Correlation of clinical benefit with target neutralization and immune response in patients with microsatellite-stable, metastatic colorectal or pancreatic cancer treated with the CXCL12 inhibitor NOX-A12 in combination with PD-1 checkpoint inhibitor pembrolizumab

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BACKGROUND

The OPERA study (NCT03168139) is a Phase 1/2 open-label clinical study to evaluate pharmacodynamic effects and safety of monotherapy with NOX-A12 and safety and efficacy of a combination of NOX-A12 with pembrolizumab in advanced microsatellite-stable (MSS), metastatic colorectal and pancreatic cancer with liver metastasis. The study comprises two weeks of NOX-A12 monotherapy followed by NOX-A12 plus pembrolizumab (Fig. 1). Here we present pharmacodynamic biomarker data from monotherapy phase with NOX-A12, as well as the clinical efficacy and safety data for the combination with pembrolizumab.

RESULTS

Twenty patients were recruited, thereof 11 with metastatic colorectal and 9 with metastatic pancreatic cancer (Table 1). Fifteen of the patients included (75%) are male, with a median age of 62 (colorectal) and 68 years (pancreatic).

Table 1: Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Colorectal Cancer</th>
<th>Pancreatic Cancer</th>
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<tbody>
<tr>
<td>Median Age (years)</td>
<td>62 (25-70)</td>
<td>68 (36-83)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/3</td>
<td>7/2</td>
</tr>
<tr>
<td>Performance Status</td>
<td>1-2</td>
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All patients were heavily pretreated with a median of 5 lines of therapy (colorectal) and 3 lines (pancreatic) of prior systemic treatment. The best response to the last prior treatment was progressive disease for all except one of the patients. All patients were confirmed to have microsatellite-stable (MSS) cancer and thus should be non-responsive to anti-PD-1 monotherapy (Kalyan 2018, J Gastrointest Oncol 8:160; Hu 2016, Clin Cancer Res 22:1236).

Serial biopsies at baseline and end of NOX-A12 monotherapy were collected for immuno-histochemistry (IHC) and cytokine analysis. Of these, 14 out of 20 patients were analyzed at baseline and 14 out of 20 patients were analyzed at end of monotherapy.

Intra-abdominal haemorrhage was the only severe adverse event (AE) during monotherapy treatment (Table 2). None of the patients experienced severe hypoglycemia, severe neutropenia or severe sepsis during monotherapy treatment. The only serious AE during combination therapy was a case of grade 3 myasthenia gravis.

A AE profile in the study was comparable with the safety profile for pembrolizumab monotherapy for the underlying disease colorectal and pancreatic cancer. Treatment with NOX-A12 monotherapy and in combination with pembrolizumab was safe and well tolerated, with 148 AEs in total, thereof 47.3% grade 1; 36.5% grade 2; 15.5% grade 3; no grade 4 and 0.7% grade 5 (Fig. 8).

CONCLUSION

In patients with microsatellite-stable metastatic pancreatic and colorectal cancer, with impaired immune systems and a high tumor load that has failed multiple prior lines of therapy, NOX-A12 plus pembrolizumab shows induction of immune response, stable disease in 25% of patients, and prolonged time on treatment vs. prior therapy for 35% of patients. This study also supports the role of CXCL12 in resistance to immunotherapy. CXCL12 is abundantly present in tumor lesions. The extent of CXCL12 neutralization in tumor tissue correlates with a high tumor response and disease stabilization. Further studies of NOX-A12 in combination with Keytruda are warranted and there is ample scope to optimize the NOX-A12 dose regimen given the safe and tolerability of tested regimens.

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