AstraZeneca, The Rosetrees Trust, CRUK. C. Swanton: Financial Interests, Personal, Invited Speaker, Activity took place in 2016: Pfizer, Celgene; Financial Interests, Personal, Invited Speaker, October 26th 2020: Novartis; Financial Interests, Personal, Invited Speaker: Roche/Ventana, BMS, AstraZeneca, MSD, Illumina, GSK; Financial Interests, Personal, Advisory Board, Ad Board - November 12th, 2020: Amgen; Financial Interests, Personal, Advisory Board, Current - since 2018: Genentech; Financial Interests, Personal, Advisory Board: Sarah Canon Research Institute; Financial Interests, Personal, Advisory Board, Joined October 2020. Also have stock options: Bicycle Therapeutics; Financial Interests, Personal, Other, Consultancy: Medicxi; Financial Interests, Personal, Advisory Board, Member of the Science Advisory Board. Also had stock options until June 2021: GRAIL; Financial Interests, Personal, Other, Consultancy agreement: Roche Innovation Centre Shanghai; Financial Interests, Personal, Advisory Board, 29 November - 1 December 2022: Novartis; Financial Interests, Personal, Invited Speaker, Oncology Collective - 2nd Nov - 4 Nov 2022 - Atlanta, USA: Roche; Financial Interests, Personal, Advisory Board, ctDNA advisory Board - 24th March 2023: AstraZeneca; Financial Interests, Personal, Invited Speaker, Pfizer Oncology 'Leading the revolution for the future: Pfizer; Financial Interests, Personal, Advisory Board, Scientific Advisory Board and Stock options from September 2023: Relay Therapeutics; Financial Interests, Personal, Advisory Board, Member of the Scientific Advisory Board: SAGA Diagnostics; Financial Interests, Personal, Full or part-time Employment, Chief Clinician since October 2017: Cancer Research UK; Financial Interests, Personal, Ownership Interest, Co-Founder of Achilles Therapeutics. Also, have stock options in this company: Achilles Therapeutics; Financial Interests, Personal, Stocks/Shares, Stocks owned until June 2021: GRAIL, Apogen Biotechnologies; Financial Interests, Personal, Stocks/Shares: Epic Biosciences, Bicycle Therapeutics; Financial Interests, Personal, Stocks/Shares, Stock options: Relay Therapeutics; Financial Interests, Institutional, Research Grant, Funded RUBICON grant - October 2018 - April 2021: Bristol Myers Squibb; Financial Interests, Institutional, Research Grant, Collaboration in minimal residual disease sequencing technologies: Archer Dx Inc; Financial Interests, Institutional, Research Grant: Pfizer, Boehringer Ingelheim; Financial Interests, Institutional, Invited Speaker, Chief Investigator for the MeRmaiD 1and 2 clinical trials and chair of the steering committee: AstraZeneca; Financial Interests, Institutional, Research Grant, Research grant from Oct 2019 - July 2023 - Genetics of CIN and SCNAs for Targeted Discovery (SCEPTRE): Ono Pharmaceutical; Financial Interests, Institutional, Research Grant, Research Grants from 2015: Roche; Financial Interests, Personal, Other, Co-chief investigator: NHS-Galleri Clinical Trial; Financial Interests, Institutional, Research Grant, from October 2022: Personalis; Non-Financial Interests, Personal, Principal Investigator, Chief Investigator for MeRmaiD 1and 2 clinical trials: AstraZeneca; Non-Financial Interests, Personal, Member of Board of Directors, From 2019-2022: AACR; Non-Financial Interests, Personal, Other, Board of Directors: AACR; Non-Financial Interests, Personal, Advisory Role, EACR Advisory Council member: EACR. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2024.103851

113MO Spatial transcriptomics-derived classification of invasive lobular carcinoma: Associations with clinical, genomic characteristics, and prognosis

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Background: Invasive lobular carcinoma (ILC) is the second most common histological breast cancer subtype. Here, we classified ILC into four subtypes based on tumor microenvironment (TME) heterogeneity and investigated their association with clinical characteristics and prognosis.

Methods: Spatial transcriptomics (ST, Visium 10X) was performed on 43 hormone receptor-positive, HER2-negative ILC frozen tumor samples. By integrating morphology and sequencing data, ILCs were classified based on TME heterogeneity. Using gene signatures, these subtypes were retrieved in METABRIC (n=122) and SCAN-B (n=853) datasets. Chi-square, Kruskal-Wallis tests, and Cox proportional hazard models analyzed associations with clinical features and survival.

Results: Four ILC subtypes were identified using ST: proliferative (P, enriched in tumor cells and proliferation-related pathways), normal-stroma enriched (NSE, enriched in fibroblasts, carcinoma in situ and EMT-related pathways), metabolic (M, enriched in endothelial cells, metabolic pathways and AR gene expression), and metabolic-immune enriched (MIE, enriched in adipocytes, macrophages, endothelial cells and metabolic-related pathways). In METABRIC, P linked to higher tumor grade ($p=0.0187$) and more copy number aberrations ($p=0.0159$). In SCAN-B, P and NSE were associated with larger and smaller tumors, respectively ($p<0.001$). P was also linked to higher tumor grade ($p<0.001$), lymph node involvement ($p=0.02$), and high Ki67 ($p<0.001$). Univariate analysis in METABRIC showed NSE and P subtypes associated with good and poor prognosis, respectively, for relapse-free interval (RFI) (HR=0.56, $p=0.027$; HR=1.8, $p=0.019$). Multivariable analysis confirmed NSE's good prognosis (HR=0.47, $p=0.03$). In SCAN-B, NSE was linked to longer RFI (HR=0.42, $p=0.0018$) and P to shorter RFI (HR=2.2, $p=0.0014$). At the multivariate, NSE remained associated with longer RFI (HR=0.54, $p=0.035$).

Conclusions: Spatial transcriptomics revealed four ILC subtypes reflecting TME heterogeneity, which were validated in external datasets and linked to distinct clinical outcomes, enhancing prognosis accuracy in ILC.

Legal entity responsible for the study: The authors.

Funding: FNRS, Télévie, Association Jules Bordet.

Disclosure: F.P. Duhoux: Financial Interests, Institutional, Advisory Board: Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, Gilead, Seagen, MSD; Financial Interests, Institutional, Invited Speaker: Novartis, Pfizer, MSD, Roche, MSD, Boehringer Ingelheim, Pfizer, Novartis, Lilly, AbbVie, Seagen, Gilead, AstraZeneca, Menarini, Immutep; Financial Interests, Institutional, Expert Testimony: Seagen, Novartis, MSD. C. Sotiriou: Financial Interests, Institutional, Advisory Board: Astellas, Vertex, Seattle Genetics, Amgen, INC, Merck & Co; Financial Interests, Personal, Advisory Board: Cepheid, Puma; Financial Interests, Personal, Invited Speaker: Eisai, Prime Oncology, Teva; Financial Interests, Institutional, Other, Travel: Roche; Financial Interests, Institutional, Other, Internal speaker: Genentech; Financial Interests, Personal, Other, Regional speaker: Pfizer; Financial Interests, Institutional, Invited Speaker: Exact Sciences; Financial Interests, Personal, Advisory Board, Stock options: Signatur Biosciences. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2024.103852

114P Comprehensive genomic profiling by liquid biopsy captures tumor heterogeneity and identifies cancer vulnerabilities in patients with RAS/BRAFV600E wild type metastatic colorectal cancer in the CAPRI 2-GOIM trial

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Background: Emerging evidence supports tumor tissue-based comprehensive genomic profiling (CGP) in metastatic colorectal cancer (mCRC). Data on liquid biopsy-based circulating tumor DNA (ctDNA) CGP are scarce and mainly retrospective. Prospective comparison between the two tests is not currently available.

Methods: The CAPRI 2-GOIM trial investigates efficacy and safety of ctDNA-driven, cetuximab-based, sequence of three treatment lines in patients with RAS/BRAFV600E wild type (WT) mCRC, as determined by local laboratory. Before first-line therapy, CGP is performed with FoundationOne (F1) CDx and F1 Liquid (F1L) CDx (324 genes) on tumor tissue DNA and plasma ctDNA, respectively.

Results: For 2/207 (0.96%) patients, no ctDNA was detected by F1L CDx. No patient displayed tumor fraction (TF) below 1%, whereas elevated ctDNA ($TF \geq 10\%$) was detected among 140/205 (68.3%) patients. 1013 genomic variants were identified. F1L CDx found KRAS, NRAS or BRAFV600E alterations in 19 patients, whose tumors were classified as RAS/BRAFV600E WT by local laboratory. Both F1 CDx and F1L CDx were available for 164/205 (80%) patients. Concordance of 61.4% between the two tests was observed. Concordance increased to 72.7% for F1L CDx with TF $\geq$10%. Concordance for genes involved in anti-EGFR resistance was found in 137/164 (83%) patients, increasing to 91.5% for F1L CDx with TF $\geq$10%. A higher number of genomic alterations was detected by F1L CDx compared with F1 CDx, including 6 cases with KRAS and NRAS alterations. Overall, 109/205 (53.2%) patients displayed at least one actionable genomic alteration (I to IIIB), according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT).

Conclusions: Baseline liquid biopsy-based CGP is feasible, has high concordance with tumor tissue-based CGP, could better recapitulate tumor heterogeneity, and is clinically informative by identifying additional actionable genomic alterations in approximately half of RAS/BRAF^{V600E} WT mCRC patients.

Editorial acknowledgement: Giuseppe Colucci.

Clinical trial identification: NCT05312398.

Legal entity responsible for the study: Gruppo Oncologico dell'Italia Meridionale (GOIM).

Funding: Partially funded by Merck.

Disclosure: D. Ciardiello: Financial Interests, Personal, Other, Travel support: Merck KGaA, Sanofi, BMS. S. Napolitano: Financial Interests, Personal, Other, Travel support: Novartis, Amgen. E. Martinelli: Financial Interests, Personal, Invited Speaker: Merck-Serono, Bayer, Merck S.p.a., ESMO; Financial Interests, Personal, Invited Speaker, Advisory board and invited speaker and travel grant: Pierre-Fabre; Financial Interests, Personal, Invited Speaker, Advisory board and Invited speakers: Incyte; Financial Interests, Personal, Invited Speaker, Advisory board and invited speaker: Servier, Roche; Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Invited Speaker, Travel grant: AstraZeneca; Financial Interests, Personal, Invited Speaker, Advisory board: MSD. E. Maiello: Financial Interests, Personal, Expert Testimony: AstraZeneca, Merck KGaA, Lily, Roche, Eisai, Pfizer. A. Avallone: Financial Interests, Personal, Expert Testimony: Amgen, AstraZeneca, Merck Sharp & Dome, Eisai, BMS. R. Bordonaro: Financial Interests, Personal, Invited Speaker: Novartis, Sanofi, AstraZeneca, Amgen, Roche, Pfizer, BMS, Janssen-Cilag, Bayer. N. Fazio: Financial Interests, Personal, Other, Steering committee: Novartis; Financial Interests, Personal, Invited Speaker: Novartis; Financial Interests, Personal, Advisory Board: Merck, MSD, Novartis, Ipsen; Financial Interests, Institutional, Invited Speaker: Astellas, MSD, Beigene, Nucana, Ipsen, FibroGen, ITM, Boehringer; Financial Interests, Institutional, Research Grant: Ipsen, Novartis, Merck; Non-