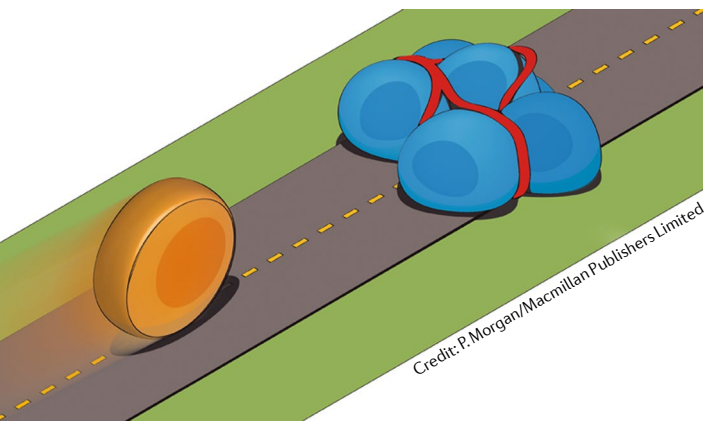
KIDNEY CANCER

Checkpoint inhibitor combination sets the wheels IMmotion

In addition to its proangiogenic roles, preclinical studies have implicated vascular endothelial growth factor (VEGF) in tumour immune evasion. Indeed, a phase I study reported the promising antitumour activity of anti-VEGF antibody bevacizumab combined with anti-programmed cell death 1 ligand 1 (PD-L1) antibody atezolizumab in metastatic renal cell carcinoma (mRCC). Now, findings from the randomized phase II IMmotion150 trial show the encouraging efficacy of atezolizumab plus bevacizumab compared with the standard of care VEGF receptor inhibitor sunitinib in mRCC.

The prospective, multicentre phase II trial randomized 305 patients with treatment-naive mRCC to three arms to compare atezolizumab plus bevacizumab, and atezolizumab alone, versus sunitinib. "The addition of a third arm with atezolizumab alone allowed the contributions of each drug to be deconstructed in the final analysis," explains investigator Kimryn Rathmell. Co-primary end points were progression-free survival (PFS) in the intent-to-treat (ITT) and PD-L1$^+$ populations (defined as PD-L1 expression on ≥1% of immune cells).



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Key secondary end points included objective response rate (ORR) and safety.

At a median follow-up period of 20.7 months, median PFS hazard ratios (HRs) for the ITT population were not encouraging for the atezolizumab plus bevacizumab versus sunitinib (HR 1.00, 95% CI 0.69–1.45, $P = 0.982$) or the atezolizumab monotherapy versus sunitinib comparisons (HR 1.19, 95% CI 0.82–1.71, $P = 0.358$). However, in PD-L1$^+$ patients, median PFS was significantly longer in those receiving atezolizumab plus bevacizumab (HR 0.64, 95% CI 0.38–1.08, $P = 0.095$), but not atezolizumab monotherapy (HR 1.03, 95% CI 0.63–1.67, $P = 0.917$), compared with the sunitinib arm. ORRs were 32%, 25%, and 29% for ITT patients, and 46%, 28%, and 27% for PD-L1$^+$ patients, in the atezolizumab plus bevacizumab, atezolizumab monotherapy, and sunitinib arms, respectively. Interestingly, a trend towards greater efficacy was noted in patients whose tumours had the highest PD-L1 expression (≥5%). Regarding safety, treatment-related adverse events were low in all arms, and were consistent with previous observations for each drug alone.

IMmotion150 also had exploratory objectives to evaluate associations between molecular biomarkers and clinical outcomes and prospectively employed whole-transcriptome and whole-exome sequencing to annotate pretreatment tumour samples. Importantly, angiogenesis, immune, and myeloid inflammatory gene expression signatures — indicative of tumour microenvironment characteristics — were strongly associated with PFS, both within and across treatment arms. Interestingly, although markers of genomic instability are predictive of response in other solid tumours, no associations were reported between mutation or neoantigen burden and PFS. "While these insights need to be validated in larger studies, they may have impact in other tumour types where immunosuppression by myeloid cells plays a role," says lead investigator David McDermott.

Overall, the IMmotion150 findings suggest that the combination of atezolizumab and bevacizumab could improve outcomes in patients with untreated, PD-L1$^+$ mRCC. Further, the exploratory biomarker analyses might help to identify future predictive biomarkers.

"The IMmotion150 study design, heavy on correlative studies, allowed for a modification to be made in the phase III IMmotion151 trial, which contributed to its success," explains McDermott. Preliminary findings from IMmotion151 (NCT02420821), released ahead of the 2018 ASCO Genitourinary Cancers Symposium, showed that median PFS was significantly longer in the atezolizumab plus bevacizumab group than in the sunitinib group, both in the ITT (HR 0.83, 95% CI 0.70–0.97, $P = 0.0219$) and PD-L1$^+$ populations (HR 0.74, 95% CI 0.57–0.96, $P = 0.0217$). Collectively, the IMmotion150 and IMmotion151 findings support the combination of atezolizumab plus bevacizumab in the first-line mRCC setting.

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ORIGINAL ARTICLES McDermott, D. F. et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat. Med.* **24**, 749–757 (2018) | Motzer, R. J. et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC) [abstract]. *J Clin Oncol.* **36**, 578 (2018)