

Avelumab in Advanced Neuroendocrine Tumours (NET) of Gastroenteropancreatic or Lung Origin

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Background: Immunotherapy agents, particularly monoclonal antibodies targeting the PD-1/PD-L1 axis, have revolutionized the treatment paradigm of multiple solid tumors. However, there is little data regarding their use in neuroendocrine tumors. Avelumab, an inhibitor of PD-L1, has shown efficacy in metastatic Merkel cell carcinoma, a disease bearing similarities to high-grade neuroendocrine tumor.

Methods: Two parallel single-arm, open-label, single-center clinical studies based at Sunnybrook Health Sciences Centre, Toronto, will seek to evaluate the impact of avelumab on patients with advanced NET of gastroenteropancreatic or lung origin. Patients with progressive, unresectable or metastatic Grade 2-3 neuroendocrine tumour or carcinoma will be eligible for accrual. The primary endpoint is objective response rate; secondary endpoints include safety, duration of response and outcomes according to irRECIST criteria. Clinically well patients with radiological progression on study may continue treatment until a confirmatory CT scan to allow for the possibility of pseudo-progression.

Results: NET-001 is a pilot study enrolling 10 patients with poorly-differentiated Grade 3 neuroendocrine carcinoma. NET-002 is a phase I/II study enrolling 26 patients with well-differentiated Grade 2-3 neuroendocrine tumor. Patients will receive avelumab (10mg/kg) IV every two weeks for a maximum treatment duration of 12 months, excepting confirmed disease progression or significant toxicity.

Conclusion: These trials will investigate the potential role of avelumab in treatment of neuroendocrine tumors. They will open for accrual in July 2017.

Trans-Anal Minimally Invasive Surgery (TAMIS) for Completion Excision of Localized Well-Differentiated Rectal Neuroendocrine Tumors

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Background: Rectal NETs (R-NETs) <2cm are often amenable to endoscopic attempts at resection, but initial resections are often incomplete, and extended monitoring or radical surgery may then be required. Trans-anal minimally invasive surgery (TAMIS) allows resection of rectal tumours while reducing surgical morbidity. Data on its use in R-NETs is scant. We aimed to assess the results of TAMIS for completion local excision of R-NETs following endoscopic resection.

Methods: We reviewed patients undergoing TAMIS for NET at our institution (2013-2017). Included patients had incomplete endoscopic resection (margin ≤ 1 mm), a visible scar on repeat endoscopy, and localized disease on systemic imaging. Full-thickness resection of the endoscopic scar was performed. Outcomes were 30-day major morbidity (Clavien-Dindo III-V), resection margin, and oncological outcomes.

Results: All seventeen patients included had G1 R-NETs. The reasons for completion excision were initial R2 resection (12), R0 resection with close margins (3), and fragmentary resection (2). Median distance from the anal verge was 7 (range, 5-13) cm. Median operating time was 41.5 (range 20-79) minutes. No major morbidity was documented. Viable tumor was found in 4 specimens, all Grade 1 with negative margins. At 18 months median follow-up, all patients were alive and asymptomatic, with no change in sphincter function and no evidence of local recurrence.

Conclusion: TAMIS is a safe and feasible approach for well-differentiated R-NETs to clear margins following incomplete endoscopic resection. It limits invasiveness of intervention and avoids time-consuming monitoring after incomplete resection.

Correlation of DOTATOC Uptake and Pathologic Grade in Neuroendocrine Tumors

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Background: ⁶⁸Ga-DOTATOC is a somatostatin analog used to detect neuroendocrine tumors (NETs). The Ki-67 protein (Ki-67) is a marker of cell proliferation and has been established as both a diagnostic and prognostic factor in the treatment of NETs. We aimed to evaluate whether a correlation exists between Ki-67 and somatostatin receptor (SSTR) PET uptake (SUVmax).

Methods: 238 consecutive DOTATOC PET scans between 2014 and 2016 were retrospectively reviewed. Patients were excluded if no pathology was available, tumors were fully resected prior to imaging, a correlate lesion between pathology and imaging could not be identified, or DOTATOC PET scan was >365 days from date of biopsy. The remaining 90 patients had pathology available, and 54 patients had Ki-67 available. DOTATOC uptake from biopsied lesions was measured and correlated with Ki-67.

Results: For the 110 lesions from 90 patients with pathology available, DOTATOC PET had a 92.7% sensitivity and 100% specificity (102 true positives; 8 false negatives) for detection of NETs. In 54 patients, we were able to obtain Ki-67 values for 63 lesions for which we had corresponding SUVmax information. There was no correlation between Ki-67 and SSTR-PET uptake ($r = -0.169$, $P = 0.252$). There were 26 grade 1 lesions (mean Ki-67 1.1%; median SUVmax 27.8), 31 grade 2 lesions (mean Ki-67 8.0%; median SUVmax 26.5), and 6 grade 3 lesions (mean Ki-67 32.9%; median SUVmax 6.2).

Conclusion: Our analysis demonstrates a high sensitivity and specificity in DOTATOC PET imaging for detection of NETs and that there is no correlation between Ki-67 and SUVmax in NETs. In Grade 1 and 2 lesions SSTR-PET provides independent information from Ki-67 that can help guide clinical management and treatment.

Phase II Trial of Cabozantinib in Patients With Carcinoid and Pancreatic Neuroendocrine Tumors

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Background: Activation of VEGFR2 and MET is implicated in driving growth of neuroendocrine tumors (NET). Cabozantinib inhibits VEGFR2, MET, AXL, and RET. We performed a two-cohort phase II study to evaluate the efficacy of cabozantinib in patients with advanced carcinoid or pancreatic NET (pNET) (NCT01466036).

Methods: Patients (pts) with progressive, well-differentiated carcinoid or pNET were treated with cabozantinib 60 mg daily. Pts were restaged after every 2 cycles for the first 6 cycles, then every 3 cycles. The primary endpoint was response rate (RECIST 1.1).

Results: 41 pts with carcinoid (median age 63 yrs, 44% male, %ECOG PS 0/1=51/49) and 20 pts with pNET (median age 55 yrs, 60% male, %ECOG PS 0/1=40/60) were accrued. Carcinoid pts completed a median of 8 (range 0-44) 28-day treatment cycles; pNET pts completed a median of 10 (0-35) cycles. 3/20 (15%) pts with pNET achieved PR (95% CI, 5-36%); 15/20 had SD. 6/41 (15%) pts with carcinoid achieved PR (95% CI, 7-28%); 26/41 had SD. Median PFS was 21.8 mo (95% CI, 8.5-32.0 mo) in pts with pNET and 31.4 mo (95% CI, 8.5 mo-NR) in pts with carcinoid. 14 pts remained on treatment at time of data analysis. Reasons for discontinuation among those who stopped therapy were progression/death (51%), withdrawal of consent/investigator decision (28%), adverse events (21%). Gr 3/4 toxicity included hypertension (13%), hypophosphatemia (11%), diarrhea (10%), lymphopenia (7%), thrombocytopenia (5%), fatigue (5%), increased lipase/amyase (7%). 81% (43/53) of pts completing ≥ 1 cycle required dose reduction from the initial 60 mg dose.

Conclusion: Treatment with cabozantinib was associated with objective tumor responses and encouraging PFS durations in patients with advanced carcinoid and pNET. While dose reduction was common, treatment was tolerable. A randomized phase III trial to confirm activity of cabozantinib in carcinoid and pNET is being developed through the Alliance for Clinical Trials in Oncology.

A Phase 1 Study of Fosbretabulin in Combination With Everolimus in Neuroendocrine Tumors (Grades 1-3) That Have Progressed After At Least One Prior Regimen for Metastatic Disease

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Background: Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are rare tumors with limited treatment options. Recent SEER database analysis shows consistent surge in incidence of GEPNETs. Current approved systemic