REALM IDx Collaborates on Three Studies Presented at ASCO 2022

- *Ambry Genetics and Thomas Jefferson University show African American individuals with prostate cancer had a lower positive rate and a higher VUS rate compared to Caucasian men, indicating critical need for greater inclusion in genetic studies. (Abstract: 10502)*

- *Ambry Genetics and Dana-Farber show that individuals with two germline pathogenic variants in CHEK2 have an average age of cancer onset that is similar to individuals with either a BRCA1 or BRCA2 concurrent pathogenic variant, and are more likely to have multiple primaries. (Abstract: 10514)*

- *Invicro co-author presents on [68Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [177Lu]-PSMA-617 in patients with mCRPC: a VISION sub-study. (Abstract: 5002)*

ALISO VIEJO, Calif., June 2, 2022 – REALM IDx, through its businesses, Ambry Genetics and Invicro, collaborated with leading third party thought leaders for the following studies being presented at ASCO 2022:

Ambry Genetics and Thomas Jefferson University Collaboration: Mutation Spectrum and Rates of Variants of Uncertain Significance Among African American Males Undergoing Prostate Cancer Germline Testing: Need for Equity in Genetic Testing.

Summary

New data presented by Ambry Genetics and Thomas Jefferson University showed that African American individuals with prostate cancer had higher rates of multiple VUS compared to Caucasian men, indicating critical need for greater inclusion in genetic studies to discern the PCA pathogenic spectrum to inform strategies for equitable genetics care delivery.

Methodology

Participants included AA men and Caucasian men with PCA who underwent a 14-gene PCA panel: ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51D, TP53. Germline analysis was performed per standard clinical testing and variant classification protocol. Descriptive statistics summarized study variables. Data were compared with Fisher's exact, Chi-squared, or two sample t-test, as appropriate. Multivariable analysis was conducted using Akaike's Information Criterion. Significance level was set a priori at 0.05.

Results

The dataset included 427 males who had a 14-gene PCA panel: Caucasian males (n=190) and AA males (n=237). 8.2% tested positive for a pathogenic/likely pathogenic (P/LP) variant; AA (5.91%) and Caucasian (11.05%). P/LP variant spectrum in AA males was narrower than for Caucasian males (AA:

BRCA2, PALB2, ATM, BRCA1; Caucasian: BRCA2, ATM, HOXB13, CHEK2, TP53, NBN). A significant difference was noted in rates of variants of uncertain significance (VUS) between AA and Caucasian males (25.32% vs. 16.32%, respectively; p=0.02) and for carrying multiple VUS (5.1% vs. 0.53%, p = 0.003).

Presentation Details

Session Title: Prevention, Risk Reductions and Hereditary Cancer.

Abstract: 10502

Presented by: Veda N. Giri, MD | Departments of Medical Oncology, Cancer Biology, and Urology, Cancer Risk Assessment and Clinical Cancer Genetics Program, Sidney Kimmel Cancer Center, Thomas Jefferson University

Time: Monday, June 6, 2022 at the 8am CT session.

Ambry Genetics and Dana-Farber Collaboration: Double Jeopardy? A Closer Look at Cancer Histories of Individuals with Multiple Germline Pathogenic Variants.

Summary

Germline multigene panel testing has led to the increased detection of multiple co-occurring pathogenic variants (PV) in the same individual. As this occurrence is still relatively rare, reports of these individuals have been limited. Therefore, this study sought to describe the clinical features of individuals with multiple PV identified at a single high-volume diagnostic laboratory.

Methodology

A retrospective review of demographics and clinical data for individuals with >1 pathogenic or likely pathogenic variant (PV) who underwent hereditary cancer panel testing (5-67 genes) between May 2012 and April 2017 was conducted. In recessive genes (i.e. *MUTYH*), PV were only included when biallelic. PVs with reduced penetrance (*APC* p.I1307K; *CHEK2* p.I157T, p.S428F, p.T476M) were excluded. In individuals with the most common combinations of genes, personal cancer history and age at cancer diagnosis was evaluated.

Results

A total of 555 individuals were identified with multiple PVs. Most individuals were female (85.1%), had a personal history of cancer (73.3%) and 26.3% had two or more primary cancers. *CHEK2* was most often seen in co-occurrence with a PV in a different gene (137 observations), followed by *ATM* (120 observations), *BRCA2* (110 observations), and *BRCA1* (88 observations). Among cases in which clinical information was provided (n=545), the five most frequent co-occurring combinations were in *ATM/CHEK2* (25), *ATM/BRCA2* (25), *BRCA1/CHEK2* (19), *CHEK2/CHEK2* (18), and *BRCA2/CHEK2* (16). Individuals with co-occurring PVs in *CHEK2/CHEK2* had the youngest age at first cancer diagnosis (mean = 41.5y; median = 40y), the highest rate of breast cancer diagnoses and other cancer diagnoses (94.4% and 57.9% of individuals, respectively), and the highest proportion of individuals with >1 primary cancer (57.9%).

Conclusions

Results indicated that individuals with two PVs in *CHEK2* have an average age of cancer onset that is

similar to individuals with either a *BRCA1* or *BRCA2* concurrent PV. Results also indicated that individuals with two PVs in *CHEK2* are more likely to have multiple primary cancers as compared to others in the cohort with concurrent PVs including those with either a *BRCA1* or *BRCA2* concurrent PV (Table). Continued studies, including comparisons to individuals with one PV, will provide valuable insight to aid in counseling and management of individuals with multiple germline PV.

PV Gene Combination	Total individuals	n Female (%) n Male (%)	Median age 1st cancer (IQR)	n female breast cancer (%*)	n other cancer (%)	n >1 primary cancer (%)
ATM/CHEK2	25	23 (92.0%) *2 (8.0%)*	43 (10.5)	20 (87.0%)	4 (16.0%)	6 (24.0%)
ATM/BRCA2	25	19 (76.0%) *6 (24.0%)*	49.5 (19.5)	11 (57.9%)	9 (36.0%)	5 (20.0%)
BRCA1/CHEK2	19	17 (89.5%) *2 (10.5%)*	44 (10.5)	9 (52.9%)	7 (36.8%)	4 (21.1%)
CHEK2/CHEK2	18	18 (100.0%) *0 (0.0%)*	40 (15)	17 (94.4%)	11 (57.9%)	11 (57.9%)
CHEK2/PALB2	18	18 (100.0%) *0 (0.0%)*	47 (18)	17 (94.4%)	2 (11.1%)	5 (27.8%)
BRCA2/CHEK2	16	15 (93.7%) *1 (6.3%)*	45 (13)	10 (66.7%)	2 (12.5%)	2 (12.5%)

Presentation Details

Session Title: Prevention, Risk Reduction and Hereditary Cancer.

Abstract: 10514

Poster: 393

Presented by: Brittany L. Bychkovsky, MD, MSc | Department of Medical Oncology, Division of Cancer Genetics and Prevention, Dana-Farber Cancer Institute

Time: Monday, June 6, 2022 at 4:30pm CT session.

Invicro Collaboration: [^{68}Ga]Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [^{177}Lu]Lu-PSMA-617 in patients with mCRPC: A VISION substudy.

Background

In the phase 3 VISION study, gallium (68Ga) gozetotide (68Ga-PSMA-11) PET/CT imaging was used to determine eligibility for lutetium (177Lu) vipivotide tetraxetan (177Lu-PSMA-617). Given that 177Lu-PSMA-617 targets PSMA, we assessed the association between quantitative PSMA imaging parameters and treatment outcomes.

Methods

In VISION, adults with mCRPC with ≥ 1 PSMA-positive (+) and no PSMA-negative lesions meeting the exclusion criteria were enrolled. In this sub-study, the association between imaging data from pre-enrollment 68Ga-PSMA-11 PET/CT scans of pts in the 177Lu-PSMA-617 group and clinical outcomes was assessed. Imaging data meeting quality requirements were analyzed for 548/551 pts. PSMA expression was quantified by 5 PET parameters: PSMA+ lesions by region, mean standardized uptake value (SUVmean), maximum SUV (SUVmax), PSMA+ tumor volume, and tumor load (PSMA+ tumor volume × SUVmean). Parameters were extracted from the whole body and 4 regions. Association between PET parameters and radiographic progression-free survival (rPFS; primary objective), overall survival (OS), objective response rate (ORR), and prostate–specific antigen 50 (PSA50) response was assessed.

Results

Most pts (92.7%) had PSMA uptake in bone. In both the whole-body and regional analyses, statistically significant associations of PSMA PET parameters to clinical outcomes were observed (whole-body data shown in Table). Higher whole-body SUVmean was associated with improved clinical outcomes; pts in the highest quartile (SUVmean: rPFS, ≥ 10.2; OS, ≥ 9.9) had a median rPFS and OS of 14.1 and 21.4 months, vs 5.8 and 14.5 months for those in the lowest quartile (< 6.0; < 5.7), respectively. Absence of PSMA+ lesions in bone, liver, and lymph node, and lower PSMA+ tumor load, were indicators of good prognosis.

Conclusions

Higher SUVmean is strongly associated with improved outcomes with 177Lu-PSMA-617; clinical efficacy for different SUV levels vs the SoC arm is being assessed. Data support use of 68Ga-PSMA-11 PET/CT scan to identify pts who will benefit from PSMA-targeted radioligand therapy.

Presentation Details

Session Title: Genitourinary Cancer—Prostate, Testicular, and Penile.

Abstract: 5002

Presented by: Andrew Armstrong, M.D. | Professor of Medicine, Duke University School of Medicine.

Invicro co-authors: Phillip Kuo M.D., Ph.D. | Senior Medical Director and Jacob Hesterman Ph.D., Distinguished Scientist. Invicro was the Imaging CRO for this sub-study supporting the development of the analysis plan, conducting the quantification and assisting with analysis.

Time: Sunday, June 5 at 8:00 am CT session.

About REALM IDx

REALM IDx, Inc. is a health care company pioneering in the field of Integrated Diagnostics (IDx), an advanced field of clinical science that brings together laboratory medicine, radiology, pathology and sophisticated artificial intelligence to derive actionable insights to predict, diagnose and treat disease. Powered by proprietary software platforms, industry-leading genomics technology from Ambry Genetics Corporation and radiology and pathology services from Invicro, LLC, the company is equipped to collect, analyze and report on multi-modal precision diagnostic data sets. REALM's extensive network of health care providers and pharmaceutical partners will drive clinical access to innovations that lead to better medical solutions for patient care. To learn more, visit REALMIDx.com.

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