INTER-LOCAL
International call for clinical trials on development of local treatment for rare and/or hard-to-treat cancers

Five leading European cancer charities are joining forces to advance international clinical research focused on local treatments for rare and/or hard-to-treat cancers. The Swedish Cancer Society (Sweden), Norwegian Cancer Society (Norway), the Scientific Foundation of the Spanish Association Against Cancer (FCAECC, Spain), Stand up to Cancer (Kom op tegen Kanker; Belgium) and the Dutch Cancer Society (KWF, the Netherlands) will collaboratively launch a funding call to stimulate cross-border clinical research in this critical area.

Researchers based in the Netherlands, Belgium, Spain, Norway, and Sweden are encouraged to form international consortia and submit joint proposals. Limited budget can also be requested for inclusion centres from other countries as well.

Background

Local treatment of hard-to-treat and rare cancers

Survival rate for many cancers has doubled over the past 40 years, with 70% of patients surviving to 10 years or longer. However, progress has not advanced equally for all types of cancer. Survival for some types of cancer is lagging behind, due to the lack of successful treatment. For hard-to-treat cancers, the 5-year survival rate is still below 25% and little or no improvement has occurred in the past decades. Also, for rare cancers, there are hardly any specific new successful therapies available, leaving patients with limited or no treatment options, especially when they have metastases. The causes of therapeutic failure for hard-to-treat and rare cancers can be multiple, such as absence of appropriate targeted approaches, tumour heterogeneity, acquired drug resistance, problems with drug penetration and problematic drug development due to the rarity of some tumour types. Moreover, hard-to-treat cancers often present significant challenges for patients, leading to a high burden on their quality of life. The aggressive nature of these cancers, limited treatment options, severe side effects of therapies and the emotional impact of dealing with a severe diagnosis all contribute to a reduced quality of life for patients. While development of anticancer drugs has significantly improved cancer treatment outcomes, they may not always be effective against certain types of cancer or in advanced stages. Therefore, the development of highly effective alternative treatment modalities is crucial, especially when cancer drug development falls short as seen in rare cancers in particular. The local treatment of cancer, for example by surgery or radiotherapy, has long been established as a highly effective treatment option, played pivotal roles in treating various types of cancer and contributed largely to improving outcomes. These local therapies have developed over the years in more minimally invasive techniques that spare healthy tissue and precisely target the tumour, which significantly improves the quality of life after treatment.

The potential for significant financial returns in drug development, where pharmaceutical companies can patent and sell drugs to wide patient populations, make drugs attractive to private investors. However, limited financial interest in the development of effective and innovative local treatment has hampered the progress in this field.

International collaboration

International multicentre collaboration in investigator-driven clinical research is mandatory to achieve adequate patient accrual and will enhance both the quality, speed, scope and impact of clinical research efforts, potentially leading to better patient outcomes, such as improvement of survival and/or quality-of life or avoidance of futile and costly treatments. International collaboration is essential to harmonize research efforts, build clinical consensus and accelerate the development,

acceptance and implementation of evidence-based guidelines. Additionally, it is instrumental in ensuring the availability of a substantial patient pool necessary for conducting phase 2 and 3 clinical trials. International collaboration also stimulates the sharing of specialized expertise, techniques and best practices, which can lead to implementation of consensus-based care pathways, improved data collection, management, and data analysis. Especially for rare cancers, international collaborations provide access to enough patients that otherwise may be difficult to study within a realistic time frame in a single country. Multinational collaboration expands the pool of potential study participants, accelerates the research process and shortens the time to achieve the much-needed patient-relevant outcomes.

In order to close the gap in resources, to promote the international development of effective local treatments, and to increase survival and quality of life of patients with hard-to-treat and rare cancers, we would like to take the initiative to set up a call to stimulate international clinical research for local treatment options for these cancer types. Through this call, the consortium partners aim to stimulate international collaboration in clinical research between the respective funding countries, and by extension across the entire European region.

The call has an indicative budget of up to 8,5 million euros.

Call criteria (subject to minor changes)

- The trial must focus on a cancer type that is **rare and/or hard-to-treat**:
    - **Rare cancers**: the cancer type must be rare, defined as having an annual incidence of fewer than 6 cases per 100,000 individuals in the European region, based on the most recent and reliable epidemiological data or registry sources.
    - **Hard-to-treat cancers:** the cancer type must be classified as hard-to-treat by a 5-year survival rate below 25%, based on peer-reviewed scientific evidence published in high-impact journals.
    - **Molecular subtypes** may be considered eligible only if the experimental intervention under investigation necessitates a specific therapeutic approach tailored to that subtype.
    - Proposals may address **any stage of cancer**, including locally advanced, recurrent, or metastatic disease, taking into account the relevance of a local/locoregional therapeutic option within the proposed study context.

- **Intervention type**:
    - **Radiation therapy** (e.g. proton therapy, photon therapy, carbon ion therapy, image-guided radiation therapy, brachytherapy)
    - **Surgical interventions** (e.g. minimally Invasive surgery, precision/ image-guided surgery)
    - The experimental intervention itself must not involve the use of drugs, tracers or other active substances. Trials with local/locoregional drug delivery as therapeutic intervention, taking into account the efficacy of the drug, are not eligible.
    - **Combination therapy with other treatment modalities** (e.g. systemic therapies, immunotherapies, or other local/locoregional therapies), is allowed but only if the experimental intervention includes local/locoregional therapy (radiotherapy or surgery) and the independent therapeutic contribution of the local/locoregional treatment can be unambiguously demonstrated. If the experimental intervention is combined with a medicinal product, that product must be part of the current standard of care.

- **Research phase:** phase 2 and/or 3 clinical trials. Preference for confirmatory or pivotal trial.

- The primary objective of the proposed trial must be **patient-relevant** and focused on the development of more **effective treatments for rare and/or hard-to-treat cancers**, with the aim of improving life expectancy. However, proposals must also provide robust assurances that the study will

give adequate and systematic attention to **the quality of life of patients (including daily life, social and professional activities)**, as well as to the secondary effects of the experimental intervention (f.e. potential side-effects, co-morbidities, functional disabilities and impact on health status), both on the short- and long-term. A side effects management plan must be an integral part of the trial application.

- **Trial designs and methodologies**: Well-controlled prospective studies, using the best-fitting trial design. This may include but is not limited to randomized trials, innovative trial designs or platform trial designs. Designs that make use of validated clinically relevant endpoints or validated surrogate endpoints are both allowed. Including real world data (for example as control arm) may be considered.
- The proposed clinical trial must clearly demonstrate that **international collaboration** is essential to generate robust and generalizable clinical evidence (f.e. ensuring adequate patient recruitment, promoting harmonization of treatment protocols or enhancing implementation of study outcomes).

- The main applicant should be based in **the Netherlands, Spain, Norway, Sweden or Belgium**. As this call aims to stimulate mainly international collaboration between the funding countries, **participation from all five funding countries is highly encouraged**. To be eligible for this call, proposals must include **partners from at least three of the participating countries.** Maximum collaboration between the funding countries will be taken into account during the evaluation of the clinical trial applications.

- The **total budget** per clinical trial application should not exceed **3 million euros**. A limited part of the budget may be requested to support inclusion centers located in Europe outside the five funding countries, but allocation will be dependent on the budget availability and must not exceed 20% of the total budget, with an absolute maximum of €500.000.

- The proposed clinical trial must be feasible and ready to initiate within the five funding countries without depending on **complementary funding** that has not yet been secured.

- Proposals must demonstrate early and sustained **involvement of patients** throughout the trial lifecycle, including:
    - Co-creation of trial objectives with patient representatives during the study design phase, ensuring alignment with patient priorities and needs.
    - Organization of patient focus groups to foster peer support and gather collective insights.
    - Consideration of the international scope of the trial by incorporating diverse cultural and healthcare perspectives from a patient point-of-view.
    - A clear description of how patient input will shape the trial's design, feasibility, and overall impact.
    - Strong emphasis on effective communication between researchers and patients, ensuring transparency, mutual understanding, and shared decision-making.

- Applicants must provide a comprehensive **implementation plan** as part of the application. This plan should:
    - Clearly demonstrate the feasibility of trial implementation across all participating countries, including a realistic and coordinated timeline for trial start-up;
    - Include evidence of early engagement with relevant stakeholders, such as regulatory authorities, health technology assessment (HTA) bodies, and clinical guideline developers;
    - Address the strategic planning for valorisation of trial outcomes, ensuring that results can be translated into clinical practice and policy.
    - Address relevant ethical issues, including recognized quality standards and norms for good research practices

- Only clinical research into local treatments, for which **no or insufficient funding** can be made available by government or industry, is eligible.

- Research in the context of a **public-private partnership** may be eligible if it is necessary for the execution of the project, appropriate agreements regarding intellectual property and co- funding are in place at the time of the proposal and if guarantees can be given on accessibility and fair price-setting after the research is completed. Commercial/industrial parties cannot apply for funding themselves under any circumstances.