with good performance (c-index$_{model}$ = 0.652, $p_{c\text{-}index}$ = 0.0290).

Conclusions Models incorporating clinical metadata and immunogenomic signatures can predict response and survival for urothelial cancer patients treated with atezolizumab. Among predictors in those models, baseline performance status is the greatest and most positive predictor of response and survival.

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663 CORRELATION BETWEEN EARLY ENDPOINTS AND OVERALL SURVIVAL IN NON-SMALL-CELL LUNG CANCER: A TRIAL-LEVEL META-ANALYSIS

[1]Shameer Khader*, [1]Youyi Zhang, [1]Daniel Jackson, [1]Kirsty Rhodes, [1]Imran Khan Anwer Neelufer, [1]Sreenath Nampally, [2]Andrzej Prokop, [1]Emmette Hutchison, [1]Jiabu Ye, [1]Feng Liu, [1]Antony Sabin, [1]James Weatherall, [1]Cristina Duran, [1]Renee Iacona, [1]Faisal Khan, [1]Pralay Mukhopadhyay. *[1]AstraZeneca, Gaithersburg, MD, USA; [2]AstraZeneca Pharma Poland, Warsaw, MD, Poland*

Background In clinical trials that assess novel therapeutic agents in patients with non-small-cell lung cancer (NSCLC), early endpoints (e.g. progression-free survival [PFS] and objective response rate) are often evaluated as indicators of biological drug activity, and are used as surrogate endpoints for overall survival (OS). Compiling trial-level data could help to develop a predictive framework to ascertain correlation trends between treatment effects for early (e.g. odds ratio [OR] for PFS at 6 months) and late endpoints (e.g. hazard ratio [HR] OS).

Methods A dataset was compiled, which included 81 randomized, controlled trials (RCTs; Phase II–IV) of NSCLC (Stages I–IV), with 35 drugs and 156 observations. The dataset was collected from multiple source databases, including Citeline, TrialTrove, clinicaltrials.gov, and PubMed. We applied random-effects meta-analysis to correlate a variety of treatment effects for early endpoints with HR OS. We performed meta-regression analyses across different data-strata, stratified by the mechanism of action (MoA) of the investigational product (programmed death protein-1/programmed death-ligand 1 [PD-1/PD-L1], epidermal growth factor receptor [EGFR], vascular endothelial growth factor receptor, and DNA damage response).

Results Low (Spearman's rho 0.3–<0.5) to moderate (rho 0.5–<0.7) correlations were observed between HR OS and (1) HR PFS, (2) OR PFS 4 months, and (3) OR PFS 6 months for PD-1/PD-L1 trials, EGFR trials, and all trials combined (Random-effects meta-regression; P<0.05). Similar correlations were observed between each of the early endpoint treatment effects and HR OS. For example, the moderate correlation observed between OR PFS 4 months and HR OS (rho-0.579; 95% confidence interval [CI]-0.800,-0.274; meta-regression R2= 72.5%) was similar to that between OR PFS 6 months and HR OS (rho-0.633; 95% CI-0.802, -0.383; R2=86.1%) for PD-1/PD-L1 trials. Note, the reported rho values are negative as a HR<1, and an OR>1, indicate benefit with the investigational product.

Conclusions Using a comprehensive summary data set in the NSCLC space, we observed low-to-moderate correlations between treatment effects for early endpoints and HR OS across RCTs of agents with different MoAs, including trials of PD-1/PD-L1 checkpoint inhibitors. Exploration of additional endpoints, beyond RECIST, is required to identify other early indicators of efficacy that might predict HR OS. By incorporating additional trial-level parameters and building composite biomarkers using machine intelligence methods, in collaboration with innovative trial design efforts, we envisage to improve the prediction of HR OS from early endpoints.

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664 APPLYING ADVANCED DATA ANALYSIS TO IMMUNOTHERAPY DRUG DISCOVERY FOR UVEAL MELANOMA

Sarah Kolitz*, Yoonjeong Cha, Sailaja Battula, Rebecca Kusko, Benjamin Zeskind, Howard Kaufman. *Immuneering Corporation, Cambridge, MA, USA*

Background Uveal melanoma is a rare variant of melanoma associated with monosomy 3, present high risk for metastatic disease, and has been resistant to all therapeutic approaches. We sought to use a novel advanced big data approach to identify potential new immunotherapy targets for the treatment of uveal melanoma.

Methods Comprehensive multiplatform analysis of 80 primary uveal melanoma specimens in the TCGA gene expression database were evaluated. There were four previously reported [Robertson *et al*, Cancer Cell, 2017] molecularly distinct subsets consisting of two high-risk, largely disomy 3 (N=38 after data QC) and two low-risk, largely monosomy 3 (N=40) patterns predictive of metastatic progression. RNA sequencing data for these subsets were analyzed at Immuneering to obtain differential expression signatures associated with prognosis. QC was performed, including principal component analysis to identify outlier samples, and gene expression changes were determined by limma-voom analysis and organized by magnitude of change and statistical significance, using Benjamini-Hochberg multiple hypothesis correction. Pathway enrichments were conducted by GSEA. Prognosis-associated genomic signatures were evaluated using an advanced big data platform to identify relevant biological perturbations in each subgroup using two- and four- subset analyses.

Results Large differences in gene expression were identified in high-risk vs. low-risk uveal melanoma samples. Volcano plots identified several independent genes differentially expressed in good vs. poor risk uveal melanoma. The most positively enriched gene expression pathways associated with poor prognosis related to innate and adaptive immune processes. This included genes associated with MHC expression, antigen processing and presentation, regulation of T cell responses, leukocyte chemotaxis, antigen binding and type I interferon responses. Transcriptomic perturbation analysis identified several associations of which the top included genes associated with overexpression of interferon-gamma and interferon-beta 1, and interferon-gamma ligand stimulation. Another major family identified was RAB31, which coordinate small GTPases involved in intracellular membrane trafficking. Prognosis-associated immune perturbations were far more highly enriched among a subset of patients, indicating differing underlying biology in a patient subset that could be relevant for treatment.

Conclusions Our data identified numerous potential therapeutic targets, many associated with tumor-immune system interactions in high-risk uveal melanoma samples. Advanced big data analysis platforms may be leveraged to identify

therapeutic targets in challenging human diseases and our data has provided new directions for immunotherapy drug development in uveal melanoma.

Trial Registration N/A

Ethics Approval N/A

Consent N/A

REFERENCES

N/A

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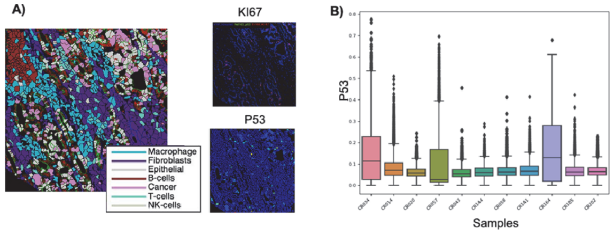
665 SPATIAL SINGLE-CELL ANALYSIS OF COLORECTAL CANCER TUMOUR USING MULTIPLEXED IMAGING MASS CYTOMETRY

[1]Minh Tran, [1]Andrew Su, [2]HoJoon Lee*, [3]Richard Cruz, [3]Lance Pflieger, [3]Ashely Dean, [1]Quan Nguyen, [2]Hanlee Ji, [3]Terence Rhodes. *[1]The University of Queensland, Brisbane, Australia; [2]Stanford University, Stanford, CA, USA; [3]Intermountain Healthcare, St. George, UT, USA*

Background Cancer research experiments often require the dissociation of cells from their native tissue before molecular profiling, leading to the loss of spatial tissue context. The cancer genomics research has shifted from mostly profiling tumour DNA mutations towards the current frontier of investigating individual genes and gene products in single cells and their immediate microenvironments. Information at this level with the spatial context enables us to link cancer–causing mutations and environmental factors to outcomes in cell signalling, responses and survival that will lead to solutions for diagnosing, predicting progression and treating cancers in different individuals. In this project we aim to capture tissue morphology, cancer cell types, multi-parameter protein contents of single cells in within morphologically intact tissue sections of colorectal tumours from 52 patients.

Methods Using Hyperion Imaging Mass Cytometry (IMC), we simultaneously profiled 16 protein markers for each tissue section, capturing molecular signatures of tissue architecture, cancer cells, and immune cells. IMC uses laser beam to accurately ablate every 1μm^2 of tissue region, generating data at subcellular resolution for FFPE tissue sections on a glass microscopy slide. We selected 2–8 regions of interest (ROI), each containing approximately 2098 cells. The ROI sizes range from 141μm x 500μm to 1121μm x 1309μm. We developed an analysis pipeline to process raw Hyperion imaging data (IMCtools), define cellular masks with information about nuclei, membrane, cytoplasm (using CellProfiler and Ilastick), and analyses cellular communities (HistoCAT). We also generated whole exome sequencing data and histopathological mages from sections of the same tissue blocks.

Results By measuring 16 multiplexed proteins, for each tissue region we were able to identify up to seven cell types and preserved their spatial location within the tissue (figure 1A). Through the spatial map of the cell types to the tissue, we showed the heterogeneity of the tumour microenvironment, such as the infiltration of macrophages and B-cells to the cancer regions (figure 1A). We found cancer cells consistently marked as positive for p53 and Ki67 proteins. Moreover, we could measure the level of p53 in every individual cell within each tissue section (figure 1B). The quantitative measurement of p53 by imaging mass cytometry was correlated with the result from traditional genomic sequencing of p53 mutations and with the histopathological annotation.



Abstract 665 Figure 1 Characterizing the complexity of colorectal cancer. A) Cell types within a region of interest, defined by 16 markers. Cancer cells are consistent to the. B) Quantifying p53 expression from Hyperion data

Conclusions Applying the Hyperion technology, we could acquire rich information from each of the precious cancer samples. The spatial data at single-cell resolution enabled us to assess the heterogeneity of tumour tissue by defining cell types, immune infiltration, and cancer-immune cell interaction within an undissociated tissue section. Future analysis and application of Hyperion data would allow us to find better predictors for colorectal cancer tissue with more accurate diagnosis and prognosis.

Ethics Approval This study was approved by the Institutional Review Board (#1050191) at Intermountain Healthcare (Salt Lake City, UT USA)

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666 ANALYZING REGULATORY REQUIREMENTS IN THE DEVELOPMENT OF IMMUNE CHECKPOINT INHIBITORS USING ARTIFICIAL INTELLIGENCE

Krish Perumal, Amin Osmani*. *Biotech Square*

Background Since the approval of the first immune checkpoint inhibitor (ICI) targeting CTLA-4 in 2011 (ipilimumab), six others, targeting the PD-1/PD-L1, have been approved by FDA for a total of more than 19 indications,[6,7,8] and the number is growing. These approvals paved the way for rapid growth in the number of candidates in the pipelines. It is critical for these candidates to pursue the right development strategy to demonstrate their potential to regulatory authorities and reach patients without delay. Unexpected challenges in such a competitive field risks leading to expensive modifications and possible discontinuations. This is compounded by the lack of clarity in important development questions such as study design,[5] the choice of endpoints and appropriate statistical methods.[1,2,3] In this regard, FDA's guidance document[4] provides a useful summary of the topics encountered by clinical development practitioners such as endpoints, clinical trial design and statistical analysis. However, it does not capture the unique challenges of the checkpoint inhibitor space, namely traditional phase I study designs and their ability to predict dosing and detect dose-related toxicities[1] and endpoint selection given the unconventional response patterns.$_2$

Methods The approval packages of the seven FDA-approved ICIs contain a wealth of information related to the focus areas, expectations and concerns of the agency. However, they run into thousands of pages, which renders manual analysis too time-consuming and/or incomplete. In this work, we use Regulatory Foresight, a proprietary AI software tool developed by Biotech Square Inc., that employs state-of-the-art techniques in Computer Vision, Natural Language Processing and