative life-prolonging treatments to this specific population of cancer patients. There is a push in the Netherlands to advance the therapeutic options in this particular cancer indication with around 200 ongoing trials, with an almost equal distribution of these trials in phase I, II and III.

Ongoing oncology clinical trials in Europe are almost split equally between single-country trials and multinational trials. In the Netherlands, almost 75% of ongoing trials in oncology are multinational studies. Interestingly, almost 60% of oncology trials



in the Netherlands are sponsored by companies (biotech/pharma companies) and 40% are investigator-initiated studies. In Europe, approximately 40% of trials are company-sponsored and around 60% are initiated by institutions or hospitals. Focusing on ongoing early-phase trials in oncology, the Netherlands follows the overall Europe-wide trend of phase I trials being primarily sponsored by companies (65% EU, 70% NL) and phase II trials being primarily conducted by institutes or academic centres (74% EU and 60% NL).

The Netherlands is in 4th position on the 2015 Global Innovation Index. For the healthcare sector, the country's innovation is notably propelled by myriad local success-stories, and particularly by the booming Dutch biotech scene, whose players concentrate their efforts on addressing unmet medical needs, thanks to the development of cutting-edge technology.

The Netherlands benefits from dedicated centers of excellence with strong international reputations, and also well-organised patient organisations, not to mention world-class expertise in rare disease treatment.

Regulatory Affairs and Recruitment in Clinical Studies

In order to start a trial in the Netherlands, you need approval from both the competent authority (CA) and ethics committee (EC), which can be processed in parallel. The Central Committee on Research Involving Human Subjects (CCMO) is the CA in the Netherlands and the approval process is based on a marginal test of the application which takes about 14 days. The central EC performs a more in-depth review of the clinical trial application (CTA). There are 23 medical research ethics committees (MRECs) in the Netherlands, with the majority of them linked to an institution such as an academic medical center or hospital.

Typical for the process in the Netherlands is also the requirement for a research declaration per study site, with approval by the department head. These declarations are part of the CTA to the central EC. The CTA can be done with one declaration and through an amendment the additional declarations from sites can be added. This is not the most straightforward process and could even endanger the attractiveness of the Netherlands as a trial country once the ECTR, the European Clinical Trial Regulation, comes into effect, with the aim of enabling more competition between countries by multinational trials. This could be a disadvantage as it might take longer before all sites are up and running for a trial with competitive recruitment. As a result, the Dutch sites might fall behind at the study start and catch up later to contribute to multinational trials. This is not going unnoticed by the clinical community, like the Dutch Clinical Research Foundation (DCRF), with several initiatives started to shorten the approval timelines at the CA as well as at the central EC level. Also, initiatives are being taken to standardise patient information forms and site agreements.

Timeline for review by the EC is 60 days after the central EC approves the CTA, the hospital board from each participating site has to give their approval.

In terms of patient recruitment for oncology trials, the Dutch are well positioned with the EU to have a somewhat higher recruitment rate (efficiency) of around 90% for oncology trials compared to 82% for all of the EU. Looking specifically at early-phase oncology trials, the Netherlands is also here more efficient in meeting recruitment numbers for phase I and I/II oncology trials, with almost 85% compared to 73% for all of the EU. For phase II trials in oncology, no difference in the recruitment rate is seen between the Netherlands and the EU[4]. The reasons behind this advantage are the excellent infrastructure of specialised hospitals and health science clusters, in combination with a raised patient awareness, involvement of advocacy groups and highly innovative novel therapies and technologies for cancer treatment.

REFERENCES

1. Global data 2017
2. Eurostat database 2014
3. Bray F. Ca Cancer J Clin 2018
4. Global data 2013

Inka Pawlitzky PhD

Inka obtained her PhD in immunology at Tufts Medical School in Boston and conducted two postdoctoral projects at the Max-Planck Institute for Immunobiology and Epigenetics and the Netherlands Cancer Institute (NKI) in Amsterdam. Moving to industry, she was a senior scientist at Leica Biosystems within oncology diagnostics. Inka joined SMS-oncology in 2017 as a consultant, where she provides expert advice on the design, setup and implementation of oncology trials.

Email: i.pawlitzky@sms-oncology.com

Yuva Oz MSc

Yuva obtained her MSc degree at the University of Heidelberg, working in centers of excellence such as DKFZ, Max Planck and EMBL. She did her PhD research in Hubrecht Institute on Chromatin Architecture and Gene Expression. After working as scientific marketer at EMBL, Yuva joined SMS-oncology in 2016 and works as Business Developer to drive clinical collaborations and account management to bridge the strategy to drug development.

Email: y.oz@sms-oncology.com