Profiloing of 1,250 neuroendocrine tumours identifies multiple potential drug targets

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Abstract #214
Identification of new drug targets may extend treatment options for neuroendocrine tumors (NET), regardless of histologic classification or primary organ site. Methods: 1,250 cases of indeterminate or indeterminate neuroendocrine tumors (all grades and sites) were identified among >50,000 cases profiled in a CLIA-certified laboratory. Biomarker profiling utilized multiple platforms: gene sequencing (next generation sequencing [NGS], Sanger or pyrosequencing), gene copy number by in-situ hybridization, and protein expression by immunohistochemistry (IHC). The results are shown relative to the total number of tests performed.

Results: Overall, drug therapy-relevant alterations were identified in 1130 of 1250 (90%) of cases. Low or absent (0 or 1+ by IHC) expression of MGMT (a biomarker of alkylating agent sensitivity, was found in 74% of NET). Sequencing of tumors showed oncogenic mutations in KRAS, NRAS, TP53, PIK3CA, FGFR2, GNAS, and HRAS; PIK3CA mutations were seen in 6/343 cases (1.6%). EGFR was found in 6/157 (1.9%) cases and 159/1250 (12%) of cases. Low or absent (0 or 1+ by IHC) expression of TS (a biomarker of gemcitabine sensitivity) was found in 813/1100 of NET (73%).

Potential Drug-amenable genetic alterations

Conclusions
- Multi-platform profiling, measuring gene amplification, mutation and/or protein expression identified alterations in 93% of NET; 91% aid in treatment selection
- Drug-amenable alterations (amplification or mutation) are found in at least 17% of all NET
- Additional biomarkers of chemotherapy sensitivity are worth exploring in a systematic study (5FU, alkylating agents, gemcitabine)
- Therapeutic selection based on information provided by a commercially available multi-platform molecular profiling service produced durable responses in select patients
- Given the expanding number of potential treatments for this group of relatively indolent tumors, further study and expansion of this panel of markers is warranted.

Methods
- All neuroendocrine tumor cases referred to Caris Life Sciences between 2009 thru Sep. 2013 from 50 states and 30 countries were evaluated; diagnoses were collected from referring physicians and classified at interval based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (immunohistochemistry), and/or gene amplification (CISH or FISH).
- Statistical analysis was performed using JMP and the Fisher two tail test was used to report p values.
- MGMT protein expression was low when <35% tumors cells stained intensity ≤ 1+.
- RRM1 protein expression was low when <50% tumor cells stained intensity ≤ 2+.
- TS protein expression was low when <10% tumor cells stained intensity ≤ 3+.