Background

• The CXCR4/CXCL12 pathway plays a critical role in the trafficking of immune cells in the tumor microenvironment (TME).

- CXCL12 is a chemokine that recruits CXCR4+ cells into the tumor microenvironment (TME).

- CXCR4 antagonists have been shown to disrupt immune cell trafficking into the TME, leading to increased CD8+ T cell infiltration.

Methods

- Patients selected based on activating mutations of the NRAS gene, BRAF V600E mutation status, and histological diagnosis of melanoma.

- Inclusion: Patients with NRAS G12D, G12V, G12C, or G12R mutation.

- Exclusion: Patients with prior treatment for metastatic melanoma.

- Patients were treated with X4P-001, an orally bioavailable CXCR4 antagonist, followed by pembrolizumab.

Results

- Treatment with X4P-001 led to a significant increase in CD8+ T cell infiltration within the tumor microenvironment.

- CD8+ T cell infiltration was assessed by multiplex IHC and flow cytometry.

- CD8+ T cell density increased by 2-fold after 3 weeks of X4P-001 monotherapy and by 4-fold after combination therapy.

- Granzyme B expression was also increased by combination therapy, indicating increased pro-inflammatory activity.

- Serum concentrations of CXCL9 and CXCL10 were significantly increased after combination treatment, consistent with immune stimulation.

- Adverse events were primarily Grade 1-2 and were managed with supportive care.

Conclusion

- X4P-001, an orally bioavailable CXCR4 antagonist, enhances immune cell infiltration and activation in the tumor microenvironment of melanoma.

- Combination therapy with X4P-001 and pembrolizumab demonstrated increased CD8+ T cell infiltration and pro-inflammatory activity.

- Further studies are needed to evaluate the long-term efficacy and safety of this combination therapy.

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