Caris Abstracts and Presentation Schedule

AACR 2024

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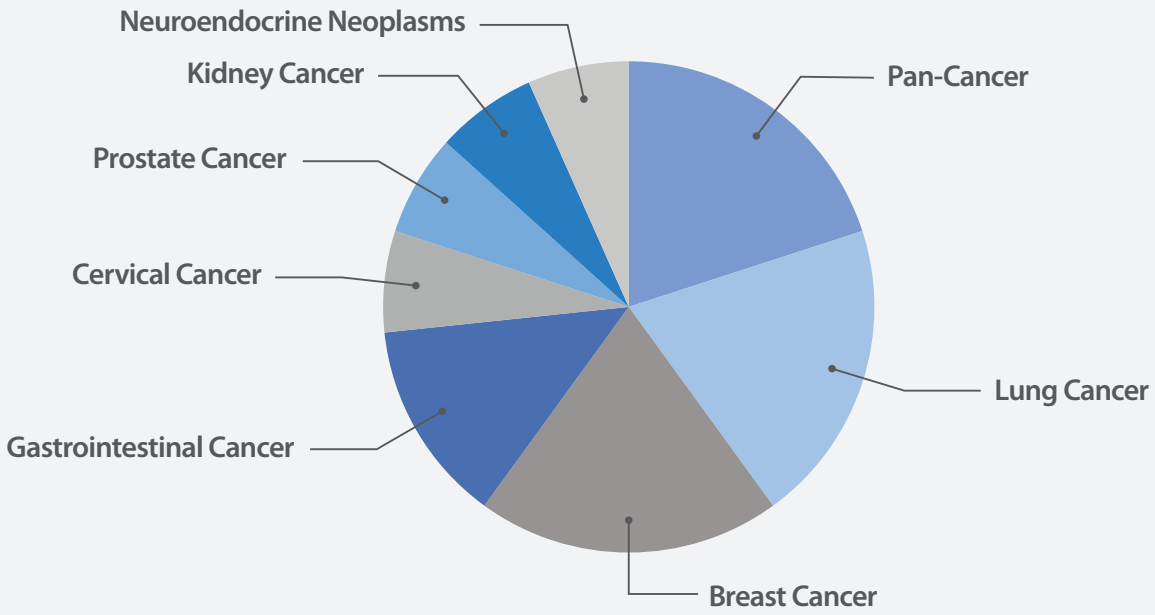
Caris Abstracts and Presentation Schedule

Caris Life Sciences comprehensive molecular profiling provides one of the broadest molecular analyses possible, leveraging whole exome (WES) and whole transcriptome sequencing (WTS) of 23,000+ genes. Tissue profiling also includes immunohistochemistry (IHC) of tumor-relevant protein biomarkers, and blood profiling with Caris Assure sequences both plasma and white blood cells to enable identification of incidental germline variants and filter out incidental CHIP variants. In collaboration with Caris Precision Oncology Alliance™ (POA) members, we are continually developing insights into a broad range of biomarkers and tumor types. As a result, this year's American Association for Cancer Research (AACR) annual meeting abstracts cover an extensive set of precision medicine insights across lung, breast, prostate, gastrointestinal, cervical, prostate, kidney, and neuroendocrine tumors. In total, Caris and our POA collaborators will present 13 abstracts, including three oral presentations in minisymposia and ten posters. These studies highlight the power of collaborative research and demonstrate that:

- Molecular profiling with a large dataset across 593,000 lifetime clinical cases allows the identification of rare biomarkers, with implications for future research.
- Comprehensive analysis including WES, WTS, and IHC drives the identification of new biomarkers and informs potential target identification for future treatment innovations.
- Caris supports the clinician across the full continuum of care from ensuring the right diagnosis of the biopsy to informing the right treatment plan for each patient.

Accepted Caris POA Abstracts By Tumor Type



Posters

SUNDAY, APRIL 7, 2024

1:30-5:00 PM PST: EXHIBIT FLOOR, POSTER SECTION 47

SESSION PO.CL06.05: TUMOR IMMUNE RESPONSE 1

Modulation of the MSS and MSI colorectal cancer immune microenvironment with FOLFOX and FOLFIRI -/+ anti-PD-1 immunotherapy

Lindsey Carlsen, Maximilian Pinho-Schwermann, Leiqing Zhang, Andrew Elliott, Kelsey E. Huntington, William J. MacDonald, Brooke Verschleiser, Laura Jinxuan Wu, Wafik S. El-Deiry

Abstract: 1189 / 23 **Presenter:** Maximilian Pinho-Schwermann

Key Findings:

- While around 90% of metastatic colorectal cancers (mCRC) are microsatellite stable (MSS) and resistant to immune checkpoint inhibition, chemotherapy-mediated immune stimulation in MSS CRC has been observed in preclinical models and clinical trials.
- Using *in vitro* and mouse models of MSS and MSI CRC as well as clinical specimens of chemotherapy-treated MSS mCRC patients, a mechanism specific to the FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) regimen was uncovered by which CD8+ T cell infiltration into MSS mCRC tumors is enhanced, but their activation is halted, potentially by suppression of cytokine *GM-CSF* and/or depletion of type 1 conventional dendritic cells (cDC1) in the tumor microenvironment (TME).
- These findings contribute to our understanding of the mechanisms of chemotherapy-dependent immune modulation and bring the field closer to harnessing these effects for therapeutic gain.

SUNDAY, APRIL 7, 2024

1:30-5:00 PM PST: EXHIBIT FLOOR, POSTER SECTION 4

SESSION PO.IM02.07: TUMOR-INDUCED IMMUNE SUPPRESSION 1: EXTRINSIC FACTORS

Identification of the actionable target *LILRB4* through genetic linkage analysis of Diversity Outbred (DO) F1 mice expressing HER2(neu)

Jennifer B. Jacob, Wei-Zen Wei, Benjamin L. Kidder, Tolulope Adeyelu, Andrew Elliott, Gerold Bepler, Joyce D. Reyes

Abstract: 114 / 18 **Presenter:** Jennifer B. Jacob

Key Findings:

- Genetic linkage analysis in mice expressing HER2(neu) identified Quantitative Trait Loci (QTL) associated with age of tumor onset in Chr 1 and X and with tumor growth rate in Chr 10.
- The QTL loci in mouse Chr X and 10 were discoveries beyond the capacity of human Genome-Wide Association Studies (GWAS), which are deficient in mapping Chr X and assessing tumor growth rate.
- Analysis of gene expression in 26 candidate genes from the 3 QTL using Caris' CodeAI clinicogenomic database found significant associations with patient survival in primary (n=3,533) and/or metastatic (n=4,870) breast cancers (21 of 26) and in lung cancer (n=11,334; 17 of 26), including 13 genes common to both breast and lung cancer.
- Focusing in particular on *LILRB4*, a transmembrane receptor involved in immune checkpoint control, follow-on single cell RNA-seq and mouse genetic studies found *LILRB4* function in multiple immune regulatory mechanisms of tumor progression, highlighting its potential as a new actionable therapeutic target.
- The reservoir of other candidate genes identified in this study await further validation.

SUNDAY, APRIL 7, 2024

3:05-3:20 PM PST: ROOM 5 - UPPER LEVEL - CONVENTION CENTER

SESSION MS.MD01.01: ADVANCING CANCER RESEARCH THROUGH AN INTERNATIONAL CANCER REGISTRY: AACR PROJECT GENIE USE CASES

MINISYMPOSIUM – ORAL PRESENTATION

cBioPortal for Cancer Genomics

Tali Mazor, Ino de Bruijn, Rima AlHamad, Calla Chennault, Corey Dubin, Jeremy Easton-Marks, Zhaoyuan Fu, Benjamin Gross, Charles Haynes, David M. Higgins, Jason Hwee, Prasanna K. Jagannathan, Mirella Kalafati, Karthik Kalletla, James Ko, Tim Kuijpers, Sowmiyaa Kumar, Priti Kumari, Ritika Kundra, Bryan Lai, Xiang Li, James Lindsay, Aaron Lisman, Qi-Xuan Lu, Ramyasree Madupuri, Angelica Ochoa, Yusuf Z. Özgül, Oleguer Plantalech, Matthijs N. Pon, Baby A. Satravada, Jessica Singh, Selcuk Onur Sumer, Pim van Nierop, Floris Vleugels, Avery Wang, Manda Wilson, Hongxin Zhang, Gaofei Zhao, Ugur Dogrusoz, Allison Heath, Adam Resnick, Trevor J. Pugh, Chris Sander, Ethan Cerami, Jianjiong Gao, Nikolaus Schultz

Abstract: 1249 **Presenter:** Ino de Bruijn

Key Findings:

- cBioPortal for Cancer Genomics is an open-source platform for interactive, exploratory analysis of large-scale clinico-genomic data.
- The site (https://www.cbioportal.org) hosts data from >390 studies from individual labs and large consortia, including AACR Project GENIE, which contains >197,000 clinically sequenced samples with clinical annotations like response, outcome, and treatment history.
- A suite of user-friendly visualizations and analyses, including OncoPrints, mutation lollipop plots, variant interpretation, group comparison, survival analysis, expression correlation analysis, alteration enrichment analysis, and cohort and patient-level visualization, enable comprehensive exploration of these data.
- cBioPortal is an open source, collaborative effort among groups at Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, Childrens Hospital of Philadelphia, Princess Margaret Cancer Centre, Caris Life Sciences, Bilkent University and The Hyve.

SUNDAY, APRIL 7, 2024

4:35-4:50 PM PST: BALLROOM 6 CF - UPPER LEVEL - CONVENTION CENTER

SESSION MS.CL01.03: BIOMARKERS PREDICTIVE OF THERAPEUTIC BENEFIT

MINISYMPOSIUM – ORAL PRESENTATION

Tissue-specific thresholds and microenvironment correlates of tumor mutation burden associated with immunotherapy benefit and prognosis in microsatellite stable cancers

Maishara Muquith, Magdalena Espinoza, Andrew Elliott, Joanne Xiu, Andreas Seeber, Wafik S. El-Deiry, Emmanuel S. Antonarakis, Stephanie Graff, Michael J. Hall, Hossein Borghaei, Dave S. Hoon, Stephen V. Liu, Patrick C. Ma, Rana R. McKay, Trisha Wise-Draper, John Marshall, George W. Sledge, David Spetzler, Hao Zhu, David Hsieh

Abstract: 1213 **Presenter:** Maishara Muquith

Key Findings:

- In a real-world clinicogenomic cohort including 70,698 patients with microsatellite-stable (MSS) cancers distributed across 27 histologies, association between tumor mutation burden (TMB) threshold and survival outcomes was assessed based on whether or not patients received immune checkpoint inhibitor (ICI) therapy.
- Twelve cancer types had at least one TMB threshold associated with survival benefit from ICI. The threshold with greatest predictive value was frequently near the high end of the range, suggesting that ICI benefit may scale with TMB.
- These results may have implications for cancer-agnostic and universal TMB cutoffs to guide the use of anti-PD-1 / PD-L1 therapies, underlining the importance of tissue context in the clinical development of ICI biomarkers.

This research was recently published in *Nature Cancer*.
https://doi.org/10.1038/s43018-024-00752-x

MONDAY, APRIL 8, 2024

9:00 AM-12:30 PM PST: EXHIBIT FLOOR, POSTER SECTION 36

SESSION PO.BCS02.04: LIQUID BIOPSY AND PRECISION ONCOLOGY

CARIS ASSURE™ VALIDATION

AI-enabled whole exome & transcriptome liquid biopsy addressing MCED, MRD, and therapy selection on a single platform

Jim Abraham, Valeriy Domenyuk, Maria Perdigones Borderias, Takayuki Yoshino, Elisabeth Heath, Emil Lou, Stephen Liu, John Marshall, Wafik S. El-Deiry, Anthony Shields, Martin Dietrich, David D. Halbert, Dominic Sacchetti, Seth Stahl, Adam Stark, Sergey Klimov, Sourabh Antani, Chadi Nabhan, Jeff Swensen, George Poste, Matt J. Oberley, Milan Radovich, George W. Sledge, David Spetzler

Abstract: 2300 / 11 **Presenter:** Jim Abraham

Key Findings:

- Caris Assure is a proprietary circulating nucleic acid sequencing platform that couples whole exome and transcriptome (WES/WTS) sequencing on white blood cells and plasma with advanced machine learning techniques to provide accurate and early cancer diagnosis, highly sensitive monitoring of minimal residual disease (MRD), and precise therapy selection on one platform.
- The test detects SNVs, INDELs, structural variants, copy number, gene expression, tumor mutational burden (TMB), microsatellite instability (MSI), fragment length, and aneuploidy of both somatic (tumor and clonal hematopoiesis) and germline origin.
- Validation studies were performed to characterize the analytic and clinical performance of Assure on over 3,000 patient blood samples.
- For early detection, stratification of blood samples from patients with stage I-IV cancer versus those with no reported cancer resulted in an AUC > 0.99 and included over 30 types of solid tumors. At 99.5% specificity, the sensitivities for stages I-IV were 73%, 80%, 76%, and 89%.
- In the MRD setting for high-risk patients, the disease-free survival of patients whose cancers were predicted to recur was significantly shorter (39.6 mo) than those predicted not to recur (93.4 mo) (HR: 5.18, 95%CI: 2.94-9.09, p<.00001).
- For therapy selection, detection of driver mutations where blood was collected within 30 days of matched tissue demonstrated high concordance with a PPA of 93.8% and PPV of 96.8%.
- CHIP correction proved to be essential as ~35% percent of patients had CHIP mutations, including KRAS, BRAF, ATM, & BRCA1/2, findings that could lead to improper therapy selection.

MONDAY, APRIL 8, 2024

9:00 AM-12:30 PM PST: EXHIBIT FLOOR, POSTER SECTION 45

SESSION PO.CL10.01: REAL-WORLD BIOMARKERS

An analysis of proviral insertion site of Moloney murine leukemia virus *PIM1* kinase expression and clinical outcomes in renal cell carcinoma

Sheldon L. Holder, Galina Lagos, Benedito. A. Carneiro, Anthony Mega, Andre De Souza, Rana R. McKay, Andrew Elliott, Chadi Nabhan, Stephanie L. Graff

Abstract: 2567 / 27 **Presenter:** Sheldon L. Holder

Key Findings:

- Molecular profiling of 147 clear cell renal cell carcinoma (ccRCC) samples in Caris' clinicogenomic database found that high expression of the oncogenic *PIM1* kinase was associated with shorter overall survival (OS) (869 vs 1,738 days) in ccRCC.
- *PIM1* enrichment in metastatic vs primary ccRCC, and association of high *PIM1* with differentially expressed genes (DEGs) involved in extracellular matrix biology, suggest that *PIM1* may influence the extracellular matrix to promote metastasis.
- 6.5-fold higher expression of cytokine IL-6 in *PIM1*-high vs *PIM1*-low RCC was consistent with prior data showing involvement of an IL-6/JAK/STAT/PIM1 pathway in ccRCC.
- Better targeted therapies are needed for *PIM1*-high RCC, where immune checkpoint inhibition is associated with poor survival, and mTOR and VEGF inhibition trend toward poorer survival, whereas high *PIM1* expression did not affect survival in papillary RCC.

SESSION PO.ET06.03: NOVEL THERAPEUTICS

Surfaceome and cancer testis antigen profiling of lung adenocarcinoma by large-scale transcriptomic analysis

Andrew Swartz, Andrew Elliott, George W. Sledge, Stephen V. Liu, Balazs Halmos, Vincent K. Lam, Taofeek K. Owonikoko

Abstract: 3361 / 18 **Presenter:** Andrew Swartz

Key Findings:

- In order to identify new therapeutic targets for lung adenocarcinoma, expression of surfaceome and cancer testis (CT) antigen genes was examined by whole transcriptome sequencing (WTS) of 9,002 tumors stratified into five subgroups based on the presence of specific driver mutations: *ALK* fusion, *EGFR, KRAS* with wild-type (WT) *STK11* & *KEAP1*, *KRAS* + *STK* or *KEAP1*, and Pan-WT (no listed driver mutations detected).
- The most highly expressed candidate genes had similar expression across subgroups, but driver-associated candidate genes with relatively high expression (> 75th percentile) in the subgroup and significant differences compared to all other subgroups were identified.
- This set of driver-associated candidate genes can help prioritize the validation and development of novel therapeutic targets in lung adenocarcinoma.

Describing the molecular landscape of cervical cancer metastases: Implications for future therapeutic targets

Matthew J. Hadfield, Sharon Wu, Alex Farrell, Matthew J. Oberley, Grace Sun, Jody Wellcome, Matthew Anderson, Don Dizon

Abstract: 3362 / 19 **Presenter:** Matthew J. Hadfield

Key Findings:

- A significant number of cervical cancer (CC) patients present with or progress to advanced disease.
- Caris testing of 2,668 cervical cancer (CC) samples (1,393 primary cervix samples, 383 local metastatic GYN samples, and 892 distant metastatic samples) enabled comparison of the molecular and immune alterations in CC primaries (CCP) vs. CC metastases (CCM) and interrogation of potential therapeutic strategies.
- CCM to lymph nodes and liver had the most distinct molecular and immune landscape compared to CCP while ovary/FT had a similar molecular profile but a distinctively cold immune profile compared to CCP.
- Additional studies will be needed to further evaluate the potential therapeutic opportunities.

MONDAY, APRIL 8, 2024

3:35-3:50 PM PST: BALLROOM 6 CF - UPPER LEVEL - CONVENTION CENTER

SESSION MS.CL10.01: APPLICATION OF REAL-WORLD EVIDENCE TO CANCER CARE

MINISYMPOSIUM – ORAL PRESENTATION

Comprehensive molecular and immunological characterization of early-onset esophagogastric cancer

Lawrence W. Wu, Sachin Kumar Deshmukh, Sharon Wu, Joanne Xiu, Alex Farrell, Vincent K. Lam, Emil Lou, Sanjay Goel, Chadi Nabhan, Ryan Moy

Abstract: 3890 **Presenter:** Lawrence W. Wu

Key Findings:

- Comprehensive molecular profiling of 5,175 esophagogastric cancer (EGC) patients identified distinct molecular signatures for early-onset (< 50 years of age, EOEGC, n=530) versus average-onset (AOEGC, n=4,645) tumors.
- EOEGC has increased frequency of *CDH1* mutations, *ARHGAP26* fusions, enrichment of epithelial mesenchymal transition (EMT) and angiogenesis pathways, decreased MAPK pathway activity, decreased frequency of TMB-high and dMMR/MSI-H, and a unique immune cell infiltrate with decreased M1 macrophages and increased M2 macrophages.
- These unique differential characteristics present therapeutic opportunities but also demonstrate the limitations of currently approved therapies in this subset of patients.

TUESDAY, APRIL 9, 2024

9:00 AM-12:30 PM PST: EXHIBIT FLOOR, POSTER SECTION 46

SESSION PO.CL01.02: PROGNOSTIC BIOMARKERS 1

Characterization of *PDLIM2* in non-small cell lung cancer

Karam Ashouri, Harris Krause, Andrew Elliott, Stephen V. Liu, Patrick C. Ma, Balazs Halmos, Zhaoxia Qu, Gutian Xiao, Ari Vanderwalde, Jorge J. Nieva

Abstract: 5201 / 9 **Presenter:** Karam Ashouri

Key Findings:

- *PDLIM2* acts as a tumor suppressor by downregulating NF-κB and *STAT3* signaling, modulating inflammation, immune response, and cell survival.
- 29,126 NSCLC cases (15,765 Adenocarcinoma, -A; 6,416 Squamous, -S) profiled by whole exome (WES) and whole transcriptome (WTS) sequencing were stratified by *PDLIM2* expression quartile (Q4: H, Q1: L).
- NSCLC-A with high *PDLIM2* expression had a unique mutational profile, increased immune cell infiltration, and favorable overall survival (OS). No difference in OS was observed between *PDLIM2*-S H vs L tumors.

WEDNESDAY, APRIL 10, 2024

9:00 AM-12:30 PM PST: EXHIBIT FLOOR, POSTER SECTION 8

SESSION PO.TB11.13: GENE EXPRESSION REGULATION IN THE TUMOR MICROENVIRONMENT

The genomic, transcriptomic, and immunologic landscape of TEM8 (*ANTXR1*) in neuroendocrine neoplasms (NENs)

Samuel A. Kareff, Harris Krause, Andrew Elliott, Peter Hosein, Emil Lou, Heloisa Soares, Matthew J. Oberley, Aman Chauhan

Abstract: 6851 / 28 **Presenter:** Samuel A. Kareff

Key Findings:

- Recent pre-clinical data suggest that therapies targeting the TEM8 receptor (coded by *ANTXR1*) may convert immunologically cold TMEs into an immune-"hot" milieu more amenable to treatment with immune checkpoint inhibitors (ICIs).
- Neuroendocrine neoplasms (NENs; N = 1,724) were profiled by next-generation sequencing of DNA (592 genes or WES) and RNA (WTS) and clustered by *ANTXR1* expression.
- NENs arising from the adrenal gland had the highest median *ANTXR1* expression, followed by those from the colon and rectum, genitourinary organs, small bowel (excluding appendix), and pancreas.
- There was no significant difference in median OS between *ANTXR1*-H vs -L tumors, no significant difference in associated pathogenic mutations, and no difference in the prevalence of TMB-H or PD-L1+.
- However, a greater proportion of B cells, M1 and M2 macrophages, and T-regulatory cells was observed in *ANTXR1*-H TMEs, which were more frequently classified as T cell-inflamed and had higher MAP kinase pathway activation compared to ANTXR1-L, suggesting that *ANTXR1*-H NENs might be more responsive to treatment with ICIs.

WEDNESDAY, APRIL 10, 2024

9:00 AM-12:30 PM PST: EXHIBIT FLOOR, POSTER SECTION 9

SESSION PO.TB11.09: IMMUNE CELLS IN THE TUMOR MICROENVIRONMENT 2

PIM kinases alter the prostate tumor immune microenvironment

Amber N. Clements, Kai Sutterby, Sachin Kumar Deshmukh, Sharon Wu, Joanne Xiu, Alex Farrell, Milan Radovich, Chadi Nabhan, Elisabeth I. Heath, Rana R. McKay, Alejandro Recio-Boiles, Noel A. Warfel

Abstract: 6875 / 19 **Presenter:** Amber N. Clements

Key Findings:

- In order to study how PIM kinases (*PIM1, PIM2,* and *PIM3*) alter the prostate TME and impact immunotherapy resistance, their expression level was analyzed in primary prostate and metastatic lymph node samples from treatment-naive metastatic hormone-sensitive prostate cancer patients.
- PIM-overexpressing prostate tumors displayed increased inflammation and infiltration of immunosuppressive immune cells, including M2 macrophages.
- Bone marrow derived macrophages treated with a PIM kinase inhibitor showed suppressed inflammasome signaling and release of the pro-inflammatory cytokine *IL-1β*.
- In a mouse model of prostate cancer, PIM inhibition in combination with immune checkpoint blockade synergistically decreased tumor growth and enhanced T cell activity.
- All these results suggest that PIM kinases play an important role in regulating the prostate TME and may be a potential target to enhance the efficacy of immunotherapy for the treatment of prostate cancer.

WEDNESDAY, APRIL 10, 2024

9:00 AM-12:30 PM PST: EXHIBIT FLOOR, POSTER SECTION 16

SESSION PO.MCB08.05: GENOMICS AND IMMUNOONCOLOGY

Comprehensive molecular and immune profiling of triple-negative invasive lobular carcinoma

Pooja Advani, Sachin Kumar Deshmukh, Sharon Wu, Jacob Andring, Joanne Xiu, Jose P. Leone, Priya Jayachandran, Stephanie L. Graff, Matthew J. Oberley, George W. Sledge Jr., Asher Chanan-Khan

Abstract: 7037 / 4 **Presenter:** Pooja Advani

Key Findings:

- Triple-Negative Invasive Lobular Carcinoma (TN-ILC) is a rare and aggressive breast cancer for which there are currently no targeted therapies or clinical trials available.
- A comprehensive analysis of the molecular and immune landscape of TN-ILC could identify novel targets and pathways for therapeutic intervention.
- Analysis of 395 breast cancers (364 invasive ductal TNBC, 31 TN-ILC) showed that TN-ILC had high TMB and AR expression, suggesting a possible role for immunotherapy (ICI) and AR antagonists in these patients.

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