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780P Cancer susceptibility mutations in Chinese patients with urothelial malignancies

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Background: Urothelial carcinoma (UCs) is the 10th most common type of cancer worldwide, which is mainly caused by environmental factors and cigarette smoking. However, few reports have shown the genetic factors related to UC pathogenesis. We sought to assess the frequency of pathogenic/likely pathogenic (P/LP) germline mutations in Chinese Urothelial cancer population.

Methods: We retrospectively collected tissue and matched blood samples from UC patients. Genomic profiling of DNA was conducted by next-sequencing technology. 102 genes associated with cancer predisposition were analysed. Only pathogenic/likely pathogenic alterations were included.

Results: Overall, 442 patients with UC were included in this study from Jan 20th, 2017 to Apr 13th, 2020. There were 303 (68.6%) male and 139 (31.4%) female patients. Median age was 66 (range, 19-93). Twenty-eight (6.3%) patients were identified to have germline mutations, including 3 (10.7%) patients with upper urinary tract urothelial tumours. The most frequently mutated genes were *BRCA2* (n=7; 25%), *PALB2 /TP53/RB1* (n=3; 10.7% each). Most of these patients (n=26; 92.9%) harbored concomitant somatic alterations, and the average mutation number is 5.5 per patient. Twenty-three (82.1%) patients had germline P/LP mutations in DNA-damage repair (DDR) genes, of which 18 (78.3%) had gene inactivation alteration. Besides DDR genes, *TP53/RB1/SMARCA4/TSC2* germline variation were identified in 5 patients. Further analysis revealed that patients with P/LP germline mutations were more likely to have early age of onset (age $\leq$ 45 years) compared with patients with no germline mutations (10.7% vs 4.3%), but there was no statistical difference (χ^2=1.153 , P=0.283).

Conclusions: This is the first study to explore the spectrum of P/LP germline mutations among Chinese patients with Urothelial malignancies. The presence of DDR germline variants could not only serve as biomarker for immunotherapy in UC, but also provide valuable information for genetic screening.

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781P Prognostic factors in patients with metastatic urothelial carcinoma who have been treated with atezolizumab

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Background: In the current study, we evaluated pretreatment prognostic factors for overall survival (OS) in patients with metastatic urothelial carcinoma who have progressed after first-line chemotherapy in the Expanded-Access Program of atezolizumab.

Methods: In this study, we present the retrospective analysis of 113 patients with urothelial cancer treated with ATZ after progression on first-line chemotherapy. Eligible patients included metastatic urothelial carcinoma patients treated with at least one course of ATZ. Univariate analysis was used to identify clinical and laboratory factors that significantly impact OS. Variables were retained for multivariate analysis if they had a statistical relationship with OS (P<0.1) and were then included the final model if P<0.05.

Results: In univariate analysis, primary tumour location in the upper tract, increased absolute neutrophil count (ANC), increased absolute lymphocyte count, neutrophil-to-lymphocyte ratio (NLR)>3, liver metastases, baseline creatinine clearance (GFR) < 60 ml/min, Eastern Cooperative Oncology Group (ECOG) performance status (≥1) and hemoglobin<10 mg/dl were all significantly associated with OS. Three of the five adverse prognostic factors according to the Bellmunt criteria were independent of short survival: liver metastases (HR= 0.323; 95% CI 0.174-0.60; P <0.001), ECOG PS≥1 (HR= 0.459; 95% CI 0.236-0.895; p=0.022), and haemoglobin level <10 mg/dl (HR= 0.373; 95% CI 0.217-0.642; P <0.001). In addition, NLR>3 (HR= 0.474; 95% CI 0.234-0.962; P =0.039) and GFR <60 ml/min (HR= 0.546; 95% CI 0.328-0.907; P = 0.019), maintained a significant association with OS in multivariate analysis. Patients were divided into three risk categories: the favourable risk group (0-1 prognostic factor; median OS=20.1 mo.), the intermediate-risk group (2 prognostic factors; median OS=10.08 mo.) and the poor-risk group (3≥ prognostic risk groups; median OS= 2.2 mo.) (log-rank P< 0.001).

Conclusions: This model confirms the Bellmunt model with the addition of NLR>3 and GFR <60 ml/min. Taken together, these factors can be used for prognostic parameters in clinical trials that use immunotherapy in patients with bladder cancer who have progressed after first-line chemotherapy.

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782P Real-world evidence of the impact of prior autoimmune disease on immune checkpoint inhibitor outcomes in patients with metastatic urothelial cancer

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Background: Patients with pre-existing autoimmune disease (AD) have historically been excluded from most immune checkpoint inhibitor (ICI) clinical trials due to concerns including potential toxicity or decreased efficacy. Real-world data support the use of ICIs for patients with ADs across multiple tumor types, however data are limited. We examined the association between pre-existing AD and ICI treatment