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Clinical Group

Global Journal of Cancer Therapy

DOI CC By

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Dates: Received: 14 January, 2017; **Accepted:** 25 May, 2017; **Published:** 26 May, 2017

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Editorial

MEK Inhibitors in Combination with Immune Checkpoint Inhibition: Should we be Chasing Colorectal Cancer or the KRAS Mutant Cancer

Editorial

In the past few years, immunotherapy, particularly immune checkpoint inhibitors, have redefined standard of care cancer treatment for numerous malignancies. However, despite the wealth of promising data and great enthusiasm, the vast majority of cancer patients still fail to respond to these therapies as single agents. In tumors which are thought of as immunogenic (e.g. renal cell, urothelial, non-small cell lung cancer (NSCLC)) the response rate to single agent immune checkpoint inhibition seems to be around 20% [1], but in still other tumors generally thought of as non-immunogenic the response rate seems to be far less. In these non-immunogenic tumor types much focus has been given to the subset of patients with high microsatellite instability (MSI-H) or mismatch repair deficient tumors which have been shown to have relatively high response rates to single agent PD-1 therapy [2]. But patients with MSI tumors often make up only a tiny fraction of patients with these non-immunogenic tumors. One clear example of this is colorectal cancer (CRC) where only 15% of patients have MSI-H disease and only 4% of patients with metastatic disease have MSI-H tumors [3]. Therefore, hundreds of trials are currently underway evaluating the combination of immune checkpoint inhibition with other treatment options in an effort to increase the percentage of patients both with immunogenic and non-immunogenic tumors who will respond to immune checkpoint inhibition. One such trial was recently conducted in CRC patients with microsatellite stable (MSS) disease.

In preclinical work the inhibition of mitogen activated protein kinase enzymes (MEK) in CRC cancer models produced MHC1 upregulation on tumor cells, as well as intratumoral T cell infiltration and enhanced anti-PDL1 activity [4]. This data suggested that patients with CRC may have an increased response rate to anti PD-L1 therapy if combined with a MEK inhibitor. To evaluate this combination, a phase Ib trial enrolled 23 patients with advanced MSS CRC to receive atezolizumab, an anti PD-L1 monoclonal antibody, and cobimetinib, a MEK inhibitor [4]. Four out of the 23 patients (17%) had a response to treatment with three responses ongoing at the time of data cutoff. Although four out of 23 patients may not seem substantial what is noteworthy is that this occurred in a traditionally non immunogenic tumor with very poor response rates to immune checkpoint inhibitors. As an example, in the phase I trial of nivolumab, the first FDA approved anti PD-1 monoclonal antibody, 19 patients with CRC were enrolled and none of them responded to treatment [5]. This trial was the first to demonstrate that checkpoint inhibition had the potential to obtain response rates in non-immunogenic tumors on par with immunogenic tumors when combined with additional therapy. However, while this demonstration is noteworthy we are left with the following question: Can MEK inhibition combined with immune checkpoint inhibition improve response rated in other traditionally non-immunogenic tumor types? Only clinical trials will tell, but even within CRC things may not be so straightforward.

Looking closer at the phase Ib trial evaluating atezolizumab and cobimetinib in CRC, we see that 20 of the 23 patients enrolled were KRAS mutant and all responses were seen in KRAS mutant disease. Therefore, it is unclear if the improved response to immune checkpoint inhibitors with cobimetinib would have been seen in KRAS wild type disease or whether this phenomenon is limited to the KRAS mutant population. Moreover, it is unclear from the published abstract if the preclinical data, which suggested that MEK inhibitors may sensitize to immune checkpoint inhibition, was limited to KRAS mutant or included wild type (WT) models and it is also uncertain if the investigators preferentially enrolled patients with KRAS mutant disease. There is great importance in understanding whether this sensitivity is limited to KRAS mutant disease as KRAS mutant disease only represents about 35-45% of CRC cancers [6]. This information will also be critical in understanding the findings of an ongoing phase 3 trial evaluating the combination of cobimetinib plus atezolizumab

Citation: Strauss J (2017) MEK Inhibitors in Combination with Immune Checkpoint Inhibition: Should we be Chasing Colorectal Cancer or the KRAS Mutant Cancer. Glob J Cancer Ther 3(1): 030-031.

and atezolizumab monotherapy versus regorafenib in 360 patients with metastatic CRC cancer [NCT02788279]. This trial is not excluding patients with KRAS WT CRC cancer and is instead aiming for a goal of 50% accrual of KRAS WT disease. Therefore, if MEK inhibition only sensitizes to immune checkpoint inhibitors in KRAS mutant disease the response rate in this phase 3 trial may be dramatically less than the one seen in the phase Ib trial. Moreover, this trial is unlikely powered to show a significantly improved response rate in the KRAS mutant subpopulation alone and so data for this combination in patients with KRAS mutant CRC may still be wanting even after the trial results are published.

Finally, if the ability of MEK inhibitors to sensitize to immune checkpoint inhibition is more a factor of KRAS mutation status then the actual tumor type itself (e.g. colorectal cancer) then this same combination may be very promising in other tumor types where KRAS mutations are seen with great frequency including pancreatic adenocarcinoma (>90%) and non- small cell lung cancer (30%) among others [7,8]. In fact early preclinical data suggests that MEK inhibitors may sensitize to immune checkpoint inhibition in a number of tumor types including breast and lung cancer [9,10]. Even so much of the early data remains limited to KRAS mutant disease so the question remains whether this phenomenon is specific to RAS mutant cancer.

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