

# Abstracts From the NCCN 23rd Annual Conference: Improving the Quality, Effectiveness, and Efficiency of Cancer Care™

The following abstracts were accepted for presentation at the NCCN 23rd Annual Conference: Improving the Quality, Effectiveness, and Efficiency of Cancer Care™ General Poster Session at the Rosen Shingle Creek resort in Orlando, Florida, on March 22 and 23, 2018. Additional abstracts will be available at JNCCN.org.

## Best Practices in Implementation and Use of Clinical Practice Guidelines

### AB2018-1. Impact of Adherence to NCCN Guidelines on Resource Use and Survival in Patients With Non–Small Cell Lung Cancer

Allicia Girvan, PhD<sup>a</sup>; Manasi Datar, PhD<sup>b</sup>; Kristin Sheffield, PhD<sup>a</sup>; Sheetal Sheth, PharmD<sup>b</sup>; Pravin Kamble, PhD<sup>b</sup>; Radhika Nair, PhD<sup>b</sup>; Stewart Wetmore, PharmD<sup>a</sup>; Gebra Cuyun Carter, PhD<sup>a</sup>; and Lee Bowman PhD<sup>a</sup>

<sup>a</sup>Eli Lilly and Company, Indianapolis, IN; and <sup>b</sup>Humana, Louisville, KY

**Background:** NCCN Guidelines help establish practice standards and inform population-based decision-making. The goal of this study was to assess the impact of NCCN Guideline adherence on resource use and survival in patients with stage III and IV non–small cell lung cancer (NSCLC). Guidelines for the study included pretreatment evaluation, receipt of *EGFR* and *ALK* testing for patients with nonsquamous NSCLC, and performance status (PS)–aligned initial therapy for patients with squamous NSCLC. **Methods:** Retrospective claims data were used from a large US national health plan with a high proportion of patients enrolled in Medicare Advantage Prescription Drug (MAPD) plans. Adults newly diagnosed with lung cancer between 2012 and 2015 were included. Non-claims clinical data sources were used to confirm NSCLC diagnosis and identify staging and histology. Logistic regression and negative binomial procedures were used to evaluate predictors of adherence to NCCN Guidelines and resource use, respectively. Survival was evaluated (MAPD only) using Cox proportional hazards model. **Results:** The adherence rate for pretreatment evaluation (n=922), receipt of *EGFR* and *ALK* testing (n=730), and PS-aligned initial therapy (n=192) was 88.2%, 43.8%, and 49.0%, respectively. Increased comorbidity scores were associated with lower odds of adherence to receipt of *EGFR* and *ALK* testing (odds ratio [OR], 0.53; 95% CI, 0.34–0.83) and PS-aligned initial therapy (OR, 0.23; 95% CI, 0.07–0.74). Patients with stage IV NSCLC had higher odds of receipt of *EGFR* and *ALK* testing (OR, 1.94; 95% CI, 1.27–2.95) compared with patients with stage III disease. Adherence to pretreatment evaluation did not have

a significant impact on any resource use. Adherence to PS-aligned initial therapy was associated with 28.0% fewer hospitalizations ( $P=.004$ ), 36.0% fewer emergency department visits ( $P=.001$ ), and improved survival (hazard ratio, 0.40; 95% CI, 0.26–0.62). Adherence to receipt of *EGFR* and *ALK* testing was associated with a 10.0% increase in outpatient visits ( $P=.022$ ). **Conclusions:** Although this study did not reveal predictors of adherence to NCCN Guidelines, potentially due to limited sample size, it demonstrated that adherence is associated with better resource use and improved survival in patients with NSCLC. Physicians should incorporate NCCN Guidelines in decision-making and maintain guideline adherence when caring for patients with NSCLC in practice settings.

### AB2018-2. Immune Checkpoint Inhibitors Versus Antiangiogenic Therapies in Advanced Non–Small Cell Lung Cancer: Bayesian Network Meta-Analysis of Severe Adverse Events

Ching-I Hsu, BS<sup>a</sup>; Jia-Lian Yang, PhD<sup>b</sup>; and Chin-Chuan Hung, PhD<sup>b,c</sup>  
These authors contributed equally.

<sup>a</sup>China Medical University Beigang Hospital, <sup>b</sup>College of Pharmacy, China Medical University, and <sup>c</sup>China Medical University Hospital, Taichung, Taiwan

**Background:** Lung cancer is the leading cause of cancer death worldwide. Non–small cell lung cancer (NSCLC) is the most commonly diagnosed cancer, often diagnosed as advanced stage. Tolerability is an essential treatment selection criterion for patients with advanced stage. Recently, immune checkpoint inhibitors (nivolumab, pembrolizumab, and atezolizumab) and antiangiogenic agents (bevacizumab, ramucirumab, and nintedanib) have become the preferred therapies for this patient population. However, which treatment is more tolerable remains unknown due to lack of a direct comparison. A systematic review was performed to compare severe adverse events (AEs) of first-line and subsequent lines of therapy in NSCLC using Bayesian model network meta-analysis (NMA). **Methods:** PubMed, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched to July 2017 for randomized controlled trials that compared first-line

and subsequent regimens containing chemotherapy (cisplatin, carboplatin, oxaliplatin, gemcitabine, paclitaxel, docetaxel, and pemetrexed), antiangiogenic agents (bevacizumab, aflibercept, ramucirumab, nintedanib, axitinib, sorafenib, vandetanib, and sunitinib), and immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab, and atezolizumab). Studies and associated data were independently extracted by 2 authors. Direct and indirect data for CTCAE grades 3–5 were combined using random-effects NMA. The GeMTC R package was used to calculate the combined odds ratios (OR) and 95% credible intervals (CrIs). **Results:** A total of 37 trials containing 16,810 patients were included. Combining direct and indirect effects showed decreased toxicity in nivolumab and pembrolizumab compared with the combination of sorafenib and platinum doublets (combined OR, 0.08; 95% CrI, 0.01–0.51, combined OR, 0.12; 95% CrI, 0.02–0.79). In terms of subsequent therapy, use of nivolumab was associated with a lower risk than most antiangiogenic therapies. Specifically, lower toxicity was demonstrated in nivolumab compared with combination ramucirumab/docetaxel and combination nintedanib/docetaxel (combined OR, 0.06; 95% CrI, 0.02–0.27, and combined OR, 0.08; 95% CrI, 0.02–0.38). **Conclusions:** Our results indicated that immune checkpoint inhibitors can be the preferred choices due to less toxicity in the treatment of advanced stage NSCLC compared with antiangiogenic therapies in the first-line and subsequent settings.

### AB2018-3. 2017 Analysis of NCCN Non–Small Cell Lung Cancer Clinical and Affordability Evidence Blocks

Shirley Nguyen Quach, PharmD; Ellen Yang, PharmD; and Kyle Downey, PharmD, MS  
Genentech, Inc., San Francisco, CA

**Background:** The NCCN Evidence Blocks are intended as a visual representation of 5 key measures to provide physicians and patients with an assessment of the variables that factor into determining a treatment regimen based on the NCCN Guidelines. Our analysis observes trends between evidence blocks ratings and category ratings for regimens in the NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC). **Methods:** The sum of efficacy (E), safety (S), quality (Q), and consistency (C) scores—ESQC sum—was calculated for each regimen, and the regimen's category recommendation was extracted from NCCN Guidelines and Evidence Blocks, version 4.2017. Category recommendations and ESQC sums were compared to determine whether higher category ratings are consistent with higher overall ESQC sum. Monthly drug cost was calculated using wholesale acquisition costs (WAC) obtained

from AnalySource (January 19, 2017) and plotted against affordability evidence block scores for each regimen to determine the relationship between cost and affordability scores. **Results:** Table 1 displays the number of NSCLC regimens by category ratings and the associated average and range of ESQC sum at a disease-state level. Higher ESQC sum averages trend toward higher category ratings, although the difference is minimal. When breaking down the regimens, driver-mutation therapies scored higher ranges and averages than non-driver-mutation therapies. Non-driver-mutation therapies were further analyzed based on histology of non-squamous versus squamous populations. Both histology groups showed overlap in ESQC sum between category recommendations. Regimens with similar monthly cost were rated different affordability scores. Monotherapy and combination therapies received contradictory affordability ratings. Results and graphs were presented at the NCCN 23rd Annual Conference. **Conclusions:** At a disease-state level, higher averages of ESQC sum trend toward higher category recommendations in NSCLC; however, the overall difference was minimal and variations arise at a granular level. There are observed inconsistencies between affordability scores and monthly drug cost. A limitation of the affordability analysis is that it only compared monthly WAC price and does not account for factors such as wastage and administration cost. Additional findings were presented at the NCCN Annual Conference.

AB2018-3: Table 1. Category Ratings to Range of ESQC Sum and ESQC Average: All Regimens

Category Rating	Number of Regimens	Average ESQC Sum	ESQC Sum, Range
1	39	14.5	11–19
2A	41	13.7	11–19
2B	4	12.8	11–16

### Epidemiology/Risks

#### AB2018-5. Proportion of Women Aged 65 Years or Older With HR-Positive/HER2-Negative Metastatic Breast Cancer That May Be at Risk of QT Prolongation in Large US Healthcare Databases

Timothy Bell, MHA<sup>a</sup>; Melea Ward, PharmD, PhD<sup>b</sup>; Jeffrey N. Trocio, MPH<sup>a</sup>; James Harnett, PharmD, MS<sup>a</sup>; and Jack Mardekian, PhD<sup>a</sup>

<sup>a</sup>Pfizer, Inc., New York, NY; and <sup>b</sup>Humana, Inc., Louisville, KY

**Background:** Metastatic breast cancer (MBC) remains incurable and presents a significant unmet medical need. Treatment selection for MBC is based on biomarkers, including hormone-receptor (HR) and HER2 status, and individual patient and clinical characteristics. Women with MBC may also have comorbidities

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or take medications that are known risk factors of QT prolongation, potentially informing treatment selection. **Objectives:** To estimate the proportion of women aged  $\geq 65$  years with HR+/HER2- MBC that may be at risk of developing QT prolongation. **Methods:** This was a retrospective cohort study utilizing the Truven Health MarketScan (TM) and Optum Clinformatics (OC) administrative claims databases to characterize baseline demographic and clinical characteristics of women with presumed HR+/HER2- MBC. The index date was defined by the first date of secondary neoplasm diagnosis. Patients' pharmacy and medical data were evaluated during the baseline period (ie, the 12-month period before MBC diagnosis) to assess risk of QT prolongation. Medications that can cause QT prolongation were evaluated within 7 days before index. Additionally, ICD-9/10-CM codes were evaluated 12 months before the index date to describe congenital long QT syndrome, cardiac disease, and electrolyte abnormalities. **Results:** There were 5,294 and 5,128 women aged  $\geq 65$  years with HR+/HER2- MBC within TM and OC, respectively, between January 2011 and March 2017. Mean (SD) age at MBC diagnosis was 75.3 (6.9) years, with 94% enrolled in Medicare. Of the 10,422 patients overall, 7.6% received a medication that can cause QT prolongation; 0.1% had a diagnosis of long QT syndrome, 18.0% had evidence of cardiovascular disease, and 9.0% had diagnosed electrolyte abnormalities. Overall, 29.0% had a comorbidity or were taking a concomitant medication that may increase the risk of developing QT prolongation. **Conclusions:** Real-world data of women aged  $\geq 65$  years with HR+/HER2-MBC demonstrated that approximately one-third are taking concomitant medications or have baseline comorbidities that increase the risk of developing QT prolongation. This analysis supports the need for pharmacy and therapeutics committee coverage policies to consider the prevalence of comorbid conditions and concomitant medications that may preclude use of specific treatments based on prescribing information in the United States.

#### Outcomes and Health Services Research

##### AB2018-6. Evaluating the Budget Impact of Nivolumab as Treatment for Advanced Hepatocellular Carcinoma

Richard Kim, MD<sup>a</sup>; Prianka Singh, PharmD<sup>b</sup>;  
Beata Korytowski, MS<sup>b</sup>; Tami Wisniewski, MPH<sup>b</sup>;  
Siguroli Teitsson, MSc<sup>c</sup>; and Meena Venkatachalam, MSc<sup>c</sup>

<sup>a</sup>Moffitt Cancer Center, Tampa, FL; <sup>b</sup>Bristol-Myers Squibb, Princeton, NJ; and <sup>c</sup>PAREXEL International, London, United Kingdom

**Background:** Nivolumab is FDA-approved in the United States for the treatment of patients with advanced hepatocellular carcinoma (HCC) previously

	Year 1	Year 2	Year 3	Years 1-3
Total budget impact, scenario without nivolumab regimens	\$627,183	\$755,166	\$859,997	\$2,242,346
Total budget impact, scenario with nivolumab regimens	\$628,579	\$760,304	\$858,600	\$2,247,483
Total incremental cost	\$1,397	\$5,137	-\$1,397	\$5,137
Budget impact	0.2%	0.7%	-0.2%	0.2%
Incremental cost PMPM	\$0.0001	\$0.0004	-\$0.0001	\$0.0001
Incremental cost PPTPM treated	\$11	\$39	-\$11	\$13

treated with sorafenib. We aimed to evaluate the financial implications of establishing nivolumab as a treatment option for patients with advanced HCC from a US payer perspective. **Methods:** A budget impact analysis was used to estimate the total incremental budget impact of adding nivolumab as a treatment option for second-line (2L) advanced HCC over a 3-year time horizon. The analysis included best supportive care and regorafenib as comparators. The base case was based on a US private health plan population of 1 million members, of which an estimated 11 patients were eligible for 2L treatment per year. Drug acquisition (Medi-Span Price Rx; September 2017), administration, adverse event (AE) management, monitoring, and subsequent treatments costs were included in the analysis. The analysis included grade 3/4 AEs that had  $\geq 10\%$  incidence reported for any comparator. AEs and frequencies were taken from CheckMate-040 for nivolumab and RESORCE for comparators. Without nivolumab, the market share is assumed to be split between best supportive care and regorafenib; in a scenario with nivolumab, uptake is assumed to be 33% in year 1 and 17% in years 2 and 3. **Results:** In the 2L advanced HCC setting, the budget impact of introducing nivolumab ranged from increases of \$1,397 and \$5,137 in years 1 and 2, respectively, to a cost savings of \$1,397 in year 3 for an eligible population of 11 patients. During the 3-year time horizon, the budget impact equated to a 0.2% budget impact or \$0.0001 per member per month (PMPM) and \$13 per patient treated per month (PPTPM). Cost savings in year 3 were primarily related to AEs and drug acquisition. Details are shown in Table 1. **Conclusions:** Based on this analysis, there was a cost savings to payers by year 3 after the addition of nivolumab as 2L treatment for advanced HCC.

The results of this analysis should be considered in the context of the unmet need for treatment options in this patient population.

**AB2018-7. Health Outcomes of Uninsured Patients With Cancer: A Retrospective Study of Free Clinic Patients in Tampa, Florida**

Abu-Sayef Mirza, MD, MPH<sup>a</sup>; Noura Ayoubi, BS<sup>a</sup>; Aldenise Ewing, PhD<sup>a</sup>; Michael Jaglal, MD<sup>b</sup>; and Smitha Pabbathi, MD<sup>c</sup>

<sup>a</sup>University of South Florida, <sup>b</sup>Tampa General Hospital, and <sup>c</sup>Moffitt Cancer Center, Tampa, FL

**Background:** Limited research is available on the health outcomes and screening practices of uninsured patients who have been diagnosed with cancer. Free clinics manage patients with a diversity of diseases, but few studies document the prevalence of surveillance. Cancer survivors are already at increased risk for poor health outcomes due to the physical and psychosocial effects of cancer diagnosis and treatment. Cancer screening use has been suspected to be lower in the uninsured population. This study examines the screening utilization of cancer survivors in free clinics. **Methods:** Data involving demographics and chronic disease measures were extracted from medical charts of patients managed in 8 free clinics from January to December 2016 in the Tampa Bay Area. Proportion for prevalence, logistic regression adjusted odds ratio, and 95% confidence intervals for associations between participant characteristics and cancer diagnoses and screening practices are reported. **Results:** In 2016, 4,804 uninsured patients were managed in 8 free clinics. From manual chart review, 86 patients (1.7%) were identified as diagnosed with cancer and 3,318 (69.1%) were identified as having no history of cancer. The patients with cancer were mostly female (65.1%) and had an average age of 54.37 years (SD, 13.42), significantly greater than patients without cancer ( $P<.001$ ). Most common malignancies included breast (19, 22.09%), prostate (8, 9.30%), melanoma (6, 6.97%), cervical (5, 5.81%), colon (5, 5.81%), squamous carcinoma (5, 5.81%), ovarian (4, 4.65%), and lung cancer (4, 4.65%). The average length of survival was approximately 8.53 years (SD, 7.55). Regarding prevention practices among patients with cancer history, 26 (30.2%) patients completed routine breast cancer screening, 17 (19.8%) routine Papanicolaou smears, 11 (12.8%) colonoscopies. These were all significantly higher rates of screening than for patients without known cancer history ( $P<.001$ ). **Conclusions:** Uninsured patients from free clinics are considered outside the health care system and represent a unique population that is understudied in the literature. The most common malignancies identified in free clinics

correlate with national epidemiology. Rates of screening practices were significantly higher in uninsured patients with cancer compared with uninsured patients without cancer. However, these screening rates are lower than nationally expected guidelines focused on quality primary prevention. Throughout the free clinic population, screening rates are lower compared with age-equivalent counterparts with employment-based health insurance.

**AB2018-8. Self-Reported Health Status and Health Behaviors of Cancer Survivors by Cancer Types: A Behavioral Risk Factor Surveillance System Study**

Andrew K. Rock, MHS, MS<sup>a</sup>; Maria Hadjikyriakou, MD<sup>b</sup>; and William C. Broaddus, MD, PhD<sup>a</sup>

<sup>a</sup>Virginia Commonwealth University, Richmond, VA; and <sup>b</sup>Inova Behavioral Health Services, Inova Fairfax Hospital, Falls Church, VA

**Background:** This study compared self-reported health status and health behaviors among survivors of 30 different types of cancer versus noncancer controls from the 2009 Behavioral Risk Factor Surveillance System (BRFSS). **Methods:** Participants from the 2009 BRFSS were classified as cancer survivors or noncancer controls. Descriptive statistics, chi-square tests, and multivariable logistic regression assessed self-reported health status and health behaviors by cancer diagnosis. **Results:** Of the 351,612 respondents, 41,293 were cancer survivors (11.7%). The most common types of cancer were nonmelanoma skin (NMSC; 23.4%), breast (15.9%), and prostate (10.9%). Self-reported health status and health behaviors varied by cancer type. Cancer types associated with self-reported health status had higher odds of poor overall health, frequent physical and mental distress, and frequent impaired activity. Survivors of cervical (odds ratio [OR], 1.64; 95% CI, 1.28–2.12;  $P<.001$ ) and lung (OR, 1.81; 95% CI, 1.14–2.87;  $P=.01$ ) cancer reported poorer life satisfaction. Survivors of breast cancer (OR, 0.72; 95% CI, 0.60–0.88;  $P=.001$ ), melanoma (OR, 0.78; 95% CI, 0.62–0.97;  $P=.03$ ), and NMSC (OR, 0.68; 95% CI, 0.58–0.79;  $P<.001$ ) had lower odds of poor social and emotional support. Frequent sleep problems occurred in survivors of bladder (OR, 1.37; 95% CI, 1.03–1.83;  $P=.03$ ), cervical (OR, 1.76; 95% CI, 1.53–2.04;  $P<.001$ ), colon (OR, 1.45; 95% CI, 1.16–1.81;  $P=.001$ ), lung (OR, 1.38; 95% CI, 1.02–1.86;  $P=.04$ ), ovarian (OR, 1.60; 95% CI, 1.17–2.19;  $P=.003$ ), and other (OR, 1.36; 95% CI, 1.14–1.62;  $P=.001$ ) cancers and leukemia (OR, 1.58; 95% CI, 1.05–2.38;  $P=.03$ ). Cigarette use was more likely in bladder (OR, 1.93; 95% CI, 1.39–2.68;  $P<.001$ ), cervical (OR, 2.83; 95% CI, 2.44–3.27;  $P<.001$ ), and liver (OR, 2.03; 95% CI, 1.01–4.08;  $P=.047$ ) cancer survivors, although cancer

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type was not associated with smokeless tobacco use. Heavy alcohol use was more likely among cervical cancer (OR, 1.54; 95% CI, 1.15–2.06;  $P=.004$ ) and NMSC (OR, 1.38; 95% CI, 1.17–1.63;  $P<.001$ ) survivors. NMSC (OR, 0.81; 95% CI, 0.74–0.88;  $P<.001$ ) was the only cancer type associated with lower odds of lack of physical activity/exercise. Survivors of stomach cancer (OR, 2.12; 95% CI, 1.19–3.78;  $P=.01$ ) were found to have a low fruit and vegetable intake. **Conclusions:** This study demonstrates that the relationship between cancer survivorship and self-reported health status and health behaviors depends on the type of cancer diagnosis. These findings should be considered in interventions aimed at improving the quality of life of cancer survivors.

#### AB2018-9. PD-L1 Testing Patterns in Stage IV Non-Small Cell Lung Cancer: Interim Analysis of a Prospective Study

Viralkumar Vaghani, MBBS<sup>a</sup>; Sheenu Chandwani, PhD<sup>b</sup>; Meita Hirschmann, MD<sup>a</sup>; Dibaj Seyedeh, PhD<sup>a</sup>; Lara Lacerda, PhD<sup>a</sup>; Emily Roarty, PhD<sup>a</sup>; Jianjun Zhang, MD, PhD<sup>a</sup>; Waree Rinsurongkawong, PhD<sup>a</sup>; Jeff Lewis, PhD<sup>a</sup>; Thomas Burke, PhD<sup>b</sup>; Jack Lee, PhD<sup>a</sup>; Jack Roth, MD<sup>a</sup>; Stephen Swisher, MD<sup>a</sup>; John Heymach, MD, PhD<sup>a</sup>; and George Simon, MD<sup>a</sup>

<sup>a</sup>University of Texas MD Anderson Cancer Center, Houston, TX; and <sup>b</sup>Merck & Co., Inc., Rahway, NJ

**Background:** Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Most patients are diagnosed with advanced-stage disease, for which cures are elusive. The current FDA-approved biomarker for checkpoint inhibitors in NSCLC is PD-L1 expression as measured by IHC 22C3 pharmDx (Dako, Inc.). In our ongoing prospective observational study, we analyzed the PD-L1 testing patterns in stage IV NSCLC at a tertiary referral cancer center. **Methods:** Patients with stage IV NSCLC initiating treatment at MD Anderson Cancer Center beginning January 1, 2017, were enrolled in the Advanced Non-Small Cell Lung Cancer Holistic Registry (ANCHoR). As of June 30, 2017, a total of 76 patients consented for the ANCHoR study and were included in this interim analysis. Patient demographic, clinicopathologic, molecular, and treatment data were populated in a prospective database. Descriptive statistics were used to examine patient characteristics, PD-L1 testing rates, type of assay used, reason for nontesting, and tumor proportion score (TPS). **Results:** Of the 76 patients, 52.6% were male, 85.5% were white, 43.4% were aged  $\geq 65$  years, 73.7% were smokers (current or former), 80.3% had an initial stage IV diagnosis, 86.8% had nonsquamous histology, 27.3% had bone metastasis, 22.1% had brain metastases, and 71.5% had a performance status of 0–1. A total of 82.9% patients (63/76) were tested for PD-L1; 13.1% (10/76)

were not tested (7 due to absence of test order by the treating physician, and 3 due to lack of enough tissue), and 3.9% (3/76) had an unknown testing status. The IHC 22C3 pharmDx assay was used in 79.4% (50/63) of tested patients; 2 were tested using Ventana SP142 assay, 1 was tested using Ventana SP263 assay, and 10 had an unknown assay. PD-L1 TPS was  $<1\%$  in 34.9%, TPS 1%–49% in 39.7%, and TPS  $\geq 50\%$  in 25.4% of patients. The PD-L1 testing rate was 93.9% in male smokers and 76.2% in female smokers (exact  $P=.017$ ). **Conclusions:** Overall, PD-L1 testing rates were high in this patient population that sought care at a tertiary referral cancer center. The predominant method used for testing was Dako 22C3 IHC assay, male smokers were more likely to be tested than female smokers, and the predominant reason for nontesting was absence of order from physician. To eliminate the discrepancy in testing, we propose that PD-L1 should be a part of reflex testing for all patients with metastatic NSCLC.

#### AB2018-10. Economic Impact of Skeletal-Related Events in Patients With Multiple Myeloma

Sikander Ailawadhi, MD<sup>a</sup>; Rohan Medhekar, PhD<sup>b</sup>; Nicole Prinicic, MS<sup>c</sup>; Robert Fowler, MS<sup>d</sup>; Oth Tran, MA<sup>e</sup>; and Sumeet Panjabi PhD<sup>f</sup>

<sup>a</sup>Mayo Clinic, Jacksonville, FL; <sup>b</sup>Amgen, Inc., Los Angeles, CA; <sup>c</sup>Truven Health Analytics, Cambridge, MA; <sup>d</sup>Truven Health Analytics, Bethesda, MD; <sup>e</sup>Truven Health Analytics, San Francisco, CA; and <sup>f</sup>Amgen, Inc., San Francisco, CA

**Background:** As multiple myeloma (MM) progresses, patients experience bone-related complications, known as skeletal-related events (SREs). Real-world data on healthcare resource use (HRU) and costs of SREs in patients with MM are limited. This analysis compared HRU and costs between patients with MM  $\pm$  SREs in a large insured US population. **Methods:** This retrospective cohort study using MarketScan (Truven Health) administrative claims databases included adults (aged  $>18$  years) with a first MM diagnosis between July 1, 2006 and September 30, 2015. SREs were identified as spinal cord compression, pathologic fracture, and radiation or surgery to bone after MM diagnosis (earliest SRE = index). Continuous health plan enrollment for 12 months before and a minimum of 1 month after index was required for eligibility. Patients were followed until the end date of disenrollment, death, or study end. Average per-patient per year (PPPY) HRU and costs were compared (using appropriate statistical tests) between patients with SRE versus propensity score-matched patients without SREs. **Results:** There were 3,116 patients each in the SRE and matched non-SRE cohort (mean age: 66 years; male: 54%–55%). Average time [SD] from MM diagnosis to first SRE was 8.1 [15.4] months, and the mean number of SREs per pa-

tient was 3.1 [3.2]. Total healthcare costs PPPY were significantly higher for patients with SREs compared with those without SREs (mean, \$191,926 [\$199,209] vs \$87,646 [\$126,530];  $P < .001$ ). Higher total costs were driven by increased HRU and costs for all categories (Table 1). The PPPY SRE-related healthcare costs were \$29,340 [\$97,313], \$36,389 [\$86,021], and \$47,285 [\$92,309] for patients with 1, 2, and  $\geq 3$  events, respectively. **Conclusions:** Patients with MM who develop SREs incur significantly higher costs and HRU compared with age-, sex-, and comorbidity-matched patients; the cost burden increases with the number of events. Prophylactic and concurrent management of bone complications with approved therapies is key to the management of SREs in patients with MM.

AB2018-10: Table 1. HRU and Costs		
Healthcare costs*; mean [SD]	SRE	Non-SRE
Inpatient	\$70,077 [\$142,095]	\$23,080 [\$62,036]
Outpatient	\$84,781 [\$97,983]	\$43,620 [\$83,644]
Pharmacy	\$37,069 [\$40,351]	\$20,946 [\$36,426]
HRU frequency*; mean [SD]		
Hospitalizations	1.7 [2.3]	0.7 [1.4]
Physician office visits	24.1 [15.3]	17.0 [12.7]
Hospital outpatient services	123.5 [214.3]	61.9 [206.1]
Emergency room visits	1.7 [3.2]	1.0 [3.6]
Prescriptions	53.7 [33.6]	39.4 [30.8]

\*All  $P < .001$ .

### Pre-Clinical Oncology

#### AB2018-11. Anti-Folate Receptor Antibody Directed, Antibody-Drug Conjugate Induces Autophagy Cell Death in High-Grade Serous Ovarian Cancer

Yunfei Wen, PhD; Faith Bartsch, BS; Cristina Ivan, PhD; and Anil K. Sood, MD

The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Cancer cells are highly dependent on folate metabolism for DNA replication, which is initiated by folate receptor 1 (FOLR1), a 38kDa GPI-anchored protein. **Methods:** We queried the Cancer Cell Line Encyclopedia database (TCGA) and found high *FOLR1* gene expression and association with worse disease-progression survival in patients with high-grade serous ovarian carcinoma (HGSOC), the most aggressive subtype of ovarian cancer. Previous studies have shown a novel autophagic cell death mechanism induced by blocking *FOLR1* activity in inhibiting tumor growth. We examined the therapeutic potential of mirvetuximab soravtansine (IMGN853), a humanized anti-FOLR1 antibody-drug conjugate (ADC) using HGSOC patient-derived xenograft (PDX) models. **Results:** At a dose of 1.0 nM, IMGN853 showed maxi-

mal effects in reducing tumor weight, decreasing ascites volume, and reducing the number of metastatic nodules in the FOLR1+ OVCA-432 orthotopic model. Treatment with IMGN853 at the 1.0-nM dose significantly extended the survival of mice bearing taxane-resistant HGSOC patient-derived tumors. Immunohistochemistry analysis revealed a  $>5$ -fold increase in cell death in both tumor cells and tumor-associated endothelial vasculature in tumors treated with IMGN853. To explore the potential of autophagic cell death induced by blocking *FOLR1* in the proliferative cancer cells, we also examined the levels of autophagy markers including beclin-1 and LC3B in the resulting HGSOC PDX tumors. Levels of beclin-1 and LC3B were substantially increased in the tumors undergoing IMGN853 treatment in comparison with control tumors. A reverse phase protein array in the protein lysates from the selected HGSOC PDX tumors was performed to identify potential signaling complexes affected by IMGN853. In addition, we determined the functional mechanisms of IMGN853 in HGSOC cells cultured in a 3D organotypic condition. On 24-hour IMGN853 treatment, membrane-tethered FOLR1 internalized into LC3-tagged autophagosomes in OVCAR432-FOLR1-positive cells, but not in A2780-FOLR1-negative cells, accompanied by increased cell death and decreased proliferation. **Conclusions:** Collectively, our results showed that IMGN853 induces an autophagic cell death in FOLR1-positive ovarian cancer cells through specific targeting of FOLR1.

### Quality Improvement

#### AB2018-12. Identifying and Overcoming Barriers in Delivering Concurrent Chemotherapy With Radiation in the Neoadjuvant Treatment of Rectal Cancer

Karthik Giridhar, MD; Priyanka Pophali, MBBS; Meera Sridharan, MD, PhD; Yucai Wang, MD, PhD; Matthew Smith, PharmD, RPh; Jayson Verdick, PharmD, RPh; Surbhi Sidana, MBBS; Alison Jacobson, RN; Laura A. McGrath, CNP; James Martenson, MD; and Joleen Hubbard, MD

Mayo Clinic, Rochester, MN

**Background:** Capecitabine (cap) is an oral chemotherapeutic agent used concurrently with radiation (XRT) for the neoadjuvant treatment of rectal cancer. Several cases were noted in our practice with delays in receiving cap prior to XRT, limiting the ability to provide radiosensitizing chemotherapy and potentially affecting patient care. A systematic retrospective review was undertaken to characterize the frequency and etiologies of cap delays, and interventions to optimize concurrent chemoXRT were implemented. **Methods:** Preintervention, we identified 113 patients with rectal cancer who underwent neoadjuvant XRT and cap

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treatment at Mayo Clinic, Rochester, from 2014–2016. We reviewed electronic medical records to collect the dates of cap prescription, lead time (interval between the initial treatment to planned XRT start date), and delay or change in treatment plan, and directly contacted the Mayo Clinic Specialty Pharmacy (MCSP) and outside specialty pharmacies (OSPs) for cap shipment dates. Postintervention (February–September 2017), we aimed to decrease the number of patients starting XRT without radiosensitizing chemotherapy by 50%. Interventions included a new patient education handout, improved multidisciplinary communication, and use of 5-fluorouracil (5-FU) if cap had not arrived by the XRT start date. **Results:** Preintervention, 86 of 113 patients received cap on the first day of XRT. Of the 27 patients with delays in receiving cap, 8 had significant delays ( $\geq 5$  days of XRT without any chemotherapy). Delays were more common when the prescription was processed at an OSP (52.9%) than at MCSP (11.4%). Two prescriptions for cap were written after the start date of XRT and no patients were switched to 5-FU. Long processing times at the OSP (average 6.7 days) and insufficient lead time were the primary barriers to delivering concurrent chemoXRT. Postintervention, all cap prescriptions were written before the start date of XRT. Receipt of cap after the start of XRT remained more common when the prescription was processed at an OSP (4/10) compared with MCSP (0/15). Although 4 patients did not have cap at the start of XRT, 3 were bridged with 5-FU. A total of 24 of 25 patients with rectal cancer received chemotherapy on the first day of XRT and none had a significant delay. **Conclusions:** The number of patients starting neoadjuvant XRT for rectal cancer without radiosensitizing chemotherapy was higher than expected. Customized patient education materials, improved multidisciplinary communication between medical teams and patients, and using 5-FU in the case of cap delay enhanced the delivery of concurrent chemoXRT.

**AB2018-13. Management of Bone Health in Patients With Breast Cancer on Aromatase Inhibitors: A Single Institution Review**

Heather Katz, DO; Mohit Harsh, MD; Nafeeza Hussain, MD; and Muhammed Omer Jamil, MD

Marshall University, Joan C. Edwards School of Medicine, Huntington, WV

**Background:** Aromatase inhibitors (AI) block the peripheral conversion of androgens to estrogen. Treatment with AIs, therefore, results in bone loss due to estrogen deficiency. Guidelines for cancer treatment–induced bone loss include supplementation with calcium and vitamin D (Gralow J, et al; J Natl Compr Canc Netw 2013). Per the NCCN Guidelines for Breast

Cancer, monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter should be performed for women taking AIs. **Methods:** A retrospective chart review was performed on 507 patients with estrogen receptor/progesterone receptor (ER/PR)–positive breast cancer treated at the Edwards Comprehensive Cancer Center from January 1, 2010, through December 30, 2015. The charts of patients who received AIs were further examined to determine whether they appropriately received both vitamin D and calcium (n=346) and a DEXA scan before AI initiation. **Results:** Of the charts reviewed, 537 patients had stage I–IV ER/PR-positive breast cancer. Of these, 346 patients (68.2%) were treated with an AI and remained on study. Of those who received AIs, 220 patients (63.5%) had vitamin D and calcium supplementation documented in their charts. 246 patients (71.1%) on AIs received a baseline DEXA scan; 38 patients (15.4%) did not receive follow-up scans, and 81 (32.9%) were not due for a DEXA scan follow-up at time of data collection. **Conclusions:** This study indicates that better compliance with NCCN Guidelines regarding baseline and follow-up DEXA scans is needed. Supplementation with calcium and vitamin D is also less than adequate to protect bone health, and adherence needs to be improved. Some strategies to improve adherence to these guidelines include direct questioning about supplementary calcium and vitamin D with proper documentation by medical assistants, more detailed physician documentation about date and results of DEXA scans, and involvement of a breast navigator to confirm that baseline DEXA scans are ordered and reviewed when starting a patient on an AI.

## Young Investigator Awards

### Clinical Oncology

**AB2018-14. Phase I Study Evaluating Safety, Tolerability, and Preliminary Antitumor Activity of Entinostat and Nivolumab With or Without Ipilimumab in Advanced Solid Tumors**

Roisin Connolly, MD<sup>a</sup>; Evanthia Roussos Torres, MD, PhD<sup>a</sup>; Zhe Zhang, PhD<sup>a</sup>; Shannon Puhalla, MD<sup>b</sup>; Joseph Eder, MD<sup>c</sup>; George Somlo, MD<sup>d</sup>; Gary Rosner, ScD<sup>a</sup>; Caden Brennen, MS<sup>a</sup>; Molly Geare, RN, MS<sup>a</sup>; Nita Ahuja, MD<sup>a</sup>; Richard Piekarz, MD<sup>e</sup>; Howard Streicher, MD<sup>e</sup>; Michelle Rudek-Renaut, PharmD, PhD<sup>a</sup>; Michael Carducci, MD<sup>a</sup>; Vered Stearns, MD<sup>a</sup>; Robert Anders, MD, PhD<sup>a</sup>; and Elizabeth Jaffe, MD<sup>a</sup>

<sup>a</sup>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; <sup>b</sup>University of Pittsburgh Cancer Institute and UPMC Cancer Center, Pittsburgh, PA; <sup>c</sup>Yale Cancer Center, New Haven, CT; <sup>d</sup>City of Hope Comprehensive Cancer Center, Duarte, CA; and <sup>e</sup>Cancer Therapy Evaluation Program (CTEP), National Cancer Institute, Bethesda, MD

**Background:** Strategies to convert triple-negative breast cancer (TNBC) to an immunogenic tumor and

facilitate improved response to immune checkpoint (IC) agents are of great interest. Preclinical data in breast cancer models suggest that epigenetic modulators alter myeloid-derived suppressor cells, rendering them less suppressive, allowing for enhanced effector T-cell activity induced by IC blockade. An NCI Cancer Therapy Evaluation Program (CTEP)–sponsored phase I clinical trial of entinostat and nivolumab ± ipilimumab in advanced solid tumors is evaluating these hypotheses (ClinicalTrials.gov identifier: NCT02453620). **Methods:** Primary objectives are safety and tolerability, and to determine the recommended phase II dose (RP2D). Secondary objectives are to evaluate whether treatment with entinostat alone or in combination with nivolumab ± ipilimumab results in increased ratio of T<sub>eff</sub>:T<sub>reg</sub> in tumor biopsies and to assess antitumor activity. Treatment consists of entinostat, 5 mg weekly x 2, before combination therapy. Dose escalation follows 3+3 design (dose level [DL]1/2: entinostat + nivolumab; DL3/4: entinostat + nivolumab + ipilimumab). Twelve subjects will be treated at DL2. After the RP2D is determined, subjects (n=15) will be enrolled for dose expansion. Mandatory blood and tissue samples are collected at baseline, after entinostat run-in, and after 8 weeks of combination. **Results:** As of September 27, 2017, 25 patients were enrolled and 23 were treated in the dose-escalation cohort (DL1=3; DL2=14; DL3=4; DL4=2). Data from DL1–3 are presented here (n=21); accrual to DL4 is ongoing. Median patient age was 60 years (range, 36–77), and the median cycles received to date is 3 (range, 1–11) with 5 patients still on therapy. Adverse events related to treatment in ≥2 patients are shown (Table 1). Possible immune-related adverse events (irAEs) included hypothyroidism (n=1; DL2), hyperthyroidism (n=1; DL3), colitis (n=2; DL2 and DL3), pneumonitis (n=2; DL2), and rash (n=4; DL2 and DL3). Only 1 dose-limiting

toxicity was observed (grade 3 pneumonitis; DL2). **Conclusions:** Combination entinostat and nivolumab ± ipilimumab appears safe and tolerable, with expected rates of irAEs. The RP2D is yet to be determined before dose expansion. Updated safety and efficacy data will be presented at a later date.

#### Outcomes and Health Services Research

##### AB2018-15. Perioperative Geriatric Care Intervention for Older Patients With Gastrointestinal Cancers Undergoing Surgical Resection

Ryan Nipp, MD, MPH; Brandon Temel, BS; Charn-Xin Fuh, BS; Esteban Franco Garcia, MD; Erin Scott, MD; Sharda Mukunda, MD; Terrence O'Malley, MD; Vicki Jackson, MD, MPH; Areej El-Jawahri, MD; and Jennifer Temel, MD  
Massachusetts General Hospital, Boston, MA

**Background:** For patients with gastrointestinal (GI) cancers, surgery often represents the only curative approach. Yet, older adults frequently experience worse outcomes compared with younger patients. We are conducting a randomized study of a perioperative geriatric care intervention versus usual care in older patients with GI cancers undergoing surgical resection. **Methods:** We are randomly assigning patients age ≥65 with GI cancers who plan to receive surgical resection of their cancer at Massachusetts General Hospital to receive perioperative geriatric care or usual care. Patients assigned to the intervention arm meet with a geriatric clinician preoperatively in the outpatient setting and postoperatively in the inpatient setting as a consultant. The geriatric clinician conducts a comprehensive geriatric assessment and makes recommendations for management to the surgical/oncology teams. We are assessing patient-reported quality of life (QoL) (EORTC QLQ-C30, scored 0–100; higher scores indicate better QoL), symptom burden (Edmonton Symptom Assessment System), depression symptoms (Geriatric Depression Scale), number of independent activities of daily living (ADLs), and falls in the past year. **Results:** From September 2016 to October 2017, we enrolled 62 of 82 patients (76%) that were approached to participate. Patients who refuse study enrollment most often cite that they are “not interested in research” (90%). Median patient age is 70 years (range, 65–89), and more than half (53%) are female. Most have pancreatic cancer (60%), followed by rectal (18%) and esophageal (16%) cancers. Most of the patients are married (74%), college-educated (65%), and retired (58%). Almost one-third report a history of diabetes (31%), and >10% report a history of stroke (13%) or lung disease (11%), but none had previously seen a geriatric clinician. At baseline, patients' mean QoL score is 65.3 (SD=22.1). Moderate/severe fatigue

AB2018-14: Table 1. Adverse Events Related to Treatment in ≥2 Patients

AE	Grade 1/2 (n, %)	Grade 3 (n, %)	Grade 4 (n, %)
Anemia	2 (9.5)	0	0
Leukopenia	2 (9.5)	0	0
Neutropenia	3 (14)	3 (14)	0
Lymphopenia	0	1 (4.5)	1 (4.5)
Thrombocytopenia	2 (9.5)	0	0
Weight loss	2 (9.5)	0	0
Fatigue	3 (14)	1 (4.5)	0
Elevated amylase	3 (14)	0	0
Hypophosphatemia	3 (14)	1 (4.5)	0
Rash	4 (19)	0	0
Pneumonitis	1 (4.5)	1 (4.5)	0
Colitis	1 (4.5)	1 (4.5)	0

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(34%), pain (19%), and lack of appetite (18%) symptoms are common. More than one-fifth report depressive symptoms (22%). Only 8% of patients are independent in all ADLs, and 21% report  $\geq 1$  fall in the past year. We currently have  $<1\%$  missing data for baseline patient-reported outcomes. For patients assigned to the intervention arm, 93% have met with a geriatric clinician preoperatively. **Conclusions:** We have successfully enrolled patients in a randomized study of perioperative geriatric care with excellent adherence to the intervention. Our baseline data highlight the unmet care needs of this population.

#### Correlative/Genetics

##### AB2018-16. T-Cell Response Parallels Clinical Responses in Patients With Metastatic Triple-Negative Breast Cancer Receiving Platinum-Based Chemotherapy Combined With PD-1 Blockade

Elias Obeid, MD, MPH; Chun Zhou, PhD; Alex McFarlane, PhD; Amanda Cornfeld, BS; Erika Davis, BS; Lisa Bealin, BS; Katherine R. Alpaugh, PhD; Kerry Campbell, PhD; and Lori J. Goldstein, MD

Fox Chase Cancer Center, Philadelphia, PA

The clinical trial is supported through the Merck Investigator Studies Program (PI: E Obeid, co-PI: LJ Goldstein). The correlative studies (presented here) are funded by the NCCN YIA (PI: E Obeid). Any opinions, findings, and conclusions expressed in this material are those of the author(s) and do not necessarily reflect those of NCCN or the NCCN Foundation.

**Background:** PD-1 blockade has shown promising clinical activity in metastatic triple-negative breast cancer (mTNBC). We designed a safety run-in to a randomized phase II trial of combination pembrolizumab (P) with carboplatin (C) and gemcitabine (G) in patients with mTNBC; correlative studies are ongoing. It remains unclear whether platinum-based chemotherapy in mTNBC results in immune activation and clinical response when combined with immune checkpoint blockade (ICB). **Methods:** Patients diagnosed with mTNBC were recruited to the safety run-in (N=6), to be followed by a randomized design of C + G  $\pm$  P (2:1 randomization; N=75). Safety run-in consists of P, 200 mg on day 1, and C (area under the curve, 2) + G (800 mg/m<sup>2</sup>) on days 1 and 8, of each 21-day cycle. Patients consented for a peripheral blood collection at precycle 1 and at posttreatment before cycle 3, to phenotype immune changes by flow cytometry. **Results:** The safety run-in (N=6) was completed in August 2017 without severe adverse events. Average patient age was 61 years (range, 51–71), and at the time of this analysis (November 2017) all subjects except for 1 remain on treatment and are experiencing response to the study drugs; number of treatment cycles (except for the 1 patient) ranges between 7 and 24. Peripheral blood data from all subjects enrolled in the safety run-in have been included in this interim analysis. We found

a trend for an increase in the activation marker CD69, on total CD4+ and CD8+ T-cell populations ( $P=.06$ ). This increase was significant in central memory and effector CD8+ T cells ( $P<.05$ ), and was close to significance in central memory and effector memory CD4+ T cells ( $P=.06$ ). We also found a significant decrease in PD-1 expression on CD4+ T-cells after treatment ( $P=.05$ ). The subject who discontinued P and received corticosteroids for a grade 2 immune-related hepatitis during cycle 2 experienced clinical disease progression at cycle 4, and had a high baseline percent of natural killer cells  $>30\%$  (above anticipated 5%–15% of lymphocytes). **Conclusions:** Although this represents a very limited number of patients, this early analysis of combining CG + P revealed evidence supporting an ability to mount an immune stimulation when adding chemotherapy to ICB in mTNBC. Furthermore, immune activation and blockade changes were accompanied by clinical responses. Although early, our results suggest that combining platinum-based chemotherapy with ICB can achieve its goal of unleashing an antitumor immune response in patients with mTNBC.

##### AB2018-17. Predicting Response to Mitotic Spindle Inhibition in Leiomyosarcoma

Edward Passen, BS; Colin Stets, BS; Bryce Demoret, BS; John L. Hays, MD, PhD; and James L. Chen, MD

The Ohio State University, Columbus, OH

This work was funded by the NCCN YIA (Chen).

**Background:** Leiomyosarcoma (LMS) is a soft tissue sarcoma with a limited treatment options. Microtubule-targeting agents (MTAs) are a common therapy for LMS; however, only a minority of patients experience a response to treatment. Predictive biomarkers are needed to improve overall response rates. A computational method developed by our laboratory was used to perform automated biomarker analysis on patients with LMS at our institution who were treated with docetaxel-containing regimens. This algorithm identified cell cycle regulators as a potential pathway of interest. Based on this finding and the mechanism of MTAs, we sought to determine whether modulation of the cell cycle, particularly the G1/S checkpoint, affected the efficacy of the MTAs (eribulin and taxanes). **Methods:** 3 internally generated (Leio-012, LMS-117, and Leio-196A) and 1 commercial (SK-LMS1) cell line were treated with eribulin and docetaxel using XTT proliferation assays to determine intermediate concentration for 50% effect (IC<sub>50</sub>) dosages. To instigate increased cell cycle, functional knockdown of p16 was performed using lentiviral constructs along with the CDK4/6 inhibitor palbociclib. Western blot analysis was used to interrogate G1/S proteins. Synergy determination was performed using CalcuSyn (Biosoft),

and standard descriptive statistics were performed using GraphPad Prism 6.0. **Results:** XTT assays showed variable sensitivity to MTAs among the 4 cell lines. 2 sensitive cell lines (<10 nM IC50)—SKLMS1 and Leio-196A—showed eribulin IC50s of 4.86 and 1.18 nM, respectively; 2 resistant cell lines (>20 nM)—Leio-012 and LMS-117—showed eribulin IC50s of 36.8 and 27.62 nM, respectively. Western blot analysis showed absence of the G1/S checkpoint regulator p16 in SKLMS1. CDK6 protein levels were lower in the resistant cell lines. p16 knockdown demonstrated sensitization of resistant cell lines relative to parental controls. Combination treatment with CDK6 inhibition and eribulin demonstrated antagonism in all cell lines. Clinical data in patients with LMS treated with gemcitabine/docetaxel demonstrated improved progression-free survival in those with G1/S mutations. **Conclusions:** Alterations in the G1/S checkpoint may correlate with MTA sensitivity in vitro and in retrospective LMS patient data. Prospective clinical trials will be required to validate this observation.

#### Best Practices in Implementation and Use of Clinical Practice Guidelines

##### AB2018-19. Impact of NCCN Guidelines for Survivorship on Use of Echocardiography in Breast Cancer Survivors

Kathryn J. Ruddy, MD, MPH<sup>a</sup>; Lindsey Sangaralingham, MPH<sup>a</sup>; Joerg Herrmann, MD<sup>a</sup>; Somaira Nowsheen<sup>a</sup>; Javid Moslehi, MD<sup>b</sup>; Heather Neuman, MD<sup>c</sup>; Ahmedin Jemal, DVM, PhD<sup>d</sup>; Tufia C. Haddad, MD<sup>a</sup>; Anne Blaes, MD<sup>e</sup>; Hector Villarraga, MD<sup>a</sup>; and Nilay Shah, PhD<sup>a</sup>

<sup>a</sup>Mayo Clinic, Rochester, MN; <sup>b</sup>Vanderbilt-Ingram Cancer Center, Nashville, TN; <sup>c</sup>University of Wisconsin School of Medicine and Public Health, Madison, WI; <sup>d</sup>American Cancer Society, Atlanta, GA; and <sup>e</sup>University of Minnesota, Minneapolis, MN

**Background:** Doxorubicin, which is potentially cardiotoxic, is administered as part of curative-intent therapy for many patients with breast cancer (BC). Since February 2015, the NCCN Guidelines for Survivorship have recommended consideration of echocardiography to monitor for asymptomatic cardiac dysfunction within 1 year after completion of anthracycline for BC survivors at increased risk of cardiac dysfunction (with age >65 years specified as an indicator of increased risk). Our objective was to assess how the publication of the 2015 NCCN Survivorship Guidelines affected real-world use of post-anthracycline echocardiography in BC survivors. **Methods:** We analyzed 2008–2016 administrative claims data from a US commercial insurance database (OptumLabs) to identify 5,598 women who received ≥1 dose of doxorubicin as part of curative-intent treatment for BC, with the final dose given between 2008 and 2015. Patients who also received trastuzumab were excluded. We assessed the proportion of patients who underwent echocardiography

during the year after their last dose of doxorubicin to determine whether this practice increased after release of the guidelines. Women aged ≥65 years were assessed separately from those aged <65 years. **Results:** Table 1 includes the proportion of patients who underwent echocardiography (%) during the year of follow-up, separating those aged <65 years from those ≥65 years. **Conclusions:** Most older patients who were treated with doxorubicin (but not trastuzumab) did not undergo a postchemotherapy echocardiogram even after publication of the 2015 NCCN Guidelines, which included the recommendation to consider echocardiography in this setting, although a small increase in the rate of post-doxorubicin echocardiography was noted in patients aged ≥65 years in 2015. It will also be important to assess rates in 2016, 2017, and beyond (when those data become available).

AB2018-19: Table 1. Proportion With echocardiogram Within First Year After Final Doxorubicin Dose

Year	Proportion of Cohort With Echocardiography	Proportion Aged <65 y With Echocardiography	Proportion Aged ≥65 y With Echocardiography
2008	134/717 (19%)	114/634 (18%)	20/81 (25%)
2009	151/762 (20%)	131/682 (19%)	20/76 (26%)
2010	121/683 (18%)	102/603 (17%)	18/77 (23%)
2011	136/671 (20%)	104/542 (19%)	32/127 (25%)
2012	156/802 (19%)	123/658 (19%)	33/141 (23%)
2013	144/619 (23%)	114/493 (23%)	30/123 (24%)
2014	146/639 (23%)	111/495 (22%)	32/137 (23%)
2015	163/705 (23%)	102/496 (21%)	59/204 (29%)

#### Pre-Clinical Oncology

##### AB2018-20. Optimizing Multiple Myeloma Patient-Derived Xenografts to Test Anti-CD46 Antibody-Drug Conjugate for Curative Potential

Michael J. Van Wyngarden, BS<sup>a</sup>; Zachary J. Walker, MS<sup>a</sup>; Brett M. Stevens, PhD<sup>a</sup>; Christophe Langouët-Astrie, BS<sup>a</sup>; Clayton A. Smith, MD<sup>a</sup>; Peter A. Forsberg, MD<sup>a</sup>; Tomer M. Mark, MD<sup>a</sup>; William Matsui, MD<sup>b</sup>; Bin Liu, PhD<sup>c</sup>; Craig T. Jordan, PhD<sup>a</sup>; and Daniel W. Sherbenou, MD, PhD<sup>a</sup>

<sup>a</sup>University of Colorado Cancer Center, Aurora, CO; <sup>b</sup>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; and <sup>c</sup>UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

**Background:** Multiple myeloma (MM) is incurable, with relapse inevitable in almost all patients. We found that anti-CD46 antibody-drug conjugate (CD46-ADC) potently and selectively inhibits MM cell-line growth in vitro and in vivo, and eliminates MM cells from ex vivo culture (Sherbenou DW et al; J Clin Invest 2016). In MM, no current therapy is capable of eliminating minimal residual disease (MRD), and thus there currently is no cure. In theory, an ADC could be curative if the target is expressed on MRD. CD46 is an

intriguing novel candidate for this because it is a functional antigen that is genetically upregulated in MM. Notably, studies using cell lines do not reflect complexities of human MM, such as MRD. Thus, we implemented a patient-derived xenograft (PDX) model of MM to facilitate testing of CD46-ADC elimination of MRD in vivo. **Methods:** Due to the dependence of MM cells on their microenvironment, the mouse model uses subcutaneously implanted human fetal bone grafts (Yacoby and Epstein, Blood 1999). The efficiency of engraftment of myeloma samples using this approach has been reported to be 33% (Kim D, et al; Leukemia 2012). We used this model to test whether relapsed late-stage disease would engraft better than newly diagnosed samples. Thus, we injected 3 newly diagnosed and 3 late-stage disease patient samples (n=3–4 mice per sample) into human bone grafts in NSG mice. Mice with long-term sustained engraftment were treated with CD46-ADC, 5 mg/kg intravenously for 4 doses. **Results:** Of mice harboring bone grafts and injected with patient samples, we observed engraftment in 8 of 19 mice (42%) via ELISA monitoring of mouse serum for restricted human free light chains matching the injected samples. At study termination, flow cytometry of the bone grafts confirmed light chain–restricted myelo-

ma cells in mice with detectable serum free light chain by ELISA. Surprisingly, the newly diagnosed samples engrafted more efficiently than the relapsed/refractory samples (70% vs 11%). Notably, a patient sample harboring a c-myc translocation engrafted in 3 of 3 mice. CD46-ADC treatment reduced engraftment (n=2), but engraftment decreased in all mice by study termination at 30 weeks. **Conclusions:** Our data suggest that treatment-naïve patient samples engraft more efficiently than heavily pretreated samples in MM PDXs that harbor human bone grafts. Further optimization of MM PDXs will allow testing of CD46-ADC and other preclinical drugs for curative potential.

**AB2018-21. Application of Desorption Electrospray Ionization Mass Spectrometry Imaging for Rapid Prostate Cancer Diagnosis**

Geoffrey A. Sonn, MD<sup>a</sup>; Shibdas Banerjee, PhD<sup>b</sup>;  
Ryan M. Bain, PhD<sup>b</sup>; Christian A. Kunder, MD, PhD<sup>a</sup>;  
Richard Fan, PhD<sup>a</sup>; James D. Brooks, MD<sup>a</sup>;  
Robert J. Tibshirani, PhD<sup>b</sup>; and Richard N. Zare, PhD<sup>b</sup>

<sup>a</sup>Stanford University School of Medicine, and <sup>b</sup>Stanford University, Stanford, CA

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