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.

**REFERENCES**

4. Clinical trial endpoints for the approval of cancer drugs and biologics’ Guidance for industry. US Department of Health and Human Services, FDA, Oncology Center of Excellence, CDER, CBER. December 2018

**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.