taRgeted thErapy for adVanced colorEctal canceR paTients

Sprawozdania

Informacje na temat projektu

REVERT

Identyfikator umowy o grant: 848098

Strona internetowa projektu

DOI
10.3030/848098

Projekt został zamknięty

Data podpisania przez KE
22 Listopada 2019

Data rozpoczęcia
1 Stycznia 2020

Data zakończenia
31 Grudnia 2024

Finansowanie w ramach
SOCIETAL CHALLENGES - Health, demographic change and well-being

Koszt całkowity
€ 5 887 273,75

Wkład UE
€ 5 887 273,75

Koordynowany przez
IRCCS SAN RAFFAELE ROMA SRL
Italy

Periodic Reporting for period 2 - REVERT (taRgeted thErapy for adVanced colorEctal canceR paTients)

Okres sprawozdawczy: 2021-07-01 do 2022-12-31

Podsumowanie kontekstu i ogólnych celów projektu

The REVERT project addresses the specific challenge of understanding at system level the pathophysiology of metastatic colorectal cancer (mCRC) in patients responding well or poorly to therapies, in order to design an optimal strategy for mCRC on a case-by-case basis, with therapeutic interventions modulated depending on the patient's features. CRC is diagnosed in more than 400,000

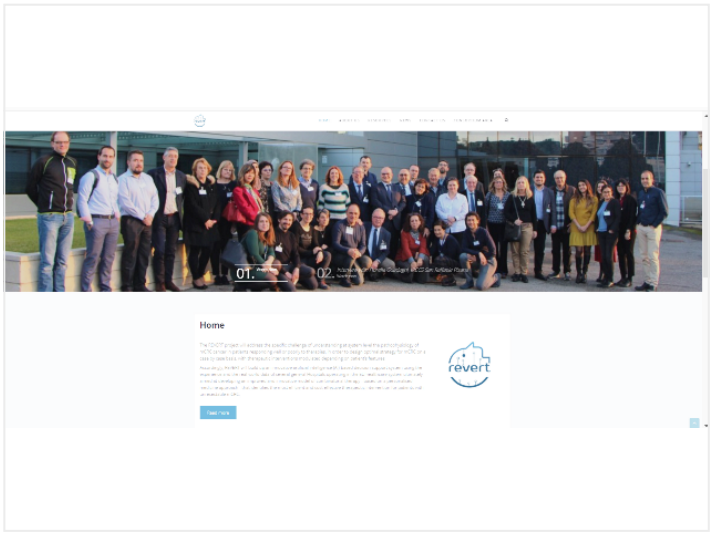
people per year in Europe, almost 50% of whom are developing distant metastases. New molecular targeting drugs currently used to treat CRC might have severe side effects and lead to high treatment costs. Therefore, in consideration of the high prevalence of CRC, the frequent development of metastases, and the cost of commonly used drugs mCRC constitutes a high economic burden to the health and social systems within the EU. Accordingly, REVERT is building up an innovative artificial intelligence (AI)-based decision support system using the experience and the real-world data of several general Hospitals and Biobanks operating in the EU healthcare system, ultimately aiming at developing an improved and innovative model of combinatorial therapy (based on a personalised medicine approach) that identifies the most efficient and cost-effective therapeutic intervention for patients with unresectable mCRC.

Prace wykonane od początku projektu do końca okresu sprawozdawczego oraz najważniejsze dotychczasowe rezultaty

the objectives through the implementation of the activities planned in the Description of Action (DoA). The “FAIR - Data Management Plan (DMP) and principle” was devised by the Coordinator, with the contribution of the other REVERT partners and the system architecture document – describing the block schema of the software application used within the REVERT project - was developed. The virtual infrastructure of the REVERT DataBase (RDB) was created according to the principles of Privacy by Design and Privacy by Default and all partners contributed to the construction of the RDB by compiling clinical, histological and molecular information. Meanwhile, partners contributed to research aimed to identify different predictive models for stratifying patients and to define rational models based on machine learning (ML). Considerable effort have been taken to harmonize biobank SOPs and to standardize preanalytical phases and choice of QC material(s) for quality monitoring of analytical phases. In-house SOPs for AI-based handling and analysis of transcriptome sequencing data has been developed accordingly. Other activities – in line with the planned tasks – during the reporting period pertain to the identification of alterations of genes important for CRC pathways and the assessment of the effect of gene expression levels on patient overall survival in different subgroups of age-stratified patients. The results showed that the identified genes have the potential to be used as targets and biomarkers for AI/ML programs for building prediction models as stated in the REVERT project proposal. While the RDB implementation was ongoing, the AI analysis was started. Finally, as the REVERT project foresees a clinical prospective, no-Profit, phase IV with Medical Device, multicenter, open label, single-arm, pharmacological pilot study to evaluate the efficacy of the best administered treatment, some of the activities were focused on the optimal strategy to meet the final protocol, which was submitted to the Registry of Clinical Trials, and first approved by the Policlinico Tor Vergata Ethics Committee (Registry N. RS149/20). The REVERT project website was launched in M3.

Innowacyjność oraz oczekiwany potencjalny wpływ (w tym dotychczasowe znaczenie społeczno-gospodarcze i szersze implikacje społeczne projektu)

REVERT aims to identify biomarkers relevant for treatment selection of mCRC patients as already established drugs can be more efficiently used by accurately stratifying the patient groups that can mostly benefit from a given combinatorial treatment. The combination of clinical monitoring with molecular testing of liquid biopsies should allow generation of new concepts in patients where no standard treatments are available. Depending on the tumour mutational status, therapies able to specifically target monoclonal antibodies against VEGF or EGFR are routinely used in combination with cytotoxic treatment. Important genes in RTK-RAS-PI3K pathways were identified in previous studies and were used in REVERT as candidate genes for the analyses. The results obtained in the reporting period, although preliminary, identified KRAS as the only gene capable of predicting patient overall survival with statistical significance in an age-stratified CRC cohort. In addition, PIP5K1A and PIK3CA were able to predict patient overall survival with statistical significance in CRC patients below age 50. This result represents a progress beyond the state of the art, as there has been lack of information on prognosis and treatment of young CRC patients. Thus, KRAS, PIP5K1A and PIK3CA may be used as biomarkers and therapeutic targets for prognosis and treatment of young patients to improve CRC treatment. The REVERT results also provided the opportunity to demonstrate that the GenXPro GmbH MACESeq approach is a cost-efficient and powerful method for cancer diagnostics in general, including mCRC. The MACE-Seq protocol applied to the samples is, indeed, well suited to generate reliable and comprehensive transcriptome profiles from cancer as well as from surrounding tissue. AI-based analysis of NGS data delivered the expected results and enabled their correlation to CRC data in international data repositories (e.g. The Cancer Genome Atlas TCGA). The identification of each patient's individual profile will help to choose the correct target treatment for mCRC patients. This approach will help to overcome the failure of a percentage of patients that do not respond to targeted therapy despite the tumour mutational status. New combination treatments, adjusted schedule and doses should offer new opportunities for mCRC patients. Although the REVERT is specifically targeting mCRC, it is expected that its results may favourably impact on other cancer types or different medical problems, as some of the Partners already demonstrated the potential of an AI approach specifically designed to exploit significant patterns in routinely collected demographic, clinical and biochemical data that could be easily adapted to different local situations or medical conditions. From available data, interpretability has been identified as a key point, no less important than the typical accuracy and performance metrics. The importance of interpretability stems from the fact that ML is increasingly used in medical contexts, where users are often inexperienced in interpreting AI metrics and results. Consequently, output must be translated into a language that physicians can understand. At the state of the art, interpretability is still barely considered in most of the works analysed, suggesting that it is a factor that can be improved to “democratize” AI in many other areas. In the first reporting period of REVERT, UCAM developed a code based mainly on Tensor Flow and Scikit-learn (among other state of the art ML libraries) that has the following features; a) it can use several ML models, b) it runs seamlessly on High Performance Computing (HPC) architectures, c) it adds an Interpretable Machine Learning (IML) layer that allows to extract explanations from the most optimal or selected ML models. This solution will be further updated during the project lifetime.



REVERT project website home

Ostatnia aktualizacja: 3 Września 2024

Permalink: https://cordis.europa.eu/project/id/848098/reporting/pl