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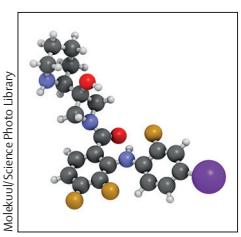
MEK and PD-L1 inhibition in colorectal cancer: a burning blaze turning into a flash in the pan



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Immunotherapy has revolutionised the treatment landscape of a wide variety of tumours. In DNA mismatch repair-deficient or high microsatellite instability metastatic colorectal cancer, single-drug or double-drug immune checkpoint inhibition have shown notable activity in both the chemotherapy-naive and chemorefractory setting. Pembrolizumab, nivolumab, and nivolumab plus ipilimumab are now approved by the US Food and Drug Administration for patients with mismatch repair-deficient or high microsatellite instability metastatic colorectal cancer who have been previously treated with standard chemotherapy. By contrast, no benefit has been observed with these drugs in patients with DNA mismatch repair-proficient, low microsatellite instability, or microsatellite-stable tumours, who account for 95% of patients with metastatic colorectal cancer and are characterised by a low number of tumour mutations, neoantigens, and infiltrating immune effector cells.

Studies have suggested that inhibition of the MAPK signalling pathway could tackle the immune resistance of mismatch repair-proficient microsatellite-stable tumours by upregulating HLA molecule expression, downregulating immunosuppressive factors, and increasing tumour-infiltrating CD8+ cytotoxic T cells.[1,2] To confirm preclinical observations and early clinical findings of synergistic activity between anti-MEK drugs and immune checkpoint inhibitors,[1–3] Cathy Eng and colleagues[4] did an international, open-label, randomised phase 3 trial of atezolizumab plus or minus cobimetinib versus regorafenib in patients with chemotherapy-refractory metastatic colorectal cancer (IMblaze370), the results of which are reported in *The Lancet Oncology*.

The trial, which enrolled 363 patients, 333 (92%) of whom had microsatellite-stable tumours, did not meet its primary endpoint, with a median overall survival of 8·87 months (95% CI 7·00–10·61) with atezolizumab plus cobimetinib (stratified hazard ratio [HR] *vs* regorafenib 1·00 [95% CI 0·73–1·38]; p=0·99) and 7·10 months (6·05–10·05) with atezolizumab alone (stratified HR *vs* regorafenib 1·19 [0·83–1·71]; p=0·34), compared with a median overall survival of 8·51 months (6·41–10·71) for standard treatment with regorafenib. Treatment effect did not differ by clinical or molecular characteristics, including microsatellite instability, *RAS* mutation status, and programmed cell death ligand 1 (PD-L1) expression. Similarly, no differences between treatment groups were observed in terms of progression-free survival, and less than 2% of patients with microsatellite-stable tumours in either investigational group achieved an objective response. The addition of cobimetinib to atezolizumab doubled the frequency of grade 3 or worse adverse events compared with atezolizumab alone (109 [61%] of 179 patients in the combination group *vs* 28 [31%] of 90 in the atezolizumab monotherapy group) and serious adverse events (71 [40%] of 179 *vs* 15 [17%] of 90).

There is great disappointment for the negative results of the IMblaze370 trial because of the scientific interest and general enthusiasm for the underlying biological rationale and supportive preliminary clinical findings, which endured throughout the study recruitment period and led to an impressively rapid accrual of just 6 months. Dwelling on potential reasons for such an unexpected failure is therefore imperative.

The IMblaze370 trial was based on intriguing data from in-vitro experiments and preclinical models. It should be noted though that controversy exists around the immunomodulatory effects of MEK inhibition, with some studies actually reporting suppression of T lymphocyte proliferative response and antigen-specific expansion and impairment of

antigen processing by dendritic cells.[5-7] Accordingly, the anticipated enhancement of the antitumour activity of atezolizumab by use of concurrent cobimetinib might have not occurred. Beyond this biological dispute, some concerns also remain regarding the clinical development strategy for this immune-targeted combination therapy. Were the preliminary results of a phase 1b trial, which ultimately showed an overall modest 10% of patients achieving an objective response, in a small group of patients with refractory microsatellite-stable metastatic colorectal cancer, promising enough to launch a large randomised phase 3 trial? One could argue that an adaptive randomised phase 2–3 trial to first confirm the superiority of combined MEK and PD-L1 inihibition over PD-L1 inhibition alone would have been more informative and more appropriate. In fact, the IMblaze370 trial does not formally address the incremental benefit of adding cobimetinib to atezolizumab in either patients with mismatch repair-proficient microsatellite-stable metastatic colorectal cancer or those with mismatch repair-deficient high microsatellite instability tumours, and any interpretation of the numerically slightly longer overall survival of the combination group compared with the monotherapy group is purely speculative. Finally, it cannot be excluded that the study results might have been partially influenced by the absence of a biomarker-enriched recruitment strategy. Beyond the immunosensitive immune inflamed phenotype, which includes most mismatch repair-deficient and high microsatellite instability tumours, at least two immunoresistant cancer-immune phenotypes (immune excluded and immune desert) have been described that are characterised by heterogeneous factors related to the host, tumour, and environment.[8] A one-size-fits-all approach is unlikely to address this diversity, and distinct immunomodulatory strategies might be required to selectively restore tumour immunogenicity and effective host immune responses in patients with mismatch repair-proficient microsatellite-stable metastatic colorectal cancer.[9]

MEK inhibitors are being tested in other immunotherapy-based combination regimens in mismatch repair-proficient microsatellite-stable metastatic colorectal cancer (NCT03377361, NCT02876224, and NCT03374254) and other tumour types, including melanoma. Nevertheless, bearing in mind the aforementioned limitations, the IMblaze370 trial appears to put an end to the suggestion that MEK inhibition might be a valid approach to unlock the inherent immune resistance of mismatch repair-proficient microsatellite-stable metastatic colorectal cancer. Notably, the expectations of the possibility of restoring anticancer immunity in these tumours through the immunomodulatory effects of targeted therapies have also been disappointed by the results of the MODUL trial,[10] which showed no benefit of adding atezolizumab to a bevacizumab-based maintenance treatment. Despite these discouraging defeats, unleashing the full potential of immunotherapy in mismatch repair-proficient microsatellite-stable metastatic colorectal cancer should remain a priority of cancer research. Novel approaches harnessing the effects of alternative immunomodulatory strategies should be urgently pursued, and hopefully groundbreaking treatments will soon be looming on the horizon.

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I declare no competing interests.

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