41P BRCA2 pathogenic variant (PV): A novel agnostic biomarker for immune checkpoint blockers (ICB)?

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Background: Immunotherapy has revolutionized cancer treatment improving survival rates for many cancer types. Unfortunately, resistances are common and predictive biomarkers are needed. Microsatellite Instability-high (MSI-H) usually predicts response to ICB in all tumour types, whereas we need more studies focusing on tumour mutational burden (TMB) to predict its role as a pan-cancer biomarker. Recent investigations in murine models and cohorts of patients (pts) have shown that BRCA2 PV improved response and overall survival to ICB compared to BRCA1 PV. The aim of this study was to evaluate the response to ICB in BRCA PV and its relation with TMB, MSI-H and prior treatments.

Methods: We conducted an unicohort retrospective study, between May 2020 and November 2022, in metastatic pts carrying BRCA1 or BRCA2 somatic PV and treated with ICB in phase I/II trials at Institute Gustave Roussy (France). Genomic analysis were performed by NGS (liquid biopsy and tumor samples). Data was extracted from electronic medical record and analysed with SPSS software.

Results: A total of 44 pts were enrolled. Median age was 54.6 years [range 29—74 years], 46.7% were female. Lung cancer was the most common tumour (20.5%) in an heterogenic histologic cohort of pts. Median previous lines of treatment was 2.7 [range 0-4]. Tissue analysis revealed 21.1% MSI-H, 36.8% TMB high, 23.8% BRCA1 PV, 38.1% BRCA2 PV. Blood analysis showed 7.3% MSI-H, 52.4% TMB high, 40,5% BRCA1 PV, 52.4% BRCA2 PV. All pts received immunotherapy, 69.8% ICB. The Objective Response Rate (ORR) was 34.1%. Pts with BRCA2 PV presented a better ORR to ICB compared to those with BRCA1 PV (28% vs. 4%, p = 0,030). Mean TMB was lower in BRCA2 PV than in BRCA1 PV pts and median previous lines of treatment was higher in BRCA2 PV than in BRCA1 PV (2.5 vs. 2.0). We didnt find a significant association between BRCA1/2 PV and MSI status. Duration of response (DoR) to ICB by more than 6 months tended to be higher in pts with BRCA2 PV than those with BRCA1 PV (32% vs. 16%, p = 0,512).

Conclusions: Pts with somatic BRCA2 PV had better ORR to ICB regardless of TMB, MSI and prior lines of treatment than those with BRCA1 PV. Further research should be carried out to confirm BRCA2 as a predictive pan-cancer biomarker to ICB in a larger cohort with BRCA WT pts as comparison.

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42P Apigenin: An immunomodulatory nutraceutical overriding PD-L1 inhibitors by halting AKT/mTOR pathway in triple-negative breast cancer (TNBC)

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Background: Despite the effectiveness of immunotherapy, serious side effects might develop. This sheds light on the immune-modulatory role of flavonoids in cancer therapy. The rationale of this study is to determine the impact of apigenin (AP) on the harmonization of innate and adaptive immune cells in the tumor microenvironment of TNBC in order to develop new strategies to minimize adverse events and boost the immune response towards cancer fighting.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated by ficoll separation from 53 TNBC peripheral blood samples. CD8+ T-and monocytes were isolated followed by differentiation of monocytes into tumor-associated macrophages (TAMs). IC50 of AP was determined on MDA-MB-231 cells by MTT assay. Treatment groups of MDA-MB-231 were: 1. AP, 2. Atezolizumab (ATE), 3. AP and cocultured with TAMs+ CD8+ cells, 4. untreated cells. Post 48 hrs, RNA isolation was done. Target genes were quantified using qRT-PCR. Supernatants (tumor cultured media) were collected for measurement of TNF- α and nitric oxide levels using ELISA. LDH cytotoxicity assay was performed on MDA-MB-231 cells. One-way ANOVA statistical analysis was performed for multiple group comparison and Student's unpaired T-test for two group comparison.

Results: In cells treated with AP, mTOR and AKT transcripts expression was significantly downregulated compared to ATE (P=0.0223, P<0.0001, respectively). Additionally, TNF-α and NO levels were decreased in AP-treated groups compared to ATE (P<0.000, P<0.0001, respectively). However, the percentage cytotoxicity was non-significant (ns) in AP-treated cells compared to ATE. In AP-treated cells and cocultured with TAMs+CD8, AKT was decreased (P<0.0001), however, mTOR expression was non-significant compared to the untreated group. In addition to decreased levels of TNF-α and NO (P<0.0001, P<0.0001, respectively) as well as percentage cytotoxicity was significant (P=0.0086) in AP-treated cells and cocultured with TAMs+CD8 compared to the untreated group.

Conclusions: Collectively, these data demonstrated apigenin as upstream regulators for AKT/mTOR pathway manipulating TNF-α and NO release in TME of TNBC patients as well as enhancing immune cells functions, suggesting potential adjuvant therapy to immunotherapy.

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43P Prognostic impact of the tumor immune microenvironment in adrenocortical cancer

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Background: Adrenocortical carcinoma (ACC) is an uncommon endocrine malignancy, usually characterized by a late detection, aggressive clinical course, and poor outcome. The tumor microenvironment (TME) which includes infiltrating immune cells plays a critical role in tumor growth, survival, and prognosis in cancer patients. The presence of tumor-infiltrating immune cells (TIIC) affect the clinical benefit from novel strategies of immunological checkpoint blockade. Anti-immune pathways like PD-L1 are used by the tumor to overcome immune system and they serve as immunotherapy targets.

Methods: The study included tumor tissue samples from 75 patients with ACC, which treated at the Endocrinology Research Centre (Russia, Moscow) between 2010 and 2022: 47 cases of conventional (62,7%), 18 cases of oncocytic (24%), and 9 cases of myxoid (12%) and 1 case of sarcomatoid (1,3%) variants of ACC. Immunohistochemical analysis of tumor tissue sections was carried out according to the standard technique with a peroxidase detection system with DAB on an automatic Leica BOND III IHC staining system using Leica reagents and protocols. Each of the 75 patients underwent histological diagnostics and a series of immunohistochemical stains for the markers of the main immune cell subsets: CD45, CD3, CD4, CD8, and CD68. The impact of PD-L1 expression and the number of TIIC considering the intratumoral and stromal distribution on pathological characteristics and clinical outcomes were analysed.

Results: The number of CD45+ immune cells in tumor parenchyma and stroma was 189 and 268 cells/mm2, respectively. However, the number of immune cells from all the analyzed populations in tumor parenchyma was higher in oncocytic compared to conventional ACC cases. The analysis of the relationship of survival with the studied factors showed that the overall survival and progression-free survival between conventional and oncocytic histological variants differ significantly. The differences in survival between conventional and oncocytic histological variants of ACC were statistically significant (p-value < 0.05). PD-L1 expression does not affect prognosis.

Conclusions: Rich T-lymphocyte response is a good prognostic factor in ACC. The study of TIIL subpopulations can be used to predict ACC outcomes.

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