Avelumab in neuroendocrine tumours of gastroenteropancreatic or lung origin

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Background:

- High-grade neuroendocrine tumours (NET) are aggressive malignancies. Recent advances in systemic treatment focus on Grade 1-2 NET, and there remain few options for advanced G3 NETs.
  - Poorly-differentiated histology confers a particularly poor prognosis in pancreatic NETs. (Tang 2015).
- Immunotherapy, particularly monoclonal agents targeting the PD-1/PD-L1/PD-L2 axis, has transformed the treatment of solid organ tumours such as melanoma, non-small-cell lung cancer and bladder cancer.
- There has been little published data thus far regarding immunotherapy in NETs. The KEYNOTE-028 study (ESMO 2017) demonstrated modest response rates for pembrolizumab in NET (12% in carcinoid tumours, 6% in pancreatic NET), but this mainly investigated G1-2 NETs.
- Two recent trials of immunotherapy (avelumab, pembrolizumab) in Merkel cell carcinoma, or neuroendocrine carcinoma of the skin, (Kaufman 2016, Nghiem 2016) have shown response rates of 32% and 56%. (Fig.1)

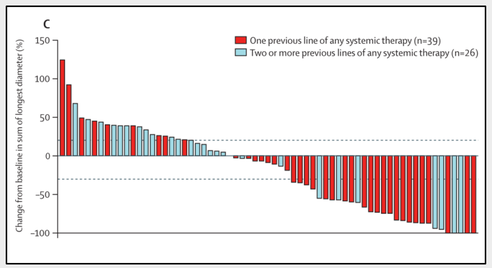


Fig:1: Waterfall plot for avelumab in Merkel cell carcinoma –from Kaufman 2016

Methods:

- We plan to conduct two parallel single-arm, open-label trials at Sunnybrook Health Sciences Centre for patients with G2-3 NETs. Avelumab will be given every 2 weeks, with CT imaging every 12 weeks. Treatment post progression is allowed until a confirmatory CT scan 4 weeks after the initial CT scan.

Key inclusion criteria:

- Histology: Grade 3 poorly-differentiated NET of GI or lung origin (NET-001); Grade 2-3 well-differentiated Net of GI or lung origin (NET-002)
  - Both functional and non-functional tumours are eligible
- Progression on imaging in last 12 months
- 0-2 prior lines of systemic therapy (excluding SSA)
- The presence of sufficient archival tissue for analysis (a core biopsy should be sufficient in most cases)

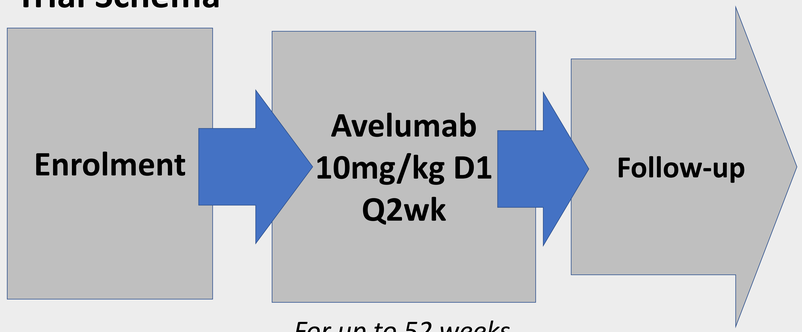
Key Exclusion criteria:

- Histology other than NET (e.g. MANEC)
- Prior use of PD-1, PD-L1, CTLA-4 inhibitors
- Current use of systemic immunosuppressants (equivalent of oral prednisone >10mg/day)
- Brain metastases which have not received local therapy, are clinically unstable, or result in neurological symptoms
- Leptomeningeal disease

Endpoints:

- Primary outcome: Response rate by RECIST v1.1
- Secondary outcomes: Safety, duration of response, OS, PFS, efficacy outcomes by irRECIST
- Correlative analyses of PD-L1 status and mutational load are planned.

Trial Schema



For up to 52 weeks

Trial status and registration

- NET-001 (G3 PDNEC) – 10 patients; NET-002 (G2-3 WDNET) – 36 patients. Planned to open end-Oct 2017
- Both trials have been approved by the Sunnybrook Research Ethics Board and Health Canada (NCT03278405, NCT03278379). The sponsor is the Sunnybrook Research Institute.
- NET-001 is supported by a grant from the Kavelmann Fonn Foundation and in-kind drug support from Merck KGaA. NET-002 is supported by a grant from Merck KGaA. Correlative components will be supported by a grant from CNETs.

References

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