Machine Learning to extract, standardize, and analyze interactions from drug and biologic applications reviewed by FDA.

Results Using Regulatory Foresight, we discovered (a) the major topics of interest and concerns of the FDA, (b) the commonalities and differences in topics between the individual ICIs, (c) the evolution of topics from the oldest to the most recently approved ICI, and (d) the unaddressed topics in official FDA guidance documents.

Conclusions This work successfully uncovers regulatory requirements in the development of immune checkpoint inhibitors using AI algorithms in order for sponsors to (a) optimize strategies for development of new drugs, (b) better understand regulatory expectations, and (c) adequately prepare for meetings and submissions to regulatory agencies. In addition this work discovers the current gaps in official FDA guidance documents so that they may be adequately addressed in future versions.

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INTEGRATED MOLECULAR CHARACTERIZATION AND THERAPEUTIC VULNERABILITIES OF NEURALLY PROGRAMMED TUMORS ACROSS 33 HUMAN INDICATIONS

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Background Neuroendocrine tumors (NETs) can arise from neuroendocrine stem cells de novo, or from tumors that develop lineage plasticity and undergo neuroendocrine transformation. De novo NETs are generally immune desert, and thus are refractory to single agent immune checkpoint inhibitors (ICIs) such as monoclonal antibodies against PD1, PDL1 and CTLA4. Transformed NETs also present a clinical challenge as there is no established therapeutic approach for these tumors. Despite the high unmet medical need, our understanding of the molecular characteristics and microenvironment of both de novo and transformed NETs remains largely incomplete.

Methods Here, we develop a machine learning-based classifier NEPTUNE (NEurally Programmed Tumor Prediction Engine) to identify neurally programmed (neuroendocrine-like or neural crest embryonic origin) tumors across 33 different human cancers and more than 10000 treatment-naïve tumors, and study their molecular and immune microenvironment characteristics.

Results We find that neurally programmed (NEP) patient tumors are characterized by low lymphocyte and myeloid cell infiltration, p53 and RB1 functional loss, chromosome arm level aneuploidy, genome-doubling, loss of REST-mediated transcriptional repression, and enrichment in NRAS mutations. Similar to neuroendocrine indications, NEP tumors exhibit two major variants: 1) well-differentiated low-proliferating, and 2) poorly-differentiated high-proliferating; with the latter being substantially more prevalent in humans and significantly more aggressive in terms of survival and time to metastasis. We find evidence that BAF complexes and de-repression of Polycomb repressive complex 2 (PRC2) targets may play roles in the neural programming of particularly poorly differentiated NEP tumors. NEP tumors also exhibit characteristics of lineage plasticity such as EMT/stem-like phenotype as well as activation of MYCN and SOX family transcription factors. These observations suggest that lineage plasticity is not restricted to the post-therapy setting, but can be seen in treatment-naïve primary tumors as well. In vitro, NEP tumor lines are most sensitive to NAMPT inhibitors, which may be due to low NAD biosynthesis enzyme expression and/or low NAD metabolite levels. Unbiased metabolite analysis also reveals that NEP tumors may be sensitive to inhibition of certain components in pyrimidine biosynthesis and urea cycle pathways. Further, we find in a pancreatic cancer metabolomic dataset that N-acetyl-aspartate and/or its synthesizing enzyme NAT8L may have potential as diagnostic biomarkers for NEP tumors.

Conclusions Our study sheds light on previously underexplored aspects of neuroendocrine tumors; defines and characterizes the novel class of neurally programmed tumors; and provides a collection of evidence to guide clinical trial design and clinical care for these tumors.

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A TOOLKIT FOR THE QUANTITATIVE ANALYSIS OF THE SPATIAL DISTRIBUTION OF CELLS OF THE TUMOR IMMUNE MICROENVIRONMENT

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Background Spatial technologies that query the location of cells in tissues such as multiplex immunohistochemistry and spatial transcriptomics are gaining popularity and are likely to become commonplace. The resulting data often includes the X, Y coordinates of millions of cells, cell phenotypes and marker or gene expression levels. In cancer, the spatial location of lymphocytes has been linked to prognosis and response to immunotherapy. While these advances have been exciting for the field, the methods currently being used are still coarse, making us severely underpowered in our ability to extract quantifiable information. Appropriate