Project context and objectives
Cervical cancer (CC) is the second most common malignancy in women worldwide. While epidemiologists at the recent IGCS meeting in Melbourne (November 2014) judged that Human Papilloma Virus (HPV) was eradicable if women were screened worldwide, the reality is that regular screening for all can presently not be reinforced in highly endemic areas (such as India, Africa and certain areas in South America) where 4/5th of the population at risk may not be aware of screening practices.

Although CC is a single diagnostic entity and infection of high-risk HPV is recognized as an important initiating event in tumourigenesis, CC exhibits differences in clinical behaviour. Stratification of CC into subclasses for progression and response to targeted treatment remains to be defined. At present, the dominant targets under scrutiny for innovative CC treatments are the following: EGFR/PI3K pathway, proliferation/DNA checkpoint and angiogenesis inhibition as well as anti-HPV vaccines. There have been recent publications (Ojesina, 2014; Wright, 2013) on high resolution genetic investigations in CC. So far, there has been no prospective assessment on patient outcome based on whole genome/exome sequencing or protein profiling of their tumours together with quality control evaluation of patient treatment. Early prospective data is available from a small phase 2 clinical trial by Institut Curie, the coordinators’ center, suggesting that EGFR inhibition at the membrane is ineffective in the presence of a downstream PI3K pathway activation (de la Rochefordière et al., 2015).

- We are lacking prognostic and predictive biomarkers for CC treatment and there is a growing need for the development of biomarkers to follow up the course of the disease.

RAIDs is a multidisciplinary co-operation between academic clinical centers, SMEs and translational research platforms. It combines Next Generation Sequencing (NGS) and Reverse Phase Protein array (RPPA) in a large patient population prior to standard therapy. It includes:

- a cognitive cohort study (BioRAIDs) intended to define tumour stratification for targeted therapies,
- as well as precision medicine trials using an HPV directed vaccine in combination with checkpoint inhibition.

In addition, high throughput screening techniques have been performed in CC cell lines, allowing to identify new drugs of relevance for advanced stage multi resistant CC. These molecules are to be validated in preclinical mouse models. Ongoing studies will assess in vitro efficacy of drug targeting according to molecular phenotypes.

The main objectives of RAIDs as stated in the DoW are:

- To identify prognostic and predictive biomarkers for standard and innovative therapies in cervical cancer patients using both high throughput genomic and proteomic approaches, the final aim being to improve treatment response for the individual patient;
- To define a set of stratification criteria for therapy in patients with cervical cancer based on the tumour's molecular profile;
- To identify underlying mechanisms causing immune tolerance of this sexually transmitted viral disease in order to facilitate innovative clinical interventions by vaccination studies (together with micro-environment modulators and/or checkpoint inhibitors);
- To improve clinical outcome of patients with cervical cancer by conducting interventional precision medicine trials.
Work performed and main technical results achieved

RAIDs started October 1st, 2012 and will end March 2017 following an 18 months extension’s approval from the European Commission. The consortium is composed of 9 research centers (Institut Curie, INSERM, KEM, IOV, TEO HEALTH, IMSP IO, IGR, NKI and HCTC), 2 universities (Erasmus and EMAUG) and 4 companies (AmBTU, Seqomics, Quanticsoft and ALMA) all from 7 European countries (France, Germany, the Netherlands, Serbia, Moldova, Romania and Hungary).

- **PROGRESS IN CLINICAL STUDIES**

  A. BioRAIDs STUDY (Ngo et al., 2015)

  The focus during the past 18 months has been on corrective actions to overcome the lag time in the international activation process of the BioRAIDs study.

  At M36 patient accrual is active in all European countries. Accrual rates have almost doubled (running at 20 patients per month) in the last couple of months. 220 patients have been accrued till date.

  HCTC (Hannover Clinical Trial center) was voted in at the 24M Steering Committee meeting as new partner to the consortium with the mission to coordinate the BioRAIDs trial as “CRO” for Germany, Moldova and Romania. In order to speed up the inclusions, additional clinical centers have been contracted and opened in Romania (IASI), Germany (Dresden) and The Netherlands (Nijmegen, pending contract signature) in June 2015. Centre in discussion:Birmingham UK.

  The quality control for MRI imaging is in the process of being set up in Serbia..

  B. DNA VACCINE TRIAL

  The phase I DNA vaccine (HPV targeted therapy) trial sponsored by NKI in the Netherlands completed patient inclusions and immunological analysis is almost finalized. At three months follow-up no clinical results were seen yet. So far, only a limited immune response is seen.

  - **SCIENTIFIC WORK** achieved during the first 36 months:

    - At Erasmus MC, an efficient pipeline to isolate circulating (tumour) DNA from serum and plasma was developed as well as methods for the detection of low-frequency mutations were successfully introduced.
    - RPPA analysis is awaiting more tumour samples to start. 20 novel antibodies for RPPA have been validated. Quality and quantity control of first tumour samples was performed awaiting the actual RPPA analyses planned to start April 2016.
    - HPV integration site analyses were initiated.
    - Exome sequencing on tumour samples is ongoing. 48 tumour samples have been sequenced till date.
    - Exome sequencing on 20 cervical cell lines has been completed and is being analyzed. Major somatic alterations and DNA copy number alteration from exome sequencing profiles confirm PI3K pathway mutations to be a dominant feature in CC
    - Pharmacological profiling of cell lines has already detected a group of drugs that synergizes with the “standard treatment” of advanced cervical cancers has now been identified A validation process is ongoing.
    - Preclinical mouse models for tumour micro-environmental studies have been developed and are published in journals with a high impact factor. Preclinical mouse data on combining vaccine and radiotherapy are published and report the efficacy of a novel dual targeting approach in a preclinically relevant animal model. A patent has been deposited.

  - **Dissemination to the public and scientific communities**

    Dissemination actions have led to a better visibility of the RAIDs project on an international level and to the wider understanding of the need for targeted approaches in the field of cervical cancer.

    Video clips explaining RAIDs have been produced (http://www.raids-fp7.eu/press/videos.html)

    A dropbox for patients requests for information in the field of precision medicine has been inserted on the RAIDs website as well as in the cervical cancer factsheet of ESGO. The dropbox allows patients to ask questions in relation to standard treatment and to innovative protocols regarding precision...
medicine in their native language. Clinicians from the RAIDs consortium will ensure feedback to patients.

RAIDs drop box - http://www.raids-fp7.eu/a-question.html

Expected final results, potential impact and use
RAIDs aims to define a set of stratification criteria based on molecular profiling. Its results will give insight into dominant genomic and protein signaling pathway alterations, enabling the identification of prognostic and predictive biomarkers for standard or targeted therapy in CC.

The RAIDs consortium aims

- to provide a safer and more efficient therapy for the individual patient;
- to raise awareness in countries with lesser screening practices;
- to improve the quality of life for women with cancer via:
  - a) the acquisition of defined molecular data for better treatment decisions,
  - b) targeted pilot trials directed at specific alterations as well as targeted vaccine trials directed against the HPV
  - c) the continuous evaluation of standards of care by comparing standards and outcome in all the RAIDs centers
- to disseminate information on innovative practices in concertation with the help of other international structures, be the clinical trial orientated [EORTC (European Oranisation for Research and Treatment of Cancer) and ENGOT (European Network for Gynecological Oncology Trials)] centers or international societies such as [ESGO (European Society for Gynaecological Oncology), ESMO (European Society for Medical Oncology) and IGCS (International Gynaecological Cancer Society)].
- to provide information on predisposing conditions for immune rejection or tolerance of this virally transmitted disease rendering immune interventions more effective
- to develop new tools and ideas on future treatments using drug combinations which may be exploited and create economic wealth

RAIDs consortium
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2. AmBTU, Amsterdam Biotherapeutics Unit, Netherlands
3. SeqQmics, Seqomics Biotechnologia Korlatolt Felelossegu Tarsasag, Hungary
4. KEOCYT, Keocyt SAS, France : This partner has left the project
5. INSERM, Institut National de la Santé et de la Recherche Médicale, France
6. AVL, Stichting Antoni Van Leeuwenhoek Ziekenhuis, Netherlands This partner merged with partner 16
7. Erasmus MC, Erasmus Universitair Medisch Centrum Rotterdam, Netherlands
8. KEM, Kliniken Essen-Mitte Evang, Huyssens-Stiftung/Knappenschaft Gemeinnutzige GmbBH, Germany
9. EMAUG, Ernst-Moritz-Arndt-Universität Greifswald, Germany
10. IOV, Institut Za Onkologiju Vojvodine, Oncology Institute of Vojvodina, Serbia
11. TEO HEALT SA, Romania
12. IMPS IO, Institutia Medico-Sanitara Publica Institutul Oncologic, Republic of Moldova
13. IGR, Institut Gustave Roussy, France
14. Quantisoft SARL, France
15. Alma Consulting Group SAS, France
16. NKI, Stichting Het Nederlands Kanker Instituut, Netherlands
17. HCTC, Hannover Clinical Trial Center, Germany. Entered the project from M24

References


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