Rational molecular assessment and innovative drug selection (RAIDs): Exome data from cervical cancer

http://www.raids-fp7.eu

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BACKGROUND

Recent retrospective data[1,2,3] identified major molecular alterations in cervical cancer (CC), but so far there has been no prospective assessment on patient outcome using a complete molecular profiling with quality control evaluation of treatment. The Cetuxicol (phase 2) clinical trial showed that the addition of Cetuximab over a 6 week period, did not improve DFS. PI3K pathway mutations in the tumor in the Cetuximab treatment arm led to a worse DFS[4]. 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.

METHODS

RAIDs is a multidisciplinary co-operation between academic clinical centers, SMEs and translational research platforms in seven European countries. It includes:

1. a cognitive cohort study (BioRAIDs)[5], one of the first prospective trials intended to define patient stratification for targeted therapies
2. a targeted clinical trial using an HPV directed vaccine
3. preclinical studies aiming at assessing new treatment strategies

Whole exome sequencing (WES) was performed on tumors and constitutional DNA from 48 BioRAIDs patients.

Bioinformatics pipelines to detect somatic mutations and clustering methods were developed in order to stratify the patients into different subtypes.

Pathways' enrichment based on ACSN maps[6], which contains a collection of cancer-related signaling network maps was used to identify pathways which are signicantly mutated.

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RESULTS

Figure 1. Bioinformatics pipelines and variant filtering for WES analyses

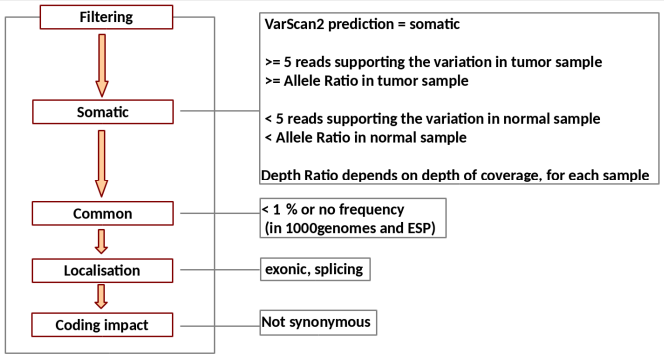


Figure 2. Driver gene mutations in CC tumors form 48 BioRAIDs patients.

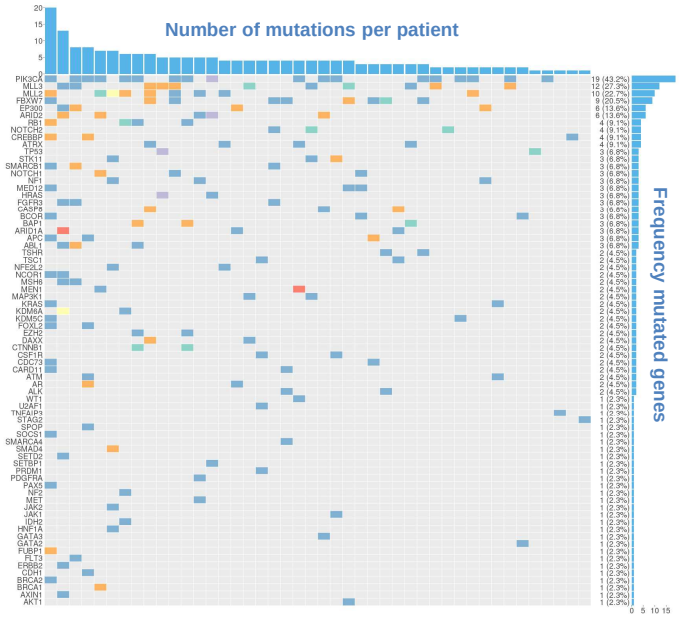
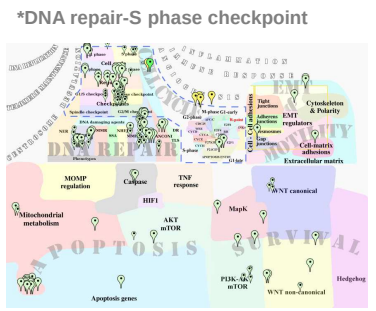
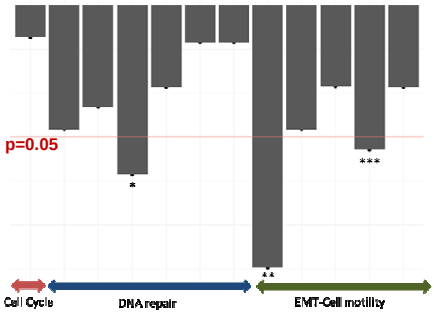
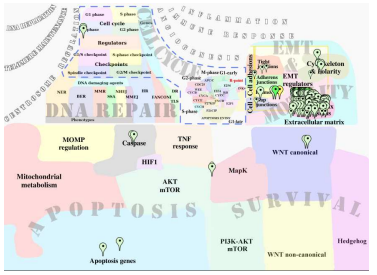
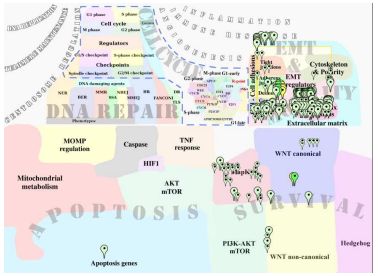


Figure 3. Pathway enrichment strategies to identify genes of interest among those which are not frequently mutated. EMT=Epithelial mesenchymal transition.









CONCLUSIONS

- Somatic mutations identified in 48 BioRAIDs CC patients using WES confirm PI3K pathway mutations to be a dominant feature in CC. Pathways' enrichment analyses highlighted significantly altered modules in DNA repair and EMT pathways.
- Bioinformatics analyses are ongoing to predict patients of high risk for residual disease or recurrence following standard therapy based on the tumour molecular pattern and proteomic analyses.
- The identification of predictive tumor/blood based biomarkers will permit the definition of new strategies for precision medicine in CC.