Therapeutic opportunities for hypermutated urothelial carcinomas beyond immunotherapy

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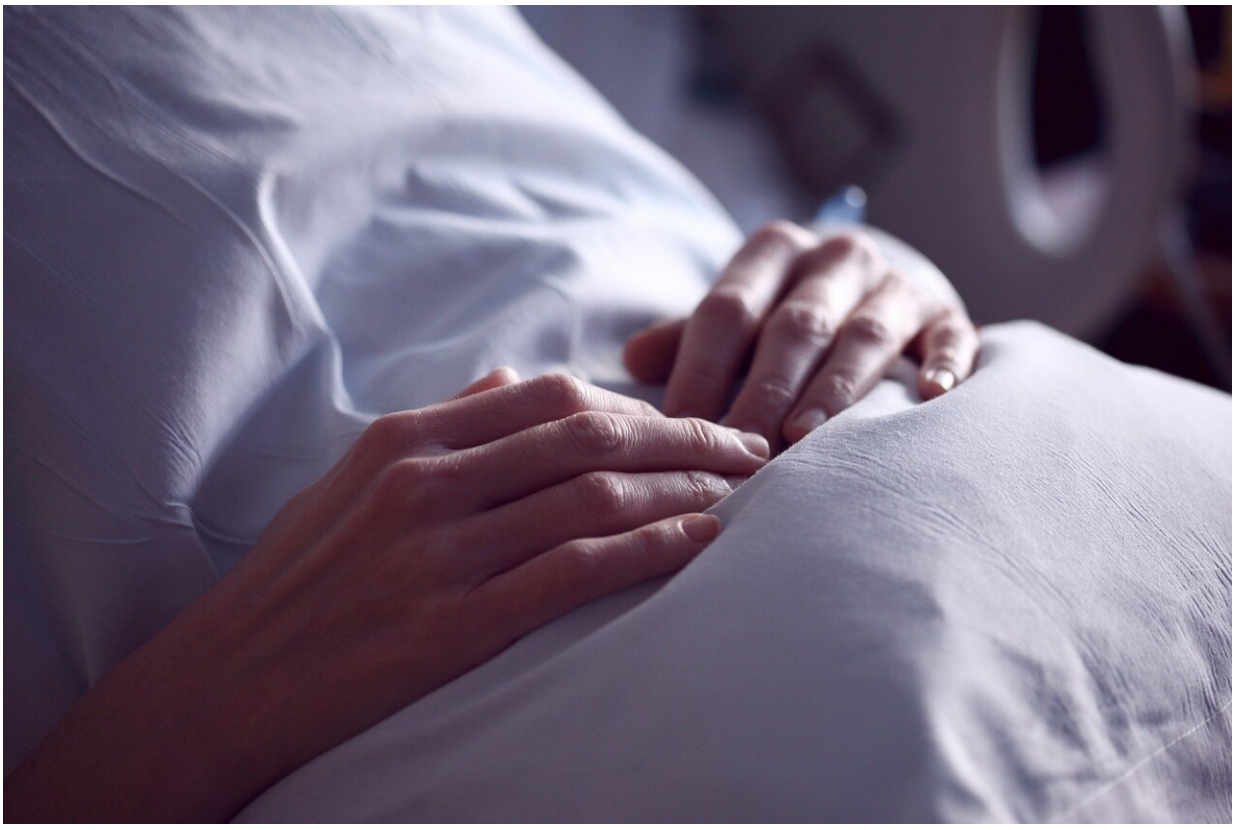

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In an editorial, in *Oncoscience* titled "Therapeutic opportunities for hypermutated urothelial carcinomas beyond immunotherapy," researcher Ioannis A. Voutsadakis from Sault Area Hospital and Northern Ontario School of Medicine discuss tumor mutation burden (TMB)—a novel clinical biomarker for prediction of checkpoint inhibitor immunotherapy response across cancers.

High TMB has been used as a tumor agnostic indication for treatment with the PD-1 inhibitor pembrolizumab. High TMB is also associated with defects in mismatch repair (MMR) proteins producing the microsatellite instability (MSI) phenotype, which is also a biomarker of response to immune checkpoint inhibitors.

"However, both biomarkers are imperfect and not all cancers with high TMB or MSI phenotype respond to immunotherapy," says Voutsadakis.

The reason for this phenomenon may relate to additional alterations present in some tumors with high TMB or may be due to differences in the immune environment of diverse cancers. Conversely, some tumors with no MMR alterations have high TMB, and their hypermutability, which is due to other defects, such as pathogenic proofreading polymerase epsilon (POLE) mutations, may still lead to immunotherapy sensitivity.

A sub-set of urothelial carcinomas possess a high TMB. Urothelial carcinomas with high TMB have only rarely MMR protein or POLE mutations but present additional alterations in higher frequency than cancers with low TMB, including mutations in several epigenetic modifiers.

"Combinatorial approaches based on immunotherapy and targeting

additional molecular defects, that are present in urothelial carcinomas, hold the hope for successful therapy of the sub-set of immune checkpoint inhibitor resistant urothelial carcinomas with high TMB and of urothelial carcinomas with low TMB," Voutsadakis says.

More information: Ioannis A. Voutsadakis, Therapeutic opportunities for hypermutated urothelial carcinomas beyond immunotherapy, *Oncoscience* (2024). DOI: 10.18632/oncoscience.596

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