depleting agent, would improve its therapeutic efficacy in triple negative breast cancer (TNBC). METHODS/STUDY POPULATION: Combination IL-12 and trabectedin was tested in the 4T1 mouse model of TNBC. 4T1 cells were injected into the mammary fat pad of female BALB/cj mice. When tumors reached 50 mm3, mice were randomly divided into 4 groups and treated with PBS, IL-12 (0.5 μg/mouse 3x/wk), 0.15 mg/kg trabectedin weekly or the combination. Tumor volumes were measured by calipers. Mass cytometry was performed on spleens and tumors using a 35-antibody panel. Plasma IFN-γ levels were measured by ELISA. The role of NK cells was evaluated via depletion with anti-asialo-GM1. The Luminex Discovery Assay was used to measure plasma cytokines and immunohistochemistry was performed for CD4 and CD8a. Linear/nonlinear mixed effects modeling was used for in vivo data analysis and applicable t- or ANOVA tests were used for in vitrodata analysis. RESULTS/ANTICIPATED RESULTS: Combination IL-12 and trabectedin led to a significant reduction in tumor burden compared to single-agent IL-12, trabectedin and control treatments (all $p<0.001$), as well as higher levels of IFN-γ (all $p<0.04$). One combination treated mouse had complete tumor regression. Splenic MDSC were significantly decreased in combination treated mice. NK depletion abrogated the effects of combination therapy. Compared to mice receiving a control antibody, NK depletion of combination treated mice led to lower levels of CCL5 ($p<0.01$) and CXCL10 ($p<0.001$) and significantly higher tumor burden ($p=0.001$). CD8+T cell levels were significantly higher in combination treated mice compared to those receiving IL-12 ($p<0.01$), and these levels were decreased when mice were depleted of NK cells ($p=0.01$). DISCUSSION/SIGNIFICANCE: TNBC represents 15% of all breast cancer diagnoses and is associated with a worse prognosis compared to other subtypes. Black women are twice as likely to be diagnosed with TNBC and more likely to die from disease than White women. Thus, there is an increasing need to develop additional therapeutic options for this disease.

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Magnetic Resonance Biomarkers of Metabolic Dysfunction-Associated Steatotic Liver Disease

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OBJECTIVES/GOALS: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major public health concern due to its increasing prevalence and association with type 2 diabetes mellitus. Non-invasive magnetic resonance-based biomarkers can aid in the monitoring of disease progression and identification of patients at risk for chronic liver disease. METHODS/STUDY POPULATION: Over 600 subjects will be recruited from the San Antonio Mexican American Family Study and from a second study, which consists of (i) T2DM patients diagnosed with either MASLD or metabolic dysfunction-associated steatohepatitis (MASH) or (ii) metabolically healthy controls. Hydrogen-1 MRS and diffusion-weighted MRI (DW-MRI) will be used to measure liver fat fraction and liver stiffness biomarkers, respectively. Several potential biomarkers of liver stiffness will be evaluated in vivo using the intravoxel incoherent motion (IVIM) model for DW-MRI. To further improve the diagnostic accuracy of patients with liver fibrosis, we will integrate MRI/MRS data with relevant clinical indicators of hepatic metabolism. Results will be compared to biopsy samples to evaluate the model's diagnostic accuracy. RESULTS/ANTICIPATED RESULTS: Based on preliminary data, we predict that IVIM will be able to accurately diagnose hepatic fibrosis in patients with MASLD, allowing it to be implemented in clinics with high-field MRI units easily. Previous studies have shown correlations between IVIM estimates and fibrosis stages, however, none included additional clinical indicators of liver disease in their models. We have already found significant differences in metabolic measurements such as fasting plasma glucose and HbA1c levels. Additionally, the use of machine learning in developing these models has shown improvements in the ability to extract features from the data. The aim is to achieve high accuracy and robustness in the staging of liver fibrosis. DISCUSSION/SIGNIFICANCE: Over 100 million people in the US are affected by MASLD. Without treatment, it progresses from hepatic steatosis to MASH, fibrosis (liver stiffening), and ultimately to hepatic cirrhosis and hepatocellular carcinoma (HCC). Continued research efforts and clinical implementation of MRI and MRS are vital in combating the growing burden of MASLD.

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Neuropsychiatric Symptom Clusters in behavioral variant frontotemporal dementia: The Role of Early Anxiety/Depression on Functional Progression

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OBJECTIVES/GOALS: To identify empiric neuropsychiatric symptom (NPS) clusters in behavioral variant frontotemporal dementia and to determine the role of early anxiety/depression on functional progression. METHODS/STUDY POPULATION: Analyses were conducted using data from the ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study, an established consortium with an ongoing cohort study of FTD patients across 18 clinical sites which includes comprehensive cognitive, neuropsychiatric, and structural neuroimaging data. A polychoric cluster analysis was performed on subjects from the ALLFTD cohort [applewebdata%3A//044E463E-34DA-4677-9EDC-B8309D14C337#_msocom_1] with early-stage disease (N=145, male 61%, median age 62 years) in order to identify empiric NPS clusters. Cox proportional hazard regression was then used to examine the association between early affective symptoms in bvFTD and subsequent functional disabilities adjusted for age, sex, level of education, and FTLD CDR global score. RESULTS/ANTICIPATED RESULTS: We identified a four-factor model as the best fit for the data: (1) an affective cluster with prominent depression, anxiety, agitation, and irritability, (2) a disinhibited symptom cluster with prominent elation and disinhibition, (3) an obsessive symptom cluster with prominent obsessive/ritualistic behavior and hyperorality, and (4) a psychotic symptom cluster with prominent delusions and hallucinations. The hazard of developing impairments in transactions, language, self-care, meal preparation, and incontinence was significantly elevated in those with early affective symptoms (depression/anxiety). DISCUSSION/SIGNIFICANCE: In this study we show that, NPS cluster into four discrete groups: (1) affective symptoms, (2) disinhibited symptoms, (3) obsessive symptoms, and (4) psychotic symptoms. Anxiety and depression are prominent within the affective symptom cluster and are associated with accelerated functional decline in a number of domains.

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