Rational molecular assessment and innovative drug selection (RAIDs): Paving the way to precision medicine in cervical cancer

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http://www.raids-fp7.eu/consortium

Background

Cervical cancer (CC) is the 2nd most common cause of cancer deaths in women worldwide, for which prognostic and predictive biomarkers are lacking. RAIDs is a EU-funded co-operation between academic clinical centers, SMEs and translational research platforms in 7 European countries, focusing on cervical cancer. The main objective of the RAIDs project is to take advantage of this tumor type, which is easily accessible for repeated biopsies, to learn how to stratify patients into targeted therapies.

The project includes:
1) a cognitive cohort study (BioRAIDs) [1], one of the first prospective trials intended to define patient stratification for targeted therapies. So far, 340 patients have been recruited.
2) a targeted clinical trial using an HPV directed vaccine
3) preclinical studies aiming at assessing new treatment strategies.

Whole exome sequencing (Seqomics, HU/ Curie, FR)

48 RAIDs samples analyzed so far:
- PIK3CA confirmed as the most frequently mutated gene in CC (43%)
- Clusters do not show any association with histological type, grade or FIGO categories
- Clusters show differences in number of mutated genes (B)
- Pathway enrichment analysis shows mutations in DNA repair, mitochondrial metabolism and EMT as key features that differentiate the five clusters (C)

dPCR to detect PIK3CA mutations in cfDNA (ErasmusMC, NL)

Detection of PIK3CA mutation in circulating cell-free DNA: evaluation as a biomarker to detect early relapse in post-treatment blood biopsies.

dPCR (= Digital PCR) is about 100x more sensitive than SNaPshot® (= primer extension-based method for the analysis of SNPs)

Reverse Phase Protein Arrays (Curie, FR)

RPPA is ongoing: 154 pre-treatment + 101 post-treatment biopsies + 23 CC cell lines. 187 highly specific antibodies are selected to study expression & activation status of:

- PISK, MEK/ERK, Wnt, ..., TGFbeta, PTK, p53, ...
- Metabolism, OXPHOS, hypoxia
- Apoptosis
- DNA repair,
- Cell cycle checkpoints
- Adhesion, EMT

Expected outcome

- Bioinformatics analyses will integrate molecular datasets to predict patients of high risk for residual disease or recurrence following standard therapy based on the tumor molecular pattern.
- The identification of predictive tumor/blood based biomarkers will permit the definition of new strategies for precision medicine in CC.

Acknowledgments: This project has received funding from the European Union’s Seventh Program for research, technological development and demonstration under grant agreement No 204910.