GERMLINE MUTATIONS IN DNA DAMAGE RESPONSE AND REPAIR GENES ARE ASSOCIATED WITH INCREASED CLINICAL BENEFIT FROM IMMUNE CHECKPOINT INHIBITORS

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**Background** Impaired DNA damage response (DDR) can impact the efficacy of immune checkpoint inhibitors (ICIs). Defects in the DDR pathway can also lead to heightened immune activation. The purpose of this study was to determine if pathogenic germline mutations in DDR pathways would increase the efficacy or toxicity of ICIs.

**Methods** We performed a single-institution retrospective analysis of all patients for whom germline DNA testing was available and who were treated with ICIs between January 1st, 2014 and September 1st, 2022. Patients without measurable disease were excluded. The best response to therapy and the incidence of immune-related adverse events (irAEs) were compared between patients that had pathogenic germline mutations in DDR genes (DDR+) and those who did not (DDR-). Clinical benefit (CB) was defined as stable disease, partial response, or complete response as determined by the treating physician. IrAEs were graded according to the Common Terminology Criteria for Adverse Events v5.0.

**Results** We identified 152 patients that met the inclusion criteria. Forty-two patients were DDR+, of which 25 had mutations in homologous recombination genes (HRD), and 11 had mutations in mismatch repair genes (dMMR). DDR+ patients were more likely to derive CB than DDR- patients in univariate and multivariate analysis (table 1) (81% vs 53%, unadjusted odds ratio [OR] = 3.81; 95% CI, 1.59 to 9.11; adjusted OR 3.58; 95% CI, 1.29 to 9.93). Adjustments were made for the line of therapy, tumor mutational burden, and history of tyrosine kinase inhibitor (all associated with CB in univariate analysis, p £ 0.05). Similar results were observed in HRD patients (76% HRD vs 53% DDR-, adjusted OR = 3.12; 95% CI, 1.00 to 9.61). dMMR patients were more likely to receive CB from ICIs in the univariate analysis (91% dMMR vs 53% DDR-, OR = 8.96; 95% CI, 1.10 to 72.89), but this did not reach statistical significance in multivariate analysis (OR = 4.99; 95% CI, 0.49 to 51.17). When dMMR patients were removed from the DDR+ group (DDR+MMR-), there remained a significant difference in CB from ICIs (77% DDR+MMR- vs 53% DDR-, adjusted OR 3.35, 95% CI 1.13 to 9.95). There were no significant differences in the rate of irAEs for DDR+ patients regardless of the subgroup.

**Conclusions** Patients with germline pathogenic DDR mutations are more likely to derive CB from ICIs without added immune toxicity. The fact that MMR intact germline DDR mutations are associated with significant CB is a novel finding.