4426P Validation of the ultrasensitive tumor-informed WGS MAESTRO MRD assay in β-CORRECT

T. Hashimoto[1], Y. Nakamura[2], G. Young[3], M.R. Palomares[4], B. Culver[5], D.W. Hall[6], A. Johnson[3], E. Oki[7], D. Kotani[8], S. Mishima[8], J. Watanabe[9], N. Akazawa[10], K. Kataoka[11], H. Bando[1], T. Kato[12], G. Costa[13], A. Mazloom[13], J. Garces[14], R.F.L. Baehner[15], T. Yoshino[1]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [2]Translational Research Support Office, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [3]Department of Clinical Development, Exact Sciences Corporation, Madison, Japan; [4]Precision Oncology, Exact Sciences Corporation, Madison, Japan; [5]Science Office, Exact Sciences, La Jolla, Japan; [6]Medical Communication Department, Exact Sciences Corporation, Madison, Japan; [7]Surgery and Science, Kyushu University - Graduate School of Medical Sciences - Faculty of Medical Sciences, Fukuoka, Japan; [8]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [9]Department of Colorectal Surgery, Kansai Medical University, Moriguchi, Japan; [10]Department of Gastroenterological Surgery, Sendai City Medical Center Sendai Open Hospital, Sendai, Japan; [11]Division of lower GI, department of gastroenterological surgery, Hyogo Medical University, Nishinomiya, Japan; [12]Department of Colorectal Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; [13]Clinical development, Exact Sciences Corporation, Madison, Japan; [14]Science Office, Exact Sciences Corporation, Madison, Japan; [15]Pathology Dept., Exact Sciences Corporation, Madison, Japan

Background: Current whole-exome (WES) based MRD assays have suboptimal limit of detection (LoD) resulting in false ctDNA-negatives. To overcome this limitation, a tumor-informed whole-genome sequencing (WGS) assay with an ultra-low LoD using minor allele enriched sequencing through recognition oligonucleotides (MAESTRO) tracking up to 5000 variants was developed. We present analytical validation results and will present clinical validation results from the β-CORRECT cohort of GALAXY in stage II-IV colorectal cancer.

Methods: LoD was evaluated in 559 contrived samples with ctDNA dilutions of 0.01 — 12.0 parts per million (ppm) tested with assays targeting either 440 single nucleotide variants (SNVs) with 10ng cfDNA input (small panel/low input) or 4550 SNVs with 30ng cfDNA input (large panel/medium input). Precision studies assessed 1079 samples with 0 — 1.2 x 10-5 ppm across three reagent lots, operator groups and sets of instruments in a single lab. Accuracy studies included 495 clinical samples tested with the WGS assay and compared to WES assay results. Clinical validation testing is in progress on 245 postsurgical patient samples. Results for sensitivity, specificity and hazard ratios for distant recurrence-free survival will be presented.

Results: For the small panel/low input condition, 276 contrived samples gave a 95% LoD of 7.19 ppm. For the large panel/medium input condition, 271 contrived samples gave a 95% LoD of 0.54 ppm. For samples at or above the LoD, precision of the qualitative result was ≥ 95% for both conditions. For ctDNA-negative samples, under reproducibility conditions, qualitative precision was 97% for small panel/low input and 100.0% for large panel/medium input. For accuracy, the WGS assay detected all 135 WES ctDNA-positive samples (positive percent agreement 100.0%) and 16 of 61 WES ctDNA-negative samples (negative percent agreement 73.8%), with all 16 detected below the WES assay LOD of 50 ppm.

Conclusions: The WGS MRD assay detects less than 1 ppm ctDNA (95% LoD of 0.54 ppm) with high precision and accuracy. Clinical validation results from ongoing analyses of the β-CORRECT post-surgical timepoint will be presented and compared with published WES tumor-informed MRD test results.

Clinical trial identification: UMIN000049334.

Legal entity responsible for the study: The authors.

Funding: EXACT Sciences.

Disclosure: T. Hashimoto: Financial Interests, Personal, Advisory Board: Guardant Health; Financial Interests, Personal, Invited Speaker: CytoGen, Takata pharmatheutical, Myriad Genetics, Miyarisan Pharmatheutical, Takeda Pharmaceuticals, Guardant Health. Y. Nakamura: Financial Interests, Personal, Invited Speaker: Chugai, Merck Biopharma, MSD K.K, Daiichi Sankyo Co., Ltd., Guardant Health Japan Corp.; Financial Interests, Personal, Advisory Board: Natera, Inc., Exact Sciences, Guardant Health Pte Ltd, Tempus AI, Pfizer, Shionogi. G. Young: Financial Interests, Institutional, Member: EXACT Sciences. M.R. Palomares: Financial Interests, Personal, Full or part-time Employment: Exact Science; Financial Interests, Personal, Stocks/Shares: Exact Science; Non-Financial Interests, Leadership Role: Exact Science; Non-Financial Interests, Institutional, Proprietary Information: Exact Science. B. Culver: Financial Interests, Institutional, Member: EXACT Sciences. D.W. Hall: Financial Interests, Institutional, Member: EXACT Sciences. A. Johnson: Financial Interests, Institutional, Member: EXACT Sciences. E. Oki: Financial Interests, Personal, Invited Speaker: Ono Pharmaceutical Co. Ltd., Eli Lilly, Bristol-Myers Squibb, MSD, Takeda Pham; Financial Interests, Institutional, Research Grant: Guardant Health. D. Kotani: Financial Interests, Personal, Invited Speaker: Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eli Lilly, MSD, Merck Biopharma, Ono pharma, Pfizer, Taiho pharma, Takeda, Sysmex, Nihonkayaku, Novartis, Guardant Health; Financial Interests, Personal, Advisory Board: Takeda; Financial Interests, Institutional, Local PI: Ono pharma, MSD, Servier, Novartis, Janssen pharma, IQVIA, Syneos health, CIMIC shiftzero, CIMIC; Financial Interests, Institutional, Funding: Ono pharma. S. Mishima: Financial Interests, Personal, Advisory Board: Exact Science; Financial Interests, Personal, Invited Speaker: Eli Lilly Japan, Taiho Pharmaceutical, Takeda Pharmaceuticals; Financial Interests, Local PI: Boehringer Ingelheim, GSK, Bayer. H. Bando: Financial Interests, Personal, Advisory Board: Guardant Health Japan; Financial Interests, Institutional, Research Grant: Ono pharmaceutical; Other, Other, Lecture fee: Ono pharmaceutical, Taiho pharmaceutical, Guardant Health Japan; Other, Other, Consultant Fee: GxD. T. Kato: Financial Interests, Personal, Invited Speaker: CHUGAI PHARMACEUTICAL CO., LTD, Eli Lilly and Company, ONO Pharmaceutical Co, Takeda Pharmaceutical Company Limited; Financial Interests, Institutional, Research Grant: CHUGAI PHARMACEUTICAL CO; Financial Interests, Personal, Coordinating PI: ASAHIKASEI. G. Costa: Financial Interests, Institutional, Full or part-time Employment: Exact Sciences; Financial Interests, Institutional, Stocks/Shares: Exact Science. A. Mazloom: Financial Interests, Institutional, Member: EXACT Sciences. J. Garces: Financial Interests, Institutional, Member: EXACT Sciences. R.F.L. Baehner: Financial Interests, Institutional, Member: EXACT Sciences. T. Yoshino: Financial Interests, Personal, Invited Speaker: Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., Ono Pharmaceutical Co., Ltd.; Financial Interests, Personal, Other, Consulting Fee: Sumitomo Corp., Indivumed; Financial Interests, Institutional, Research Grant: Bristol-Myers Squibb K.K., Caris MPI, Inc., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Exact Sciences Corporation, FALCO biosystems Ltd., Medical & Biological Laboratories Co., Ltd., Merus N.V., Miyarisan Pharmaceutical Co., Ltd., MSD K.K., Natera Inc., Nippon Boehringer Ingelheim Co ., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sysmex Corp., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd.. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2026.08.4677

4427P This abstract has been removed because it was not presented at the ESMO Congress 2026

https://doi.org/10.1016/j.annonc.2026.08.5638

4428P Evaluation of cell cycle—specific targetable protein expressions in metastatic breast cancer progressing under CDK4/6 inhibitor therapy

M. Keskinkilic[1], G. Polat[2], M. Sevindik[3], F.S. Delek[4], S. Kum Sengezer[4], Z. Sultan Altun[4], M. Güray Durak[5], T. Yavuzsen[6]

[1]Department of Medical Oncology, Izmir Democracy University, Izmir, Türkiye; [2]Medical Oncology, Dokuz Eylul University - Faculty of Medicine, Izmir, Türkiye; [3]Department of Medical Pathology, Dokuz Eylul University - Faculty of Medicine, Izmir, Türkiye; [4]Department of Basic Oncology, Dokuz Eylul University, Izmir, Türkiye; [5]Department of Medical Pathology, Dokuz Eylul University, Izmir, Türkiye; [6]Department of Internal Medicine, Dokuz Eylul University - Faculty of Medicine, Izmir, Türkiye

Background: Despite the substantial clinical benefit of CDK4/6i in HR+/HER2-negative MBC, primary and acquired resistance remain major challenges. This study investigated the association of CDK7, Cyclin A, and Cyclin A1 expressions with progression and survival outcomes in patients receiving first-line CDK4/6i.

Methods: This retrospective translational study included 117 patients with HR+/HER2-negative MBC treated with first-line CDK4/6i. Immunohistochemical analyses of CDK7, Cyclin A, and Cyclin A1 were performed on archived tumor samples from primary or metastatic lesions. Associations between biomarker expression and survival outcomes were analyzed using appropriate statistical tests.

Results: In the study, which had a median follow-up period of 46.5 months, disease progression was observed in 38.5% of patients and death in 27.4%. 47.9% had de novo metastatic disease, and 52.1% had metachronous metastatic disease. CDK7 positivity was detected in 22.0% of the tumors. Although CDK7 expression was not significantly associated with overall progression or survival, early progression rates were numerically higher in CDK7-positive tumors both within the first 12 months (30.8% vs. 18.7%, p=0.185) and within the first 6 months (11.5% vs. 5.5%). Cyclin A expression showed no association with progression or survival outcomes. In contrast, increased Cyclin A1 expression showed a numerical association with early resistance patterns. Progression within the first 12 months was observed in 17.4% of cyclin A1-negative tumors, 27.6% of mildly positive tumors, and 100% of moderately positive tumors. Furthermore, cyclin A1-positive tumors showed a higher rate of progression within the first 6 months compared to cyclin A1-negative tumors (19.4% vs. 2.3%, p=0.003).

Conclusions: In HR+/HER2-negative MBCs treated with first-line CDK4/6 inhibitors, CDK7 and especially Cyclin A1 expression were observed to have potential associations with early resistance patterns, while Cyclin A expression did not show a significant clinical correlation. This suggests that these proteins may serve as translational biomarkers and potential therapeutic targets in metastatic breast cancer resistant to CDK4/6 inhibitors.

Legal entity responsible for the study: The authors.

Funding: Dokuz Eylul University Department of Scientific Research Projects.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2026.08.4679

4429P A chromosomal instability signature identifies patients with BRCA wild-type cancers who benefit from PARP inhibitors across four HRD-associated cancer types

D. Gómez Sánchez[1], M. Schmidt[1], A. Price[2], S. Nandakumar[3], M. Ahmed[4], D.M. Muldoon[5], A. Alsaafin[6], S. Graves[7], M. Sullivan[7], B. Weigelt[8], C. Bandlamudi[9], E.M. O'Reilly[10], W. Park[11], P. Razavi[12], W. Abida[13], N. Schultz[14], M. Berger[3], S. Shah[15], J. Garcia-Aguilar[16], F. Sanchez-Vega[17]

[1]Computational Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, United States of America; [2]Department of Center For Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, United States of America; [3]Computational Oncology, Memorial Sloan Kettering Cancer Center, New York, United States of America; [4]Breast Cancer, MSKCC - Memorial Sloan Kettering Cancer Center, New York, United States of America; [5]Department of Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, United States of America; [6]Department of Computational Oncology, Memorial Sloan Kettering Cancer Center, New York, United States of America; [7]Department of Ovarian Cancer, Memorial Sloan Kettering Cancer Center, New York, United States of America; [8]Department of Pathology , MSKCC - Memorial Sloan Kettering Cancer Center, New York, NY, United States of America; [9]Data Science, MSKCC - Memorial Sloan Kettering Cancer Center, New York, United States of America; [10]Department of Medicine, Memorial Sloan Kettering Evelyn H. Lauder Breast Center, New York, United States of America; [11]Pancreatic Cancer, MSKCC - Memorial Sloan Kettering Cancer Center, New York, United States of America; [12]Department of Medicine, MSKCC - Memorial Sloan Kettering Cancer Center, New York, United States of America; [13]Medicine, Memorial Sloan Kettering Cancer Center, New York, United States of America; [14]Computational Oncology, MSKCC - Memorial Sloan Kettering Cancer Center, New York, United States of America; [15]Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, Commack, United States of America; [16]Colorectal Cancer, MSKCC - Memorial Sloan Kettering Cancer Center, New York, United States of America; [17]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, United States of America

Background: PARP inhibitors (PARPi) benefit some BRCA wild-type (BRCAwt) patients, yet no pan-cancer biomarker exists to reliably identify this patient subset. Selecting for specific DNA repair gene alterations has shown limited predictive value, and existing companion diagnostics like Myriad MyChoice are tumor-type-specific and lack cross-tumor validation. Chromosomal instability (CIN) signatures, copy number-based genomic features quantifiable from FDA-approved panels such as MSK-IMPACT, offer a scalable alternative.

Methods: CIN signatures were derived from 55,028 MSK-IMPACT copy number profiles. Signature CX3, capturing HRD scars, was z-score normalized against 659 pan-cancer BRCA-altered samples, with $z \geq 0$ defining a binary biomarker (CX3-High vs CX3-Low). This threshold was evaluated in four PARPi-treated cohorts (N=337): advanced high-grade serous ovarian cancer (HGSOC; n=91), metastatic breast cancer (n=134), metastatic castration-resistant prostate cancer (mCRPC; n=81), and metastatic pancreatic cancer (n=31). Head-to-head comparison with Myriad GIS was performed in HGSOC.

Results: Among BRCAwt patients, CX3-high predicted greater PARPi benefit: longer PFS in HGSOC (HR=0.40, p=0.004, n=88) and OS (HR=0.36, p=0.034), longer PFS in breast cancer (HR=0.48, p=0.011, n=71) across receptor subtypes, higher PSA50 and RECIST response rates in mCRPC (33% vs 10% and 33% vs 0%; n=26), and a strong but underpowered trend in pancreatic cancer (HR=0.34, p=0.17, n=16). Against Myriad GIS (n=89), CX3 showed AUC=0.89, comparable PFS prediction (HR=0.42 vs 0.34), and reclassified Myriad HRD+ patients (median PFS 32.9 vs 8.6 months, p=0.05). Across the pan-cancer MSK-IMPACT cohort, 7,126/53,208 (13%) BRCAwt samples were CX3-high, 57% outside the four evaluated tumor types, suggesting broader PARPi applicability than currently recognized.

Conclusions: CX3, a HRD-linked CIN signature derived from routine panel sequencing, identifies BRCAwt PARPi responders across four cancer types with a single tumor-agnostic threshold. It matches Myriad MyChoice with added reclassification power, requiring no additional testing and expanding PARPi eligibility at a pan-cancer level.

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center.

Funding: Has not received any funding.

Disclosure: E.M. O'Reilly: Financial Interests, Personal, Advisory Board, Travel reimbursement only: BioNTech, Pfizer; Financial Interests, Personal, Advisory Board, +Spouse: Ipsen; Financial Interests, Personal, Advisory Board: Merck, AstraZeneca, Novartis, Astellas, BMS, Exelixis, Agenus, Moma Therapeutics; Financial Interests, Personal, Advisory Board, Spouse: Genentech/Roche, Eisai, Autem; Financial Interests, Personal, Other, Data and Safety Monitoring Board: Ability Pharma; Financial Interests, Personal, Invited Speaker: Research To Practice; Financial Interests, Institutional, Local PI: Genentech/Roche, Arcus, Elicio, AstraZeneca, Tango Therapeutics; Financial Interests, Personal and Institutional, Coordinating PI: BioNTech; Financial Interests, Institutional, Coordinating PI: Pertzye; Financial Interests, Institutional, Research Grant: Parker Institute; Financial Interests, Personal and Institutional, Local PI, Consulting personal - uncompensated: Revolution Medicine; Financial Interests, Personal and Institutional, Local PI, Clinical trial Advisory Board: Agenus; Non-Financial Interests, Other, Scientific and Medical Advisory BoardUncompensated: Pancreas Cancer Action Network; Non-Financial Interests, Member of Board of Directors, Vice-ChairUncompensated: National Pancreas Foundation; Non-Financial Interests, Other, Scientific advisory Board-Uncompensated: Hirshberg Foundation; Other, Other, Editor: American Society of Clinical Oncology, American Association of Cancer Research (AACR); Other, Other, PI SPORE Grant to MSK (institution): NCI/NIH; Other, Other, Investigator on grant (to institution): BreakThroughCancer. W. Park: Financial Interests, Personal, Other, Consultancy: Astellas; Financial Interests, Personal, Invited Speaker, Continuing Medical Education: American Physician Institute, Integrity; Financial Interests, Personal, Advisory Board: Revolution Medicines, Regeneron Pharmaceuticals, Innovent Biologics; Financial Interests, Personal, Other, Workshop for scientific collaboration: Amgen; Financial Interests, Personal, Other, Consulting: KeyQuest, IMGT, Expert Connect, TD Cowen, Guidepoint; Financial Interests, Personal, Invited Speaker: EPICS, SignifyMD, PER, Decera; Financial Interests, Institutional, Advisory Board: Saccharo Inc.; Financial Interests, Institutional, Other, Co-inventor of microhomology-mediated end-joining deletion footprint (MDF), a POLQ-associated deletion signature linked to genomic instability, neoantigen generation and immune activation in HRD cancers; intellectual property filed through MSKCC: Memorial Sloan Kettering Cancer Center; Financial Interests, Institutional, Research Grant: Merck, Break Through Cancer, Parker Institute for Cancer Immunotherapy, The Society of MSK, National Institute of Health - National Cancer Institute; Financial Interests, Institutional, Trial Chair: Astellas; Financial Interests, Institutional, Local PI: Lepu Biopharma, Amgen, Revolution Medicines, Verastem Oncology. P. Razavi: Financial Interests, Personal, Advisory Board: Novartis, AstraZeneca, Pfizer, Inivata, SAGA Diagnostics, Prelude Theraputics, Lilly, Regor Pharmaceuticals, Neogenomics, Natera, Biovica, Myriad, Foresight Diagnostics; Financial Interests, Institutional, Funding: Grail Inc, Novartis; Financial Interests, Institutional, Research Grant: AstraZeneca, Tempus, Guardant, Biotherenostics, Inviate, SAGA Diagnostics, Foresight, Personalis, Myriad; Non-Financial Interests, Advisory Role: Tempus. M. Berger: Financial Interests, Personal, Advisory Board: Eli Lilly, AstraZeneca; Financial Interests, Personal, Invited Speaker: SOPHiA Genetics; Financial Interests, Personal, Royalties: SOPHiA Genetics; Financial Interests, Personal and Institutional, Funding: Boundless Bio. F. Sanchez-Vega: Financial Interests, Personal, Invited Speaker, Participation as a speaker in the AI for Oncology meeting in Milan, May 2025: Istituto di Tumori Milano; Financial Interests, Institutional, Local PI, Research support for breast cancer project.: AstraZeneca. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2026.08.4680