Abstracts From the NCCN 2022 Annual Conference

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HIGHLIGHTS OF THE NCCN 2022 ANNUAL CONFERENCE

YOUNG INVESTIGATOR AWARDS

YIA22-001: Development of hKIT Chimeric Antigen Receptor T-Cells as Dual Hematopoietic Stem Cell Transplantation Conditioning and Immunotherapeutic Agents for Cure of Pediatric Acute Myeloid Leukemia
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Acute myeloid leukemia (AML) is a frequent subtype of cancer that affects thousands of children and adults worldwide. Current treatments generally consist of harsh, conventional chemotherapy and/or hematopoietic stem cell transplantation (HSCT); therapies that cause significant morbidity and mortality, but often do not cure the disease. Unfortunately, AML patients experience an overall 5-yr survival rate of only 50%. Leukemic stem cells (LSCs) have been shown to perpetuate and maintain AML, and standard chemotherapies targeting the bulk of AML blasts tend to minimally effect LSCs. In this project we aim to leverage longstanding work on non-myoeloblastic conditioning strategies to develop a novel array of chimeric antigen receptor (CAR) T cells that target the hKIT receptor expressed by human HSCs, LSCs, and leukemic blasts in order to improve AML treatments and facilitate long lasting remissions. To develop hKIT CAR-T cells, the heavy and light chains of internally developed anti-hKIT mAb clones were first incorporated into a validated retroviral vector that encodes CD28 and CD3x intracellular costimulatory and signaling domains. Human T-cells were then transduced and analyzed via fluorescence-activated cell sorting (FACS) for CAR expression and CAR-T cell product phenotypic and in vivo anti-leukemia activity to adequately guide the translational development of this targeted dual function non-genotoxic conditioning regimen with anti-leukemic effects.

YIA22-002: A Common Polymorphism in 3β-Hydroxysteroid Dehydrogenase Promotes Resistance to Radiotherapy in Prostate Cancer
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Purpose/Objective(s): Half of all men with advanced prostate cancer inherit at least one copy of the HSD3B1 A1245C allele, which increases intracellular levels of the steroidogenic enzyme, 3βHSD1. Higher levels of this enzyme drive intracellular conversion of androgen precursors and have been associated with more rapid emergence of CRPC. We investigated whether 3βHSD1 levels were associated with response to androgen deprivation and radiotherapy. Results: Prostate cell lines expressing the variant HSD3B1 allele had an average 3.13-fold higher proliferation rate and clonogenic survival increased by 2 logs at a dose of 800 cGy compared to corresponding HSD3B1 knockdown cells. Variant HSD3B1 cell lines exhibited more efficient DNA repair kinetics with a significant reduction in residual γH2AX foci and smaller COMET tail moment 24 hrs following a single dose of radiation. Comparing HSD3B1+ vs HSD3B1- cells, there was increased expression of DDR genes, including non-homologous end joining, homologous recombination, and mismatch repair.
Induction of DDR genes following radiation was significantly more pronounced in HSD3B1 variant cells. A large database of 681 CCF prostate cancer patients with whole transcriptome data was queried and showed a direct correlation between AR signaling and increased DDR gene activity. Enzalutamide (Enza) pretreatment of HSD3B1 + cells decreased the clonogenic survival by 1 log at a single fraction dose of 8 Gy compared to vehicle treatment. Enza pretreatment resulted in significant increase in residual DSBs 24hrs after radiation, suggesting Enza blocks AR mediated DDR activation that drives radio-resistance in var HSD3B1 prostate cancer cells. **Conclusion:** In summary, increased intracellular 3βHSD1 associated with a common germline polymorphism, promotes prostate cancer radioresistance by upregulating the DNA damage response in the presence of adrenal steroid hormone precursors (Figure 1). This work has implications for optimizing combined radiation and androgen directed therapy and nominates HSD3B1 genotype as a predictive biomarker of treatment response. An NCCN sponsored prospective validation cohort is currently accruing.

**YIA22-003: Quantifying Minimal Residual Disease in Patients With Small Cell Lung Cancer**

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**Background:** Small cell lung cancer (SCLC) is a neuroendocrine malignancy that accounts for approximately 10-15% of all lung cancers.1 Blood-based next generation sequencing (NGS) assays of circulating tumor DNA (ctDNA) in patients with SCLC can detect canonical SCLC tumor
associated mutations. Our project aims focus on utilizing SCLC ctDNA to identify minimal residual disease (MRD) among patients with limited stage and extensive stage SCLC (LS-SCLC and ES-SCLC, respectively). Methods: We utilize a longitudinal, prospective blood-banking protocol approved by the Vanderbilt University Medical Center (VUMC) Institutional Review Board (IRB #030763). All SCLC patients presenting to VUMC are eligible, and we collect longitudinal blood samples up to every three weeks. We have partnered with Guardant Health to analyze specimens from patients with LS-SCLC using the Reveal assay, specifically assessing whether the combination of ctDNA NGS and epigenetic methylation profiling can detect MRD within this high-risk cohort. Guardant Reveal is a custom multomic assay evaluating ~500 genes and ~4Mb of differentially methylated regions. The presence of ctDNA is determined by a lung cancer-specific bioinformatics classifier that identifies tumor-derived somatic variants and methylation profiles without the need for separate tumor tissue or peripheral blood cell analysis. Results: Over the first 15 months of the funding award we have consented 23 new SCLC patients (7 with LS-SCLC and 16 with ES-SCLC), and we have collected 157 unique plasma samples from VUMC SCLC patients. We have completed a pilot analysis utilizing Guardant Reveal with treatment naïve samples and identified ctDNA in 5 of 6 LS-SCLC patients. The staging of these patients in the pilot analysis included two patients with stage I disease (IA2 and IA3), one patient with stage IIB disease, two patients with stage III disease (IIIB and IIIC), and one patient with stage IVA disease encompassable in one radiation port. Conclusions: The NCCN Young Investigator Award has been a catalyst for an invaluable, longitudinal biobanking resource to quantify MRD in SCLC. We are proceeding with a partnership with Guardant Reveal to analyze end-of-treatment samples among patients with LS-SCLC, and we are advancing our MRD analysis in patients with ES-SCLC. Ultimately, we hope this work leads prospective trials incorporating ctDNA as an integral biomarker in the management of patients with SCLC.

YIA22-004: The Feasibility of a Digitized Peer-To-Peer Patient Support System for Patients With Locally Advanced Head and Neck Cancer Undergoing Chemoradiation
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Background: Patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) undergoing multimodality treatments that result in significant morbidity. For patients undergoing definitive chemoradiation, functional deficits and significant decrease in quality of life contribute to tremendous social isolation. Peer-to-peer (P2P) support programs have a number of beneficial effects including improved satisfaction with medical care, improved mood, and decreased social isolation. Online support groups represent a new and vastly underused and understudied medium. While there have been a few studies evaluating online support groups, to our knowledge none of these have focused specifically on patients with SCCHN. The goal of the current study is to conduct a randomized controlled trial (RCT) of a digitized peer-to-peer communication system for patients with newly diagnosed locally advanced SCCHN. Methods: This is a pilot feasibility study of a digitized smart-phone enabled P2P application. Eligible patients are at least 18 years old, able to speak/read English, and slated to start definitive chemoradiation for their locally advanced SCCHN at Moffitt Cancer Center. The mobile application serves as a digitized patient support group/P2P communication system. Patients are randomly assigned in a 2:1 ratio to receive the mobile application or standard of care supportive services. A convenience sample of thirty patients are chosen for this pilot study. Results: To date, eighteen patients have been enrolled to the study. Eleven patients were randomized to the intervention arm, and seven patients were randomized to the standard of care arm. Baseline surveys were administered to enrolled patients. Of the patients who filled out baseline surveys, the majority of patients (62%) desired to be matched with someone undergoing similar therapy, 25% preferred someone with comparable age, and 13% preferred someone of their own gender. One patient was unable to fill out baseline surveys due to worsening of their medical condition. Due to the COVID-19 pandemic, the trial was closed for the eight months but is now open to accrual. Conclusions: This trial is currently open and accruing patients. Feasibility will be analyzed after completion of study recruitment.

YIA22-005: A Randomized Trial of Choice Architecture and Mailed Colorectal Cancer Screening Outreach in a Community Health Setting
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Background: Effective prevention and screening exists for colorectal cancer (CRC) but is underutilized, particularly in community health settings. Colonoscopy and fecal immunochemical testing (FIT) are both considered top-tier tests according to guidelines, but it is not clear how to offer...
choice through mailed outreach. Insights from behavioral science suggest that opt-out framing may increase participation, while choice overload may reduce uptake. **Methods**: This is a 3-arm randomized trial aimed at increasing rates of CRC screening by outreach to patients’ homes using choice architecture informed by behavioral science principles. We will randomize approximately 738 patients in a 1:1:1 ratio to one of three study arms: 1) colonoscopy only, 2) choice between colonoscopy or FIT, and 3) FIT only. The setting is a community health center in southeastern Pennsylvania with a baseline screening rate of 22%. Patients aged 50-74 who are overdue for CRC screening by screening guidelines will be enrolled (with a waiver of informed consent) if they have been seen at least once in the past 3 years for an outpatient visit. We will exclude patients at high risk of CRC (who should receive colonoscopy) or history of metastatic cancer. All patients will receive a letter from the health center informing them that they are overdue for CRC screening and requesting their participation in screening per their group assignment. Those in the colonoscopy arms will receive information about scheduling at a local endoscopy center. Those in the FIT arms will receive a FIT kit with instructions for completion. If screening is not completed, participants will additionally receive a reminder mailing or text message 2 months after initial outreach, and a final reminder phone call 3 months after initial outreach. The primary study endpoint is the completion of CRC screening within 6 months, and the secondary outcome is the choice of screening test. At the conclusion of the intervention, 20 participants in each of the three study arms will be randomly selected for a follow-up phone interview. **Results**: We have recently started enrollment, and we will describe our study population and present lessons learned regarding study implementation. **Conclusions**: The results of this trial will inform community health centers on how best to offer the choice of CRC screening to patients through mailed outreach. Trial Registration: clinicaltrials.gov NCT04711473

**YIA22-006: Characterization of Transcription-Replication Conflicts in KRAS-driven Pancreatic Cancer**
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**Background**: Transcription is a major cause of replicative hindrance in cancer cells; leading to replication stress. Oncogenes place significant demands on both replication and transcription. As a result, frequent encounters between replication and transcription machineries cause increased rate of transcription-replication conflicts (TRCs). Oncogenic KRAS mutations are a hallmark of pancreatic ductal adenocarcinoma (PDAC). The goal of the present study was to define the link between oncogenic KRAS and TRCs in PDAC. **Methods**: A doxycycline-inducible KRAS(G12D) vector was stably transfected YIA22-006 Figure 1. A. Western Blot: HPNE cells were stably transfected to express KRAS(G12D) oncogene upon doxycycline induction. This resulted in expected downstream activation of Akt pathway and DNA damage. B. Immunocytochemistry and C. Flowcytometry demonstrate accumulation of TRCs upon KRAS induction in HPNE cells as assessed by PCNA-RNAPII proximity ligation assay. D. Dot blot assay. HPNE parental cells (P), and two clones (1 & 2) stably transfected with doxycycline-inducible KRAS(G12D) oncogene were assessed for DNA-RNA hybrids (R-loops) with or without KRAS(G12D) induction for 3 weeks. Genomic DNA was blotted and probed with R-loop specific antibody (S9.6).
in the human pancreatic ductal-derived (HPNE) cells. KRAS(G12D) induction, Akt activation, and DNA damage (gH2AX) was verified by western blot. The impact of KRAS(G12D) on TRCs in this system was evaluated by RNA Polynucleotide II and Proliferating Cell Nuclear Antigen (RNAPII-PCNA) proximity ligation assays (PLA - immuno- cytochemistry and flow cytometry). TRCs characterized generally generate unusual non-B DNA structures such as DNA-RNA hybrids (R-loops) which were evaluated by dot blot using anti-R-loop (S9.6) antibody. In human PDAC cell lines, TRCs were evaluated by isolating proteins on nascent DNA (iPOND) and probing for RNAPII. Gene expression of TRC resolution factors in tumor vs. normal tissues was quantified using TCGA and GETX datasets, respectively. **Results:** Doxycycline-induction in HPNE-KRAS(G12D) cells resulted in over-expression of KRAS(G12D) and downstream signaling which reached a plateau at 72h (Fig 1). Compared to control cells without doxycycline treatment, doxycycline-treated cells demonstrated significant increase in TRCs (immunocytochemistry and flow cytometry PLA) and R-loops (S9.6 dot blot). Induction of TRCs was associated with DNA damage as measured by gH2AX phosphorylation. A panel of PDAC cells lines (Panc1, Mia-Paca2, and BxPC3) exhibited enhanced TRCs compared to control immortalized normal HPNE cells. This was orthogonally validated in Panc-1 cells using iPOND. Gene expression analysis demonstrated significant enrichment of TRC proteins in PDAC tissues compared to normal pancreas (p<0.001). **Conclusions:** Oncogenic KRAS induction in HPNE cells causes enhanced TRCs, R-loops and DNA damage. Human PDAC cells lines demonstrate high levels of TRCs compared to immortalized normal ductal cells. The findings support further investigation of TRC mechanisms as a therapeutic vulnerability in KRAS-driven PDAC.

**YIA22-007: Adaptive Nutrition and Exercise Weight loss (A-NEW) Study for Breast Cancer Survivors With Overweight or Obesity**

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**Background:** Obesity is associated with poor quality of life in breast cancer (BC) survivors. In the Look AHEAD trial, participants losing 3-6% of initial weight at 2 months had higher odds of ≥5% weight loss after 1 year, and 45% of participants attained ≥5% weight loss after 2 months. From an ongoing non-randomized clinical trial in BC sur- vivors with excess weight, we examined 2-month weight loss response. **Methods:** Women with stage 0-III BC, who completed local therapy and chemotherapy, with a body mass index (BMI) ≥27 kg/m² were enrolled on a 6-month BWL consisting of remote coaching, online curriculum and tracking of diet, activity and weight. Participants completed demographic surveys and were weighed in clinic at baseline and 2 months. Weight loss at 2 months stratified patients into those with ≥5% weight loss (FAST-BWL), and those without (SLOW-BWL). We performed a descriptive analysis of demographics and % weight loss from baseline to 2 months. **Results:** As of 10/20/2021, a total of 25 patients enrolled on trial. One withdrew before starting BWL, and one withdrew before week 9. Of the 23 currently on study, 20 completed the 2-month visit, and 3 are in the first 8 weeks. Among the 20 participants, majority were Caucasian with ECOG 0 (80%) and postmenopausal (90%). The median age at enrollment was 60.5 [range 40, 73] and many were employed (65%). Most had stage I (70%) and II (20%) breast cancer. The median time from diagnosis to study enrollment was 3.5 years [0.64-9.34]. Over half received mastectomy (55%), chemotherapy (50%) and endocrine therapy (65%); only 10% received anti-Her2 therapy. None used tobacco, and median alcohol consumption was 1.25 [0.14] drinks per week. Mean baseline weight was 213 (SD 32) pounds and mean baseline BMI was 35.4 (5.98). Mean HbA1c was 5.5% (0.47), total cholesterol 200 (22), LDL 114 (24), and triglycerides 126 (65). After 2 months of BWL, 9 (45%) attained ≥ 5% weight loss (FAST-BWL), and 11 (55%) did not (SLOW-BWL). These preliminary results are consistent with our preliminary assumptions. **Conclusions:** Our results suggest that BC survivors with obesity receiving BWL demonstrate a similar proportion of attaining 5% weight loss early on as the non-cancer population with obesity. As target enrollment is 55 patients, updated data will be reported at conference. Understanding initial weight response will inform populations that may benefit from augmentation with anti-obesity medication.

**YIA22-008: Identification of Biomarkers That Predict Responses to Immunotherapy in Merkel Cell Carcinoma**

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Merkel cell carcinoma (MCC) is an aggressive skin tumor with the highest case-by-case fatality rate among all skin cancers. The incidence of MCC is rising rapidly, with projections that the number of cases will increase by 30% from 2013 to 2025. The recent introduction of anti-PD1/PDL1 immunotherapy has revolutionized the treatment of MCC; however, ~50% of patients do not respond. Investigating the mechanisms of response and resistance for otherwise fatal, advanced MCCs is an
important clinical need. We have performed WES and bulk-RNA sequencing on 45 FFPE tumors that underwent anti-PD1/PDL1 immunotherapy. We identified Merkel Cell Polyomavirus status using both immunohistochemistry and alignment to viral genome. We used complementary bioinformatics algorithms on both DNA-Seq and RNA-Seq reads. A match between at least three of the four methods at the two-field resolution was accepted as the haplotypes. We then determined association of certain MHC classes with response or non-response, stratified by viral status. For MHC types associated with response, we used NetMHCPan 4.1 on the viral proteins to determine likely neoantigens. We also calculated the MHC evolutionary divergence score and examined association with response status. We observed that C*04:01 is associated with response in virus positive tumors. It was enriched in responders (5 patients) compared to non-responders (3 patients). We observed the peptide sequence MFDEVSTKF from the MCPyV small T antigen has a 64.62 nM predicted binding affinity and a 0.99 score from NetMHCPan4.1. We also observed that the B*08:01 (1 responder:5 non-responder) and B44 supergroup (2 responders:7 non-responders) are correlated with non-response in virus negative tumors. We found a higher HLA divergence score is associated with better response in both virus positive and virus negative tumors. These results may aid in prognostication of patients with advanced MCCs and may serve as an aid in informed decision making for clinicians.

BEST PRACTICES IN IMPLEMENTATION AND USE OF CLINICAL PRACTICE GUIDELINES

BPI22-014: Independent Validation of the PREDICT Prognostication Tool in U.S. Breast Cancer Patients Using the National Cancer Database (NCDB)

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Background: PREDICT (https://breast.predict.nhs.uk/tool) is an online prognostication tool that was developed and validated using cancer registry information in approximately 6,000 women early stage breast cancer treated in the UK. Predict estimates the impact of different adjuvant interventions on breast cancer mortality including: surgery alone, chemotherapy, trastuzumab, bisphosphonates, and/or endocrine therapy. This validated tool is not widely used in the U.S., and has never been validated using data from breast cancer patients treated in the U.S. Our aim was to conduct an external validation of the PREDICT algorithm in predicting 5 and 10-year overall survival (OS) outcomes using real-world outcomes among breast cancer patients with the NCDB. We hypothesized that the predict UK tool would accurately predict OS outcomes among breast cancer patients in the NCDB. Methods: NCDB was queried for patients with primary invasive breast cancer diagnosed between 2004-2012. Patients with bilateral or metastatic breast cancer, no breast surgery, or missing critical clinical
information were excluded. Prognostic scores were calculated using nhs.predict version 1.4.0. External validity was approached by assessing statistical discrimination through area under the receiver-operator curve (AUC) and calibration comparing the predicted number of deaths to the observed number of deaths in terms of OS in relevant sub-groups. **Results:** A total of 708,652 eligible patients with complete 5-year follow up and 233,455 patients with complete 10-year follow up were identified in NCDB, with median follow up times of 97.7 months and 137.2 months, respectively. AUC statistics for 5 and 10-year OS prediction were 0.772 and 0.778, respectively. Calibration results showed relatively close agreement between predicted and observed deaths (Figure 1). Absolute 5- and 10-year mortality differences between predicted and observed were 0.02%-0.09% and 0.01%-0.11%, respectively although subtle overestimation was observed as anticipated. **Conclusions:** The PREDICT tool was successfully validated using NCDB patient data and accurately predicted 5 and 10-yr OS in a contemporary population of U.S. patients with early-stage breast cancer.

**Background:** Chronic lymphocytic leukemia (CLL) and other Non-Hodgkin’s lymphomas (NHLs) are associated with broad immunosuppression, conferring a greater risk for infection-related morbidity and mortality. During the SARS-CoV-2 pandemic, patients with these conditions have been shown to be more susceptible to severe cases of infection. Vaccination against SARS-CoV-2 generally protects against severe disease, but there is scarce data on immune response in those with lymphoid malignancies. Our study aims to analyze antibody (Ab) response to vaccination against SARS-CoV-2 in patients with CLL, Waldenstrom macroglobulinemia (WM) and other NHLs. **Methods:** 398 patients with lymphoid malignancies seen between January and October 2021 were screened for eligibility. Ab titers using the Access SAR-COV-2 assay developed by Beckman Coulter Inc were obtained after the completion of a vaccination series with Pfizer (n=146), Moderna (n=90), Johnson & Johnson (n=1) or multiple brands (n=3). A response was defined as a positive total Ab or spike protein Ab. Groups were compared using chi-square tests, and a p-value of <0.05 was statistically significant. **Results:** 240 patients with post-vaccination SARS-CoV-2 Ab results were included. Ab response was 50% in CLL, 67% in WM, and 71% in the remaining NHLs. In the CLL cohort (n=181), current or prior cancer therapy at any time led to a lower rate of positive Ab’s compared to treatment-naïve patients (36% vs. 68%; p=0.000019), and response was particularly low in patients who had received anti-CD20 immunotherapy at any time (28% vs. 61%; p=0.000032). There was a trend towards lower Ab response in patients who received anti-CD20 agents within a year from vaccination compared to those who had these therapies more recently.

**Table 1. Antibody Response Rate in CLL, WM and Other NHL after SARS-CoV-2 Vaccination**

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>All Patients</th>
<th>Moderna</th>
<th>Pfizer</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL (n = 181)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ No Treatment (n = 79)</td>
<td>50% (91/181)</td>
<td>68% (54/79)</td>
<td>66% (29/44)</td>
<td>0.60</td>
</tr>
<tr>
<td>▪ Any Treatment (n = 102)</td>
<td></td>
<td>36% (37/102)**</td>
<td>29% (19/68)</td>
<td>0.026</td>
</tr>
<tr>
<td>▪ BTK Inhibitor (n = 76)</td>
<td></td>
<td>33% (25/76)**</td>
<td>23% (11/48)</td>
<td>0.0072</td>
</tr>
<tr>
<td>▪ Anti-CD20 Ab (n = 66)</td>
<td></td>
<td>32% (21/66)**</td>
<td>26% (11/42)</td>
<td>0.19</td>
</tr>
<tr>
<td>▪ BCL-2 Inhibitor (n = 30)</td>
<td></td>
<td>37% (11/30)</td>
<td>29% (9/31)</td>
<td>0.35</td>
</tr>
<tr>
<td>WM (n = 21)</td>
<td>67% (14/21)</td>
<td>88% (7/8)</td>
<td>54% (7/13)</td>
<td>0.11</td>
</tr>
<tr>
<td>Other NHLs (n = 38)</td>
<td>71% (27/38)</td>
<td>80% (8/10)</td>
<td>70% (19/27)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Comparing antibody positivity in respective subgroups among patient who received either the Moderna or Pfizer vaccination. P-value calculated using chi-square testing and a value of < 0.05 is considered statistically significant. **Some patients excluded from subsequent p-value calculation due to receiving doses from different vaccine brands. †Denotes current or prior therapy with specified CLL therapy and antibody response to vaccination. Some patients are included in multiple rows due to receiving multiple classes of treatment.

Ab, antibody; BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; NHLs, non-Hodgkin’s lymphomas; WM, Waldenstrom macroglobulinemia.
than one year prior (20% vs. 37%; p=0.14). For CLL patients, there was a significant difference in Ab response when receiving the Moderna series (61%) compared to Pfizer (44%) (p=0.028). More information is summarized in Table 1. Conclusions: This study provides data from a large cohort of patients with CLL and other NHLs on Ab response to SARS-CoV-2 vaccination. Active or prior therapy for CLL was associated with lower rates of Ab response to vaccination, especially when treated with anti-CD20 therapy, which is consistent with prior publications. However, we also found a significant increase in Ab response rates after Moderna SARS-CoV-2 vaccination in treated CLL patients compared to other vaccine series.

CLO22-056: Phase 1 Trial of Concurrent Nab-Paclitaxel and Cisplatin With Radiotherapy for Locally Advanced Cervical Cancer
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Concurrent chemoradiotherapy using platinum-containing chemotherapy is the treatment of choice for stages IB3-IVA cervical cancer. A preclinical evaluation of the radiation-modulating effects of nab-paclitaxel in tumor showed that nab-paclitaxel acted as a radiosensitizer and produced supra-additive effects when combined with radiation. However, the use of concurrent nab-paclitaxel and cisplatin with radiation has not been tested for cervical cancer. This study aimed to assess the maximum-tolerated dose (MTD) of nab-paclitaxel (Keaill®) in combination with a fixed dose of cisplatin when given concurrently with radiotherapy to patients for locally advanced cervical cancer (LACC). Method: We conducted a single-center, open-label, single-arm, phase I trial (ClinicalTrials.gov Identifier: NCT04017377). We enrolled patients with stage IB2-IVA cervical cancer. Chemotherapy was administered intravenously on day 1 of radiotherapy weekly. Chemotherapy consisted of at least four cycles of cisplatin 40 mg/m2 and nab-paclitaxel with escalating doses (10, 20, 33, 50, 70 mg/m2). Radiotherapy consisted of intensity modulated radiation therapy in a 50.4 Gy in 28 fractions for five days weekly and intracavitary brachytherapy in a 30 Gy in 5 fractions twice a week. Dose escalation followed a 3 + 3 design. The DLT was defined as grade 3 or 4 nonhematologic toxicity, excluding nausea, vomiting and alopecia, decreased appetite and fatigue, or grade 4 hematologic toxicity. Results: This study was initiated in September, 2019, and enrollment ended in August 2021. 22 patients were enrolled. Overall, 4 patients (18.0%) experienced DLTs. A DLT was first observed in 1 of 3 patients at 33 mg/m2 (Grade 3 Hypokalemia) but was not observed in the next 3 patients at the same level. 2 patients experienced DLTs (Grade 3 Vascular access complication) at 50mg/m2 and 70 mg/m2 dose level respectively. Another DLT (Grade 3 Perineum edema) was observed in 70mg/m2 dose level. The MTD of nab-paclitaxel was found at 50 mg/m2/week. Other major side effects included grade 1-3 leukopenia, diarrhea, and nausea/vomiting. All patients were evaluable for response: 20 patients complete and 1 patient partial responses were obtained with an overall response rate of 95.5%. Conclusion: Weekly administration of 50 mg/m2 nab-paclitaxel when associated to cisplatin 40 mg/m2/week and concurrent radiotherapy can be considered a tolerable and clinically feasible for the treatment of LACC.

CLO22-088: Phase II Trial of Trifluridine/Tipiracil in Combination With Irinotecan in Advanced Biliary Tract Cancers (BTCs)
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Purpose: Patients with advanced BTCs have therapeutic options. After progression on gemcitabine and cisplatin, there is no standard of care option available. In our previous phase II trial, we had demonstrated activity with single agent trifluridine/_tipiracil, in advanced, refractory BTCs. Here, we determine the safety and efficacy of trifluridine/Tipiracil in combination with irinotecan in a phase II trial setting for refractory, advanced unresectable BTCs. Methods: In this single-arm, open-label phase II clinical trial, 28 patients (27 evaluable patients) were enrolled and were treated with: trifluridine/Tipiracil is 25 mg/m2 (days 1-5 of 14-day-cycle) and irinotecan 180 mg/m2 (day 1 of the 14-day cycle). The primary endpoint for the study was 16-week PFS rate. 2-stage Simon design was used for early stopping for futility, where 6 or more successes in first 25 evaluable patients would be a successful trial. This study had 80% power to detect a true 16-week PFS rate of 30%, with a 5% significance level when the true 16-week PFS rate is 10%. Patients with BTCs who had progressed on at least one line of systemic therapy were eligible. Pre-treatment biopsies were performed for organoid development. Results: The median age was 68 years and subtypes were intrahepatic (59%), extrahepatic (33%) and gallbladder cancer (8%). No. of prior lines of therapies included: 1 (37%), 2 (41%), 3 (22%). 16-week PFS was 37% (10/27; 95% CI: (19-58%)), thereby meeting the criteria for success for the primary endpoint. The ORR and DCR were 20% and 45%, respectively. Median OS was 52.6 weeks (95% CI: 33.6-NE). The most common grade 3/4 toxicities were neutropenia (29%), lymphopenia (15%), hypertension (15%), thrombocytopenia (11%), elevated alkaline phosphatase (11%),
fatigue (7%), and diarrhea (7%). 9 out of 27 (33%) and 14/27 (52%) had dose reductions secondary to AEs (cytopenias and fatigue) for trifluridine/tipiracil and irinotecan, respectively and 1 patient discontinued the therapy due to adverse events. **Conclusions:** The combination of trifluridine/tipiracil plus irinotecan is a safe and efficacious treatment for refractory metastatic and unrespectable BTCs. PFS and OS outcomes are promising compared to previous trials in advanced BTCs. A larger randomized trial is needed to confirm these results. This study was approved and funded in part by the NCCN Oncology Research Program from general research support provided by Taiho Oncology, Inc.

**OUTCOMES AND HEALTH SERVICES RESEARCH**

**HSR22-163: Real World Data and Independent Predictors of Clinical Outcomes With CDK Inhibitors in Metastatic ER+ Breast Cancer Patients**

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**Background:** Cyclin-dependent kinase 4/6 inhibitors (CDKI) with endocrine therapy (ET) are the standard of care in hormone receptor-positive (HR+) metastatic breast cancer (MBC). However, real world data can corroborate progression free survival (PFS) and overall survival (OS) benefits outside of clinical trials and identify independent prognostic factors. **Methods:** A retrospective review was performed in 269 patients with HR+ MBC treated with a CDKI. OS was measured from the date of start of CDKI to the date of death or last follow-up. PFS was measured from the date of start of CDKI to progression or death, whichever occurred earlier, and to the date of last follow-up for survivors without progression. Survivor distribution and difference in OS/PFS was examined by Kaplan-Meier and log-rank tests. The effects of liver lesions and bone-only disease in OS/PFS was estimated after controlling for age and de novo MBC using multivariable Cox regression model. **Results:** Median PFS and OS for the entire cohort were 21.5 months and 57.6 months, respectively. 84.1% of patients with bone-only disease were alive at 60 months compared to 41.8% in patients with mixed bony and visceral metastases (p=0.004). Similarly, patients with bone-only disease were significantly more likely to be progression free at 60 months (34% vs 13.8%, p=0.0003). Bone-only disease was an independent predictor of more favorable PFS (HR 0.48, 95% CI 0.31-0.74, p=0.001) and OS (HR 0.38, 95% CI 0.18-0.79, p=0.01). Patients with liver metastases prior to starting CDKI were less likely to be alive at 60 months compared to patients without liver metastases (26.1% vs. 59.8%, p=0.0008). Similarly, 48-month PFS was significantly lower in patients with liver metastases vs. those without them at 7.7% and 30.3% respectively (p<0.001). On MVA, the presence of liver metastases was an independent predictor of inferior PFS (HR 2.53, 95% CI 1.76-3.62, p<0.0001) and OS (HR 2.24, 95% CI 1.35-3.74, p=0.002). By contrast, no significant differences in PFS or OS were observed by age, race, or type of CDKI utilized. **Conclusions:** In our study, patients treated with CDKIs had observed median OS/PFS comparable to those reported in clinical trials, thus further supporting their use in a real-world population. Patients with bone-only disease and liver metastases represent clinical entities at opposite extremes for PFS/OS and are independent prognostic predictors.

**HSR22-174: Are We ‘Choosing Wisely’? A Case of Unnecessary Staging Imaging in Older Patients With Prostate Cancer**

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**Background:** In April 2012, the American Society of Clinical Oncology launched Choosing Wisely (CW) recommendations with the aim to enhance the value of cancer care by reducing the use of low-value services. One of the CW recommendations is to not use imaging procedures for the staging in early-stage prostate cancer patients who are at low risk of developing metastasis. In this study, the impact of CW on staging imaging in older early-stage prostate cancer patients was assessed. **Methods:** Using the Surveillance Epidemiology, and End Results-Medicare linked database, a retrospective cohort study was conducted for men age >66 years diagnosed with less than T1c/T2a or T2 not otherwise-specified incident prostate cancer with Gleason score of ≤6 or prostate specific antigen level of ≤10 ng/ml during 2007-2015 (N=55,705). The proportion of patients who received at least one staging imaging procedure including Positron Emission Tomography, Computerized Tomography, and radionuclide bone scans in three months prior to three months following cancer diagnosis were identified. An interrupted time-series (ITS) analysis and segmented regression were conducted to evaluate the impact of CW on the rate of staging imaging use. A sensitivity analysis was performed by identifying at least one claim of staging imaging procedure expanding to six months following cancer diagnosis. **Results:** Half of older men enrolled in Medicare (50.4%) received staging imaging pre-CW compared to 43.7% post-CW. From the ITS analysis, it was found that there was a significant 0.18% point per quarter reduction in the rate of staging imaging use pre-CW (p<0.0001). There was a continued decline of 1.02% point per quarter immediately post-CW implementation. There was a significant 0.31% point per quarter decrease in the rate of staging imaging use due to CW program (p<0.0001). Sensitivity analyses
showed that 55.0% of men received staging imaging pre-CW while the percentage dropped to 48.1% post-CW. ITS analysis showed a significant 0.25% point per quarter decline in the rate of staging imaging use resulting from CW program (p < 0.0001). **Conclusion:** The ASCO’s CW recommendation of not to use staging imaging in patients with early-stage prostate cancer coincided with a significant decline in the use of unnecessary staging imaging procedures post-CW. Our study findings demonstrate that ASCO’s CW is a powerful strategy to enhance value-based cancer care in patients with early-stage prostate cancer.

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**PRE-Clinical Oncology**

**PCL22-188: Reuterin in the Healthy Gut Microbiome Suppresses Colorectal Cancer Growth Through Altering Redox Balance**

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**Background:** Alterations of the intestinal microbiome are common in colorectal cancer (CRC) patients and stage-specific shifts have been identified within the microbiota of CRC patients. We interrogated bacterial-derived metabolites to evaluate their therapeutic potential in CRC. **Methods:** The work utilizes patient samples, cell lines and mouse models. The study was approved by the institutional review board, biosafety committee, and unit for laboratory animal care at the University of Michigan.

**Results:** Fecal metabolites isolated from healthy patients and wild-type mice suppressed proliferation of CRC cells, but metabolites isolated from CRC patients and CRC mice induced no significant change to CRC cell proliferation. An untargeted metabolomics identified the most abundant microbial metabolites in wild-type mice and the fifty most abundant bacterial-derived metabolites were screened based on inhibition of cell proliferation. Reuterin, produced by Lactobacillus reuteri, was found to be the most potent inhibitor of growth and microbial profiling revealed that Lactobacillus reuteri and its metabolite, reuterin, are downregulated in both murine and human CRC. In a broader survey of cancer-cell lines, reuterin was shown to potently inhibit proliferation and induce cell death of CRC, lymphoma, ovarian, melanoma, and pancreatic ductal adenocarcinoma cells, but not in noncancerous human colon cells. A multiomics approach including metabolomics, transcriptomics, and proteomics revealed reuterin treated CRC cells had an upregulated oxidative stress response and enriched glutathione metabolism. Reactive oxygen species were found to increase in a dose-dependent manner in CRC cells following reuterin treatment, but not in normal colon cells. Implanted tumors from both mouse and human colon cancer cell lines, as well as a sporadic genetic model of colon cancer, had reduced growth, reduced Ki67 expression, and increased reactive oxygen species in mice gavaged with L. reuteri, but not L. reuteri genetically engineered to not produce reuterin.

**Conclusion:** Advanced CRC tumors have an altered metabolome that permits cancer growth. We identified a commensal species Lactobacillus reuteri that is reduced in mouse and human colon cancer. L. reuteri potently reduces colon cancer growth in syngeneic and sporadic models without toxicity and is an excellent translational candidate.