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BLADDER CANCER

Mechanisms of anti-PDL1 resistance

New data published in *Nature* show that the clinical outcome of patients with metastatic urothelial carcinoma (mUC) treated with atezolizumab depends on tumour phenotype with regard to $CD8^+$ T effector (T_{eff}) cells, tumour mutation burden (TMB), and transforming growth factor-β (TGFβ) signalling in fibroblasts. In a mouse model, co-administration of antibodies against programmed cell death 1 ligand 1 (PDL1) and against TGFβ resulted in robust antitumour immunity and tumour regression. These findings elucidate mechanisms of immune checkpoint inhibitor (ICI) resistance that affect patient outcome, and indicate strategies to improve patient selection for current agents and for the development of new combination therapies.

ICI treatment, for example with atezolizumab, can result in durable responses in patients with mUC, but many tumours are resistant to this therapy. Initially, PDL1 expression was thought to be a promising biomarker of response but further research indicated a lack of reliability and the need for a better understanding of the factors that influence treatment effectiveness to establish better biomarkers.

"In our paper, we identified candidates for this second generation of biomarkers through analysis of a large cohort of patients with mUC treated with atezolizumab," Sanjeev Mariathasan from Genentech, USA, one of the corresponding authors, tells *Nature Reviews Urology*. "To take this work further and assess potential cause-and-effect relationships — and thus possible new targets — we also used animal models to explore our most promising findings."

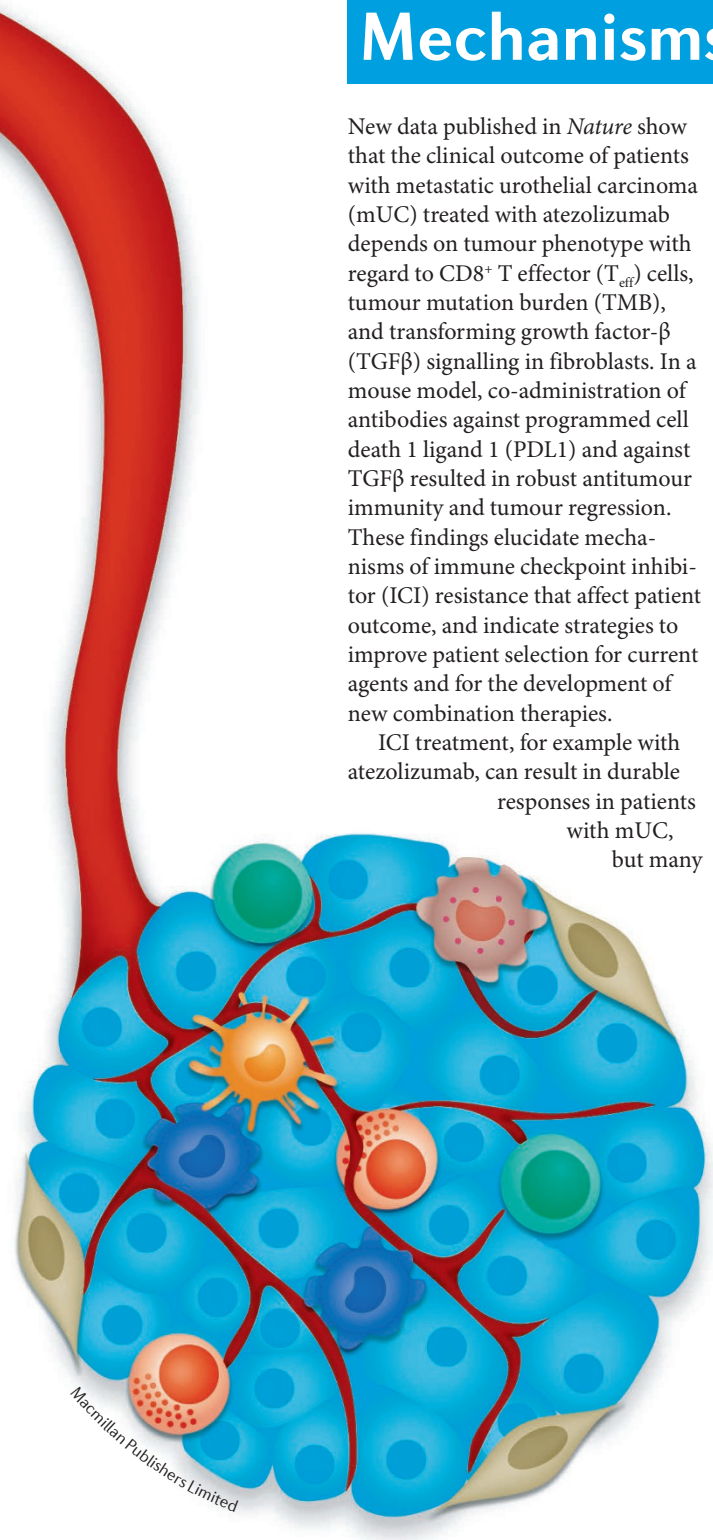
Analysis of tumour samples from patients in the IMvigor210 trial collected before therapy showed that PDL1 expression on immune cells, but not tumour cells, was associated with ICI response, and that a gene signature associated with T_{eff} cells correlated both with PDL1 expression and with response. Next, the researchers confirmed that TMB also correlated with ICI response. DNA replication, DNA damage response (DDR), and cell cycle pathways were particularly associated with TMB, and tumours with ≥1 mutation in DDR or cell cycle regulator gene sets had higher TMB and response rates. Further analysis showed that genes involved in the TGFβ signalling pathway were associated with a lack of response. Both *TGFB1* and *TGFBR2* had increased expression in non-responders, which was associated with reduced overall survival.

The team then investigated the relationship between ICI response, T_{eff} cell localization, and TFGβ signalling. Response was lacking especially in tumours in which T_{eff} cells were absent from the tumour parenchyma and instead located in the peritumoural stroma, which is rich in fibroblasts, and a TGFβ signalling signature was associated with nonresponse in these tumours only.

The team used a mouse model of murine mammary carcinoma that recapitulates the immunological determinants discovered in human mUC to further test their findings. Treatment with antibodies against PDL1 or TGFβ alone had minimal effects, but co-administration of the agents resulted in a reduction in tumour burden, which was dependent on T_{eff} cells. Additional experiments indicated that TGFβ and PDL1 inhibition synergized to reprogramme peritumoural fibroblasts and increase T_{eff} cell numbers in the tumour parenchyma.

"Our results prompt three directions for the future: first, improving patient selection for immunotherapy by incorporating new biomarkers, such as TMB; second, exploring combined therapy of TGFβ and PDL1 inhibition in clinical trials; third, related phenomena in colorectal cancer indicate that some strategies to reverse a lack of response to ICIs could be indication agnostic, potentially broadening the applicability of this work," concludes Mariathasan.

Clemens Thoma



ORIGINAL ARTICLE Mariathasan, S. *et al.* TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. *Nature* **554**, 544–548 (2018)
FURTHER READING Siefker-Radtke, A. & Curti, B. Immunotherapy in metastatic urothelial carcinoma: focus on immune checkpoint inhibition. *Nat. Rev. Urol.* **15**, 112–124 (2018)