

EPV007/#582

DNA DAMAGE REPAIR IS ALTERED BY INHIBITION OF DISCOIDIN DOMAIN RECEPTOR 2 (DDR2) THROUGH METABOLIC REWIRING IN HOMOLOGOUS-RECOMBINATION PROFICIENT OVARIAN CANCER MODELS

¹E Stock*, ²K Cho, ¹E Lomonosova, ¹A Schab, ¹A Oplt, ¹H Noia, ¹S Bruce, ¹D Khabele, ¹L Kuroki, ¹A Hagemann, ¹C Mccourt, ¹P Thaker, ¹D Mutch, ¹M Powell, ²L Shriver, ²G Patti, ¹K Fuh. ¹Washington University, Gynecologic Oncology, St. Louis, USA; ²Washington University School of Medicine, Department of Chemistry, St. Louis, USA

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Objectives Discoidin Domain Receptor 2 (DDR2) is a receptor tyrosine kinase which binds fibrillar collagen. Previous work from our lab demonstrated that DDR2 inhibition increases sensitivity to olaparib in homologous recombination (HR) proficient ovarian cancer. This study aimed to understand the mechanism of DDR2 inhibition increasing sensitivity to olaparib.

Methods Three DDR2-expressing human ovarian cancer cell lines, ES2, COV362, and PEO4, with short hairpin control and DDR2 knockdowns were used. The HR status after irradiation and DNA damage response after treatment with olaparib was determined using immunofluorescence. In vivo metabolomics analysis of ES2 tumors was performed after injection of U-13C-glucose tracer.

Results All cell lines had a 2-fold increase in RAD51 foci after irradiation indicating HR proficiency. DDR2 knockdown induced HR deficiency. To confirm that DDR2 regulated HR, DDR2 knockdown cells were rescued with DDR2 wild-type (DDR2-WT rescue) in order to re-express DDR2. DDR2-WT rescue cells were again HR proficient. On western, BRCA1 expression was decreased in cells without DDR2 expression through decreased activation of the PI3K pathway. Knockdown of DDR2 increased DNA damage and repair through non-homologous end-joining both at baseline and after treatment with olaparib. These findings reversed in DDR2-WT rescue cells. In vivo metabolomics analysis of tumors without DDR2 expression found decreased pentose phosphate pathway activation including decreased ribose-5-phosphate, an intermediate essential for DNA repair through nucleotide biosynthesis.

Conclusions DDR2 inactivation sensitizes HR proficient ovarian cancer cells to olaparib through induced HR deficiency and metabolic rewiring possibly leading to impaired DNA damage repair. Current experiments are underway to confirm metabolomics findings.

EPV008/#139

ROLE OF KI67 IN PREDICTING SURVIVAL IN RH+/HER2- BREAST CANCER ACCORDING TO AXILLARY NODAL INVOLVEMENT

N Mejri, Y Berrazega*, H Rachdi, I Harhira, H Boussen. *University hospital Abderrahmen Mami Ariana, Medical Oncology, Tunis, Tunisia*

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Objectives We aimed to evaluate the cut-off value of Ki67 that predicted survival in luminal breast cancer and investigated its survival impact according to axillary lymph node involvement.

Methods We retrospectively selected 321 cases of histologically confirmed, early stage, breast cancer treated between 2011–

2015. All patients had ER and/or PR positive (>10% expression) and HER2- tumors. We evaluated the prognostic value of several cut-off levels of Ki67 in terms overall survival (5-year OS): 14%, 20%, 30% and 50%. We also considered different subgroups according to axillary lymph node involvement: pN0(38%), 1–3pN+(35%) and ≥4pN+(27%). We used Kaplan Meier method and Cox regression models to evaluate survival.

Results Median age was 49 years-old, 42% were menopausal. Media Ki67 was 28%. Sixty four percent of patients had mastectomy, 93% received chemotherapy and 88% radiation therapy. On overall population, after median follow-up of 51 months, we observed a significant difference in OS only with the Ki67 cut-off of 30% (67 vs 64 months, p=0.04, HR=0.79 IC à 95% [0.6–0.87]). In node negative pN0 population, Ki67 cut-off=20% was significantly associated with OS (72 vs 65 months, p=0.03, HR=0.83[0.63–0.92]). In node positive tumours different Ki 67 cut-off values did not predict survival except in ≥4pN+ group, where patients with Ki67>50% had significantly worse OS compared to patients≤50% (63 vs 30 months, p=0.01, HR=0.31 IC à 95% [0.22–0.65]).

Conclusions Ki67 level in RH+/HER2- breast cancer predicted survival with the cut-off value of 30%. Ki67 had an impact on survival with a cut-off=20% in node negative and 50% in ≥4pN+ tumours.

EPV009/#143

MAGNETIC RESONANCE ACCURACY IN DIAGNOSING THE SIZE OF DUCTAL CARCINOMA IN SITU – PRELIMINARY RESULTS OF A SYSTEMATIC REVIEW AND META-ANALYSES

¹M Robalo Cordeiro*, ²R Roque, ¹M Figueiredo-Dias. ¹University Hospital Center of Coimbra, Gynecology Department, Coimbra, Portugal; ²Portuguese Institute of Oncology Coimbra, Medical Oncology Department, Coimbra, Portugal

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Objectives To evaluate the accuracy of Magnetic Resonance Imaging (MRI) in measuring the pure Ductal Carcinoma In Situ (DCIS) size, against pathology, to better understand the MRI role in the management of this non-invasive intraductal breast neoplasm.

Methods Potential eligible studies in MEDLINE, Embase and Google Scholar, until January-2021 were considered, and systematic review and meta-analysis according to the published protocol (Prospero - CRD42021232228) was performed. Outcomes of mean differences and accuracy rates using IBM® SPSS® v26 and random-effect model in platform R v3.3.2 were analysed.

Results Twenty-two cross-sectional studies were selected and 15 proceeded to meta-analyses. MRI accurately predicted 55% of tumours size and according to Bland-Altman plots, concordance between MRI and pathology was greater for smaller tumours. In meta-analyses, the difference of the means between MRI and pathology is 3.85 mm (CI95% [-0.92;8.60]) with considerable heterogeneity (I²=96.7%). Subgroup analyses showed similar effect sizes between different MRI fields, acquisition times and contrasts, but lower heterogeneity in studies using Gadolinium (I²=48.7%) and 3-Tesla MRI (I²=57.2%). Results were concordant in low risk of bias