



Commentary on from Bench to Bedside: A Comprehensive Review of Pancreatic Cancer Immunotherapy. Slow Improvements in Meaningful Clinical Benefit

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Received date: Sep 22, 2016; Accepted date: Sep 29, 2016; Published date: Oct 4, 2016

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Citation: Kunk PR and Rahma OE (2016) Commentary on from Bench to Bedside: A Comprehensive Review of Pancreatic Cancer Immunotherapy. Slow Improvements in Meaningful Clinical Benefit Immunother Open Acc 2: 127. doi:[10.4172/2471-9552.1000127](https://doi.org/10.4172/2471-9552.1000127)

Commentary

As shown in From Bench to Bedside: A Comprehensive Review of Pancreatic Cancer Immunotherapy by Kunk et al. [1], the prognosis of pancreatic cancer remains dismal despite decades of innovative treatment approaches. Although we have currently a better understanding of the pancreatic immune microenvironment, particularly the dense stroma and its role in the immune escape of cancer cells, early efforts to alter this microenvironment into meaningful clinical benefit have been disappointing. Recently the results of two immunotherapy clinical trials in pancreatic cancer have been announced with disappointing outcomes. The ECLIPSE trial was a phase 2b trial that failed to show an improved survival using the listeria-based vaccine that expresses mesothelin (CRS-207) alone or in combination with GVAX (an allogeneic vaccine that is engineered to secrete GM-CSF) compared to chemotherapy [2]. The second trial (IMPRESS), a phase 3 study of algenpantucel-L vaccine (irradiated allogeneic pancreatic cancer cells transfected to express murine alpha-1,3-galactosyltransferase) in combination with standard of care vs. standard of care alone in patients with resected pancreatic cancer, did not achieve its primary endpoint of improving overall survival [3]. These negative studies illustrate the challenging pancreatic tumor immune microenvironment and the fact that using cancer vaccines alone may not be sufficient to illicit a meaningful humeral and cellular immune response that could translate to clinical benefit.

Accordingly, the field is moving toward combination therapies of cancer vaccines, chemotherapy, radiation therapy, and immune checkpoint inhibitors. Of particular interest will be the results of the

FOLFIRINOX followed by GVAX with ipilimumab (anti-CTLA-4) trial (NCT01896869); GVAX in combination with CRS-207 with or without nivolumab (NCT02243371) trial; and IDO inhibitor in combination with gemcitabine and nab-paclitaxel (NCT02077881) trial in metastatic pancreatic cancer. Furthermore, the lack of standard of care in the neoadjuvant setting represents a golden opportunity to investigate the effect of immunotherapy on the pancreatic tumor immune microenvironment. GVAX with or without nivolumab is currently being investigated in the neoadjuvant setting (NCT02451982) and we are currently investigating the effect of chemoradiation in combination with pembrolizumab (anti-PD-1) compared to chemoradiation alone on the pancreatic tumor-infiltrating lymphocytes (NCT02305186). The results of these trials may change the landscape of pancreatic cancer treatment by incorporating immunotherapy agents in future clinical trials design that builds on the benefits of combinational modalities.

References

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