Caris Abstracts and Presentation Schedule

AACR 2025

CARIS® LIFE SCIENCES

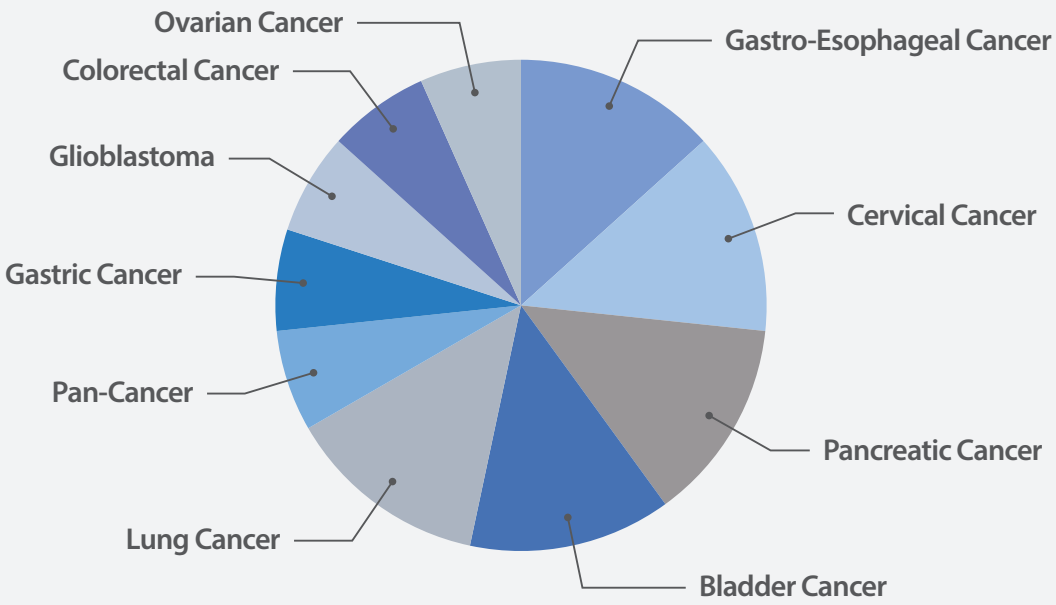
Where Molecular Science Meets Artificial Intelligence.

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 and CH variants. In collaboration with Caris Precision Oncology Alliance™ (POA) members, Caris is 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 glioblastoma, and lung, gastric, gastro-esophageal, colorectal, pancreatic, bladder, ovarian, and cervical cancers. In total, Caris and POA collaborators will present 14 abstracts, including two oral presentations and twelve posters. These studies highlight the power of collaborative research and demonstrate that:

- Comprehensive molecular profiling including WES & WTS in tissue and blood, as well as IHC in tissue, improves understanding of cancer molecular biology, drives the identification of novel biomarkers, and informs potential target identification for future treatment innovations.
- 580,000+ cases with matched molecular and outcomes data makes it possible to assess the efficacy of current therapies and guide clinical trial design.
- 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 27, 2025

2:00-5:00 PM CDT: SECTION 22

SESSION PO.ET06.04. MOLECULAR CLASSIFICATION OF TUMORS FOR DIAGNOSTICS, PROGNOSTICS, AND THERAPEUTIC OUTCOMES

Clinical, biologic, and immunogenic characteristics of gastro-esophageal cancers (GEC) harboring *CLDN18::ARHGAP* fusions

Axel Grothey, Amber Fifield, Kieran Sweeney, Heinz-Josef Lenz, Matthew Oberley, Sanjay Goel, Shuanzeng Wei, Andrew Elliott, Bradley Somer

Abstract: 496 **Poster Board #:** 8 **Presenter:** Axel Grothey

Key Findings:

- *CLDN18::ARHGAP* fusions define a distinct subtype of gastro-esophageal cancer (GEC), but their biologic relevance is poorly understood.
- In a cohort of 4,430 GEC tumors, whole transcriptome sequencing (WTS) revealed 262 tumors (6.1%) harboring a *CLDN18::ARHGAP* fusion.
- In addition to WTS, the tumor profiles included patient characteristics, outcomes data, DNA sequence (592 gene or whole exome) and PD-L1 and CLDN18 protein expression from immunohistochemistry (IHC).
- Fusion-positive tumors were more frequently CLDN18 IHC+, had more frequent *HER2* and *HER3* mutations, less frequent *RHOA, CDH1,* and *KRAS* mutations, a lower prevalence of the immunotherapy-related biomarkers TMB-H, dMMR/MSI-H, and PD-L1+, lower infiltration of CD8+ T cells and M1 macrophages, and higher infiltration of M2 macrophages.
- Together these data suggest that GECs with *CLDN18::ARHGAP* fusions have distinct clinical and biologic features that suggest lower immunogenicity.

SUNDAY, APRIL 27, 2025

2:00-5:00 PM CDT: SECTION 29

SESSION PO.CL01.12. DIAGNOSTIC BIOMARKERS 2

Functional characterization of *SMARCA4* genomic variants

Shivani Jagannathan Murali, Bharath Kumar Karre, Cristina Ivan, Kelly Craven, Stephanie Williams, Shikha Mahajan, Asfetaw Abera, Chao Sima, David Spetzler, Milan Radovich, Heather O'neill, Ravi Chakra Turaga

Abstract: 674 **Poster Board #:** 7 **Presenter:** Shivani Jagannathan Murali

Key Findings:

- A pan-cancer analyses of over 350,000 clinical molecular profiles from Caris examined *SMARCA4* genomic variants, including fusions from whole transcriptome sequencing (WTS) and protein truncating (PTVs) and non-truncating variants (non-PTVs) from DNA sequencing.
- Patients with *SMARCA4* PTVs had poor prognosis compared to those without *SMARCA4* variants in non-small cell lung cancer (NSCLC) and uterine endometrial cancer (EC).
- IHC for *SMARCA4* (N- & C-terminal) and *SMARCA2* from 35 cases showed that those with *SMARCA4* PTVs typically exhibited complete loss of *SMARCA4* and increased *SMARCA2* protein expression.
- Such tumors deficient in *SMARCA4* are candidates for treatment with synthetically lethal *SMARCA2* inhibitors. Other classes of *SMARCA4* variants may also be eligible for treatment but should be assessed individually, considering co-occurring mutations, copy number amplifications, and fusion partners.

SUNDAY, APRIL 27, 2025

2:00-5:00 PM CDT: SECTION 50

SESSION LBPO.ET01. LATE-BREAKING RESEARCH: EXPERIMENTAL AND MOLECULAR THERAPEUTICS 1

Targeting *ATM* modulates oncogenic pathways and amplifies chemotherapy efficacy in small cell lung cancer

Debdatta Halder, Utsav Sen, Vrinda Jethalia, Subhamoy Chakraborty, Yosuke Dotsu, Andrew Elliot, Ari Vanderwalde, Deniz Demircioglu, Dan Hasson, Triparna Sen

Abstract: LB016 **Poster Board #:** 16 **Presenter:** Debdatta Halder

Key findings will be made available on April 25, 2025.

MONDAY, APRIL 28, 2025

9:00 AM-12:00 PM CDT: SECTION 12

SESSION PO.MCB05.02. GENOME MAINTENANCE: MECHANISMS AND NOVEL THERAPEUTICS

Recurrent *PRKCI* gene fusions represent a drug target in gastric cancer and esophageal junction cancer

Shivani Jagannathan Murali, Bharath Kumar Karre, Cristina Ivan, Chao Sima, Asfetaw Abera, David Spetzler, Milan Radovich, Heather O'neill, Ravi Chakra Turaga

Abstract: 1474 **Poster Board #:** 10 **Presenter:** Shivani Jagannathan Murali

Key Findings:

- Examination of whole exome (WES) and whole transcriptome (WTS) molecular profiles of 6,437 esophageal junction carcinoma (EJC) and 3,615 gastric adenocarcinoma (GAC) cancer cases identified *PRKCI* fusions in 0.19% of EJC and 0.3% of GAC.
- RNA expression of *PRKCI* was significantly higher in *PRKCI*-fusion positive than in fusion-negative cases, and almost half (46.7%) of *PRKCI*-fusion positive cases had *PRKCI* copy number amplification.
- All the *PRKCI* fusions lacked the *PRKCI* N-terminal regulatory domain, leading to constitutive activation of the encoded PKCι kinase protein.
- This study suggests that PKCι kinase inhibitors may improve survival and outcomes for patients with *PRKCI* fusions in EJC and GAC.

MONDAY, APRIL 28, 2025

9:00 AM-12:00 PM CDT: SECTION 26

SESSION PO.CH02.01. PROTEOMIC SIGNATURES IN CANCER

Improving capability for biomarker discovery of glioblastoma-enriched poly-ligand profiling library using Aptamer Capture Microarrays

Xixi Wei, Justin Saul, Daniel Martin, Alexis Rodin, Anna Walton, Danielle Richard, Tassilo Hornung

Abstract: 1895 **Poster Board #:** 25 **Presenter:** Xixi Wei

Key Findings:

- The Adaptive Dynamic Artificial Poly-ligand Targeting (ADAPT) platform for therapeutic target discovery employs aptamer enrichment to identify cancer-type-specific biomarkers from formalin-fixed paraffin-embedded tumor tissue (FFPE).
- An aptamer library previously selected on GBM tissue by Systematic Evolution of Ligands by Exponential enrichment (SELEX) has now been used to stain clinical GBM patients' and normal FFPE tissues. The bound aptamer species were identified by next generation sequencing (NGS).
- Using Aptamer Capture Microarrays (ACM) to isolate sub-pools of aptamers that bound preferentially to GBM tissues from the GBM-enriched library showed enhanced discrimination of tissue staining specificity.
- This novel application of microarray capture to further optimize aptamer library selection is expected to improve the ability to identify cancer biomarkers.

MONDAY, APRIL 28, 2025

9:00 AM-12:00 PM CDT: SECTION 30

SESSION PO.CL01.15. METASTASIS BIOMARKERS / PROGNOSTIC BIOMARKERS 1

Comprehensive molecular and immunological characterization of *CLDN18.2* in pancreatic cancer

Midhun Malla, Sachin Deshmukh, Timothy Samec, Sharon Wu, Joanne Xiu, Mehmet Akce, Garima Gupta, Qasim Hussaini, Darryl Outlaw, Rebecca Arrend, Aakash Desai, Arnab Basu, Purnachandra N. Ganji, Mark Evans, Heinz-Joseph Lenz, Emil Lou, Dani Castillo, Rachna Schroff, David Spetzler, Bassel El-Rayes

Abstract: 2026 **Poster Board #:** 28 **Presenter:** Midhun Malla

Key Findings:

- Claudin 18 (CLDN18), a transmembrane protein that maintains a tight junction between cells, is an emerging biomarker in pancreatic cancer (PC), particularly its *CLDN18.2* isoform.
- *CLDN18.2* mRNA expression was quantified in 9,837 PC samples tested by NGS (592 gene or WES), WTS, and IHC (PD-L1) at Caris.
- High *CLDN18.2* expression was associated with better overall survival (OS) in primary and metastatic PC, and above median levels of NK cells in the tumor microenvironment were a contributing factor.
- Overall, *CLDN18.2* expression is associated with distinct genomic alterations, a differentially modulated immune microenvironment and PC patients' survival.
- Prospective clinical trials using novel approaches to target *CLDN18.2* in PC are underway.

MONDAY, APRIL 28, 2025

2:00 -5:00 PM CDT: SECTION 7

SESSION PO.TB10.08. TARGETING THE TUMOR MICROENVIRONMENT: A BRAVE NEW WORLD

FXIIIa-mediated transferrin sequestration drives cancer stem cell phenotype in colorectal cancer

Savannah Gregg, Rio Boothello, Sareh Bayatpour, Shoja M. Haneefa, Adam Hawkridge, Umesh Desai, Gretchen Hubbard, Andrew Elliott, Jose J. Trevino II, Leopoldo Fernandez, Mary Garland-Kledzik, Bhaumik Patel, Adam Khader

Abstract: 2688 **Poster Board #:** 5 **Presenter:** Savannah Gregg

Key Findings:

- Tumors, often described as wounds that do not heal, exhibit cross-linked fibrin (XLF) clots, which may harbor cancer stem cells (CSCs).
- Factor XIII (FXIII), a transglutaminase, functionalizes XLF clots by incorporating additional protein into the matrix.
- *FXIII* expression and its correlation with survival in colorectal cancer (CRC) were examined in the CARIS CODEai database and The Cancer Genome Atlas (TCGA).
- *FXIIIA1* RNA expression was 2.7-fold higher in CRC peritoneal metastasis (PM) compared to primary sites, and higher expression correlated with poor survival in all stages.
- This finding informed follow-on work to identify proteins enriched by high FXIIIa activity in CRC cell lines grown in an XLF spheroid model.
- The XLF spheroid model identified transferrin (Tf) and iron saturation as crucial to promoting the CSC niche, marking Tf as a possible target for therapeutic intervention.

MONDAY, APRIL 28, 2025

2:00 -5:00 PM CDT: SECTION 14

SESSION PO.MCB05.01. ORIGINS AND MECHANISMS OF GENOMIC INSTABILITY

Association of cyclin E1 expression with genomic instability in ovarian cancer

Ajay Obla, Michelle Kinder, Chifei Sun, Heather Bullins, Cynthia Timmers, Ming Poi, Sharon Wu, Edoardo Missiglia, Bettina Bisig, Krisztian Homicsko

Abstract: 2846 **Poster Board #:** 13 **Presenter:** Ajay Obla

Key Findings:

- CCNE1 DNA amplification (AMP), messenger RNA (mRNA) expression, and cyclin E1 protein expression were analyzed for their association with replicative stress in 8,127 high-grade serous ovarian cancer (HGSOC) samples from Caris, supplemented by 1,177 samples from The Cancer Genome Atlas (TCGA).
- The Caris samples were profiled by DNA (592 gene or WES) and RNA (WTS) sequencing, from which genomic loss of heterozygosity (gLOH) and homologous recombination deficiency (HRD+/–) status were calculated.
- CCNE1 AMP was more frequent and mRNA expression higher in BRCA1/2 wild-type than in BRCA1/2 mutant tumors. CCNE1 mRNA expression was also higher in HRD– than HRD+ tumors.
- CCNE1 AMP was associated with low LOH, but CCNE1 mRNA expression was significantly higher in LOH-H compared with LOH-L cases.
- These data demonstrate that CCNE1 AMP and RNA/protein expression are associated with replicative stress in HGSOC. Their impact on clinical outcomes should be further investigated.

MONDAY, APRIL 28, 2025

2:50-3:00 PM CDT: ROOM S406 (VISTA BALLROOM) – MCCORMICK PLACE SOUTH (LEVEL 4)

SESSION CTMS02. AIMING FOR CURE: ADJUVANT AND NEOADJUVANT APPROACHES

CLINICAL TRIALS MINISYMPOSIUM – ORAL PRESENTATION

Pre-operative abemaciclib in localized cisplatin-ineligible MIBC with tissue and ctDNA molecular response validation (CLONEVO)

Bishoy M. Faltas, Mohamed Osman, Mark G. Evans, Daniel J. Margolis, Cora N. Sternberg, Jones T. Nauseef, Ana M. Molina, David M. Nanus, Neal A. Patel, Rohit K. Jain, Amie Patel, Michael Sigouros, Jyothi Manohar, Hiranmayi Ravichandran, Amanda Reid, Majd Al Assaad, Giovanni Medico, Giorgio Inghirami, Benjamin D. Hopkins, Juan Miguel Mosquera, Philip Abbosh, Manuel Hidalgo, William F. Hooper, Nicolas Robine, Olivier Elemento, Namrata Peswani, Suzanne Cole, Douglas S. Scherr, Scott T. Tagawa

Abstract: CT127 **Presenter:** Bishoy M. Faltas

Key findings will be made available on April 25, 2025.

MONDAY, APRIL 28, 2025

3:40-3:55 PM CDT: ROOM E451– MCCORMICK LAKESIDE CENTER (LEVEL 4)

SESSION MS.ET01.01: CONTINUUM OF INNOVATION: BIOLOGICAL THERAPEUTIC AGENTS

MINISYMPOSIUM – ORAL PRESENTATION

Kinase fusion landscape of pancreatic cancer

Shivani Jagannathan Murali, Bharath Kumar Karre, Cristina Ivan, Chao Sima, Asfetaw Abera, David Spetzler, Milan Radovich, Heather O'neill, Ravi Chakra Turaga

Abstract: 3781 **Presenter:** Ravi Chakra Turaga

Key Findings:

- Study of molecular profiles (WES & WTS) of 12,418 pancreatic primary and metastatic tumors identified more than 200 cases with recurrent oncogenic kinase fusions.
- The identified oncogenic kinase fusions were typically 3' partners, with their expression regulated by the corresponding 5' partners.
- Beyond well-known fusions, there were recurring fusions in *RPS6KB1*, *ROCK1*, and *STK3*.
- The most frequent fusion partners, all highly expressed in pancreatic tumors, were *ATP1B1*, *CLTC*, *DNAJB*, *EML4*, and *SND1*.
- Most kinase fusions showed higher expression than the native kinase in fusion-negative cases.
- The frequency of kinase fusions was higher in metastatic sites, particularly the liver, compared to primary tumors, suggesting a role in metastatic progression.

TUESDAY, APRIL 29, 2025

9:00 AM-12:00 PM CDT: SECTION 35

SESSION PO.EN01.01. MOLECULAR, PRECLINICAL, AND CLINICAL ENDOCRINOLOGY

The *ERBB4* exon skipping isoform JMA-CYT2 is the dominant isoform of *ERBB4* gene fusions

Shivani Jagannathan Murali, Bharath Kumar Karre, Cristina Ivan, Chao Sima, Asfetaw Abera, David Spetzler, Milan Radovich, Heather O'neill, Ravi Chakra Turaga

Abstract: 4761 **Poster Board #:** 28 **Presenter:** Shivani Jagannathan Murali

Key Findings:

- In a comprehensive analysis of *ERBB4* fusions in 216,176 solid tumors of 24 types, *ERBB4* fusions were detected in 0.25% of cases.
- Notably, 63.1% of *ERBB4* fusions involved the 3' end of the gene, with loss of the signal peptide and potential impairment of cell membrane translocation.
- The 83% prevalence of the ubiquitination-resistant JMa-Cyt2 isoform and retention of the cytoplasmic kinase domain in most fusions suggest that *ERBB4* fusions may contribute to oncogenesis through a STAT5A-dependent mechanism, independent of PI3K.
- These findings underscore the potential of *ERBB4* fusions as therapeutic targets and suggest gamma-secretase inhibitors as a promising treatment option.

TUESDAY, APRIL 29, 2025

9:00 AM-12:00 PM CDT: SECTION 51

SESSION LBPO.CL02. LATE-BREAKING RESEARCH: CLINICAL RESEARCH 2 / ENDOCRINOLOGY

GPR171, a prognostic marker of improved survival in cervix cancer: A Deep South Consortium in Oncology (DSCO) Project

Tanvi Joshi, Elisabeth Murphy, Sagar Chokshi, Kevin J. Lee, Sharon Wu, Joanne Xiu, Matthew J. Oberley, Britt K. Erickson, Charles A. Leath, Symmes Johnson, Bunja Rungruang, Rodney P. Rocconi, Nathaniel Jones, Jennifer Scalici

Abstract: LB261 **Poster Board #:** 10 **Presenter:** Kevin J. Lee

Key findings will be made available on April 25, 2025.

WEDNESDAY, APRIL 30, 2025

9:00 AM-12:00 PM CDT: SECTION 32

SESSION PO.CL01.06. LIQUID BIOPSY: CIRCULATING NUCLEIC ACIDS 4 / PREDICTIVE BIOMARKERS 1

Non-synonymous mutations in the IFN-γ pathway are predictive of response to immune checkpoint inhibition in NSCLC

Alexander Azizi, Arvind Ravi, Marzia Capelletti, Nicholas Haradhvala, Natalie Vokes, Stephen-John Sammut, Steven Ressler, Milan Radovich, Justin Gainor, Gad Getz

Abstract: 7140 **Poster Board #:** 4 **Presenter:** Alexander Azizi

Key Findings:

- In the Stand Up to Cancer-Mark Foundation (SU2C-MF) study of non-small cell lung cancer (NSCLC) patients, alterations in genes of the interferon gamma (IFN-γ) signaling pathway were associated with better clinical outcomes following PD-(L)1 immune checkpoint inhibition (ICI).
- To validate these results and examine predictive vs. prognostic significance of IFN-γ alterations, 1,070 cases from the Caris multimodal database were assessed and 88 cases (8.2%) with IFN-γ pathway mutations and ICI treatment were identified.
- Leveraging outcomes from matched claims data, alterations of the IFN-γ pathway were associated with significantly improved OS, independent of other factors such as TMB and PD-L1 status.
- Interestingly, in a cohort of NSCLC patients not treated with ICI, IFN-γ pathway alterations did not associate with OS.
- In summary, IFN-γ pathway alterations predict improved ICI outcomes and could guide immunotherapy stratification in NSCLC, but they are not prognostic.

WEDNESDAY, APRIL 30, 2025

9:00 AM-12:00 PM CDT: SECTION 42

SESSION PO.PS01.07. SOCIOECONOMIC, LIFESTYLE, AND BIOLOGICAL DRIVERS OF CANCER RISK AND SURVIVAL: CLINICAL OUTCOMES AND TREATMENT GUIDELINES

The effects of socioeconomic deprivation on the tumor microenvironment of bladder cancer

Tom Marco, Kenneth Barker, Jesse Ritter, Numaan Mahmood, Rishab Srivastava, Amith Rao, Isaac Zarif, Ricardo Estrada Mendizabal, Sachin Deshmukh, Edgar Tapia, Jose Guillen-Rodriguez, Juan Chipollini, Alejandro Recio-Boiles

Abstract: 7392 **Poster Board #:** 20 **Presenter:** Tom Marco

Key Findings:

- Bladder cancer patients with lower socioeconomic status (SES) often present with more aggressive disease and face poor outcomes.
- In a retrospective analysis of 93 patients (63 male and 30 female) ranging from age 33 to 92, each patient's neighborhood level of SES was scored using the Area Deprivation Index.
- Each patient's tumor microenvironment and mutational landscape was characterized and compared utilizing NGS (592 gene or WES) and WTS Sequencing.
- Lower SES bladder cancer patients had fewer CD8+ cells, less dendritic cell infiltration, and a low frequency of TMB-H, indicating a lower level of adaptive immune response present in the tumor microenvironment.

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