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Turning Up the 'Heat' can Make Some Tumors Respond to Immunotherapies

Combining Anti PD-1/L1 with MEK Inhibitors for 'Cold' Colorectal Tumors

In 2011, the first checkpoint inhibitor – ipilimumab, an antibody that inhibits the checkpoint protein CTLA-4 – was approved to treat advanced melanoma. However, the overall clinical benefit was modest: a recent consolidated analysis of 12 ipilimumab trials demonstrated that an OS plateau of 22% started at 3 years and extended up to 10 years in some patients.[1] While this approval is a landmark event in the immune-oncology field, the fact that only one in five patients experienced lasting benefit is disappointing and immediately raises the question of how to increase the proportion of responding patients. One hope was to identify other checkpoint inhibitor targets whose inhibition would provide better efficacy/safety. Preliminary efforts have been successful in this regard: antagonism of the PD-1 pathway is generally considered to be more efficacious and better tolerated than ipilimumab. In heavily pre-treated patients, the three approved drugs (nivolumab, pembrolizumab, and atezolizumab as monotherapies) targeting the PD-1 pathway demonstrated reasonable rates of response compared to other types of drugs in a wide range of tumor types.[2] Furthermore, the responses were often durable, suggesting that survival benefits would be realized, as had already been demonstrated in melanoma and lung cancer.[2] However, as in the case with CTLA-4, antagonism of PD-1 has also not generally achieved ORRs above 50% and thus the issue remains – how can a larger percentage of patients be made to respond? Development efforts are ongoing and successful blockade of many more checkpoint targets are likely to materialize in the next five years as we come to better understand the myriad pathways that can be co-opted by the tumor to escape immune destruction.[3]

Another serious obstacle has been the fact that some tumor types such as pancreatic, prostate, and the majority of colorectal (CRC) tumors are entirely 'cold', that is, the checkpoint inhibitors can elicit no responses whatsoever in these tumors, unlike melanoma, RCC, and lung which are considered 'hotter'. In general, tumor types that have a higher mutational load resulting in the expression of neoantigens are more immune-responsive. These tumors also have a favorable microenvironment that is conducive to immune attack. Microsatellite instability-high (MSI-H) colorectal tumors also have a high mutational load due to the fact that they are mismatch repair (MMR) deficient. MSI-H CRCs have a superior outcome compared to microsatellite stable (MSS) CRCs.[4] When MSI is high and MMR is deficient, the expected five-year survival exceeds 90% versus less than 75% for an MSS profile.[4] Based on these features, as one might predict, MSI-H patients respond well to PD-1 blockade/ For example, a recent report indicated that MSI-H CRC patients, receiving pembrolizumab, have a superior progression-free survival.[5] However, MSI-H is only 5-15% of overall CRC. Therefore, more therapies are needed for the majority of CRC patients who are predominantly MSS. Testing blockade of novel checkpoint inhibitors will continue aggressively for such cold tumors.

In addition, a second sensible approach to improving clinical benefit is the oncologist's traditional strategy: combination therapy. Combining checkpoint inhibitors with either immunotherapies or targeted agents could improve response rates and not only benefit a larger proportion of patients with immune-responsive tumors but also perhaps, activate tumor types that are relatively cold.

At the recent ASCO 2016 meeting in Chicago, exciting results were presented indicating that cold MSS tumors that had stymied immune-oncologists until now were not so unyielding after all. Johanna Bendell and colleagues revealed preliminary results from a trial which demonstrated that combining a targeted agent that inhibits MEK1/2 with a checkpoint inhibitor can be effective in some of these cases.

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NCT01988896 is a Phase Ib dose escalation and cohort expansion study of cobimetinib plus atezolizumab. Cobimetinib, a selective MEK1/2 inhibitor, has shown little or no activity by itself in CRC patients even though the Ras/Raf/MEK pathway is known to be frequently dysregulated in cancer. Atezolizumab, as expected, also demonstrated minimal activity in the MSS CRC population as single agent. In this study, all CRC patients (N=23) had received prior oxaliplatin and irinotecan and the median number of prior therapies was three. In the CRC dose expansion cohort, 96% were KRAS mutant (N=20) and 4% wt, whereas with regards to MSI status, 30% were MSS and 70% unknown.[6] Confirmed response rates were 20% in KRAS mutant patients and 17% in all CRC. There were four partial responders (durable responses, with two of four patients continuing treatment) and one patient had stable disease. Significantly, three of the four patients were MMR-proficient (MSI-low or MSS) and one did not have tumor tissue to test (MSI-status unknown). No correlation was observed between PD-L1 expression and response. There were no grade 4 or 5 AEs and no DLTs were reached, and the side effect profile was in accordance with what was observed in Phase I studies of these two agents.[6]

One reason these clinical findings are so interesting is that they are based in part on a new appreciation for what MEK inhibitors do to T cells in the tumor microenvironment.[7] Since MEK signaling is downstream of the TCR, one might expect that its inhibition would reduce the activity of tumor reactive cytotoxic T cells. Instead, MEK inhibition leads to a dramatic increase (> 4 fold) in the number of CD8 positive T cells and in addition synergizes with PDL-1 inhibition.

Taken together, the clinical and basic research results open up a new avenue for combining an 'emerging' immune checkpoint inhibitor (PD-1/L1) with an 'established' growth/survival signaling pathway inhibitor (MEK1/2). It is quite possible, perhaps even likely, that blocking these pathways will be active in more than just CRC. Furthermore, this represents notable progress and introduces the hope that other tumor types previously considered cold could also be made to respond to immunotherapies.

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