

3012MO**Metastasis dissemination and divergence timing in TRACERx**

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Background

While metastatic disease causes most cancer-related deaths, mechanisms of metastatic spread are not fully understood. The TRACERx program is a longitudinal, multi-center, prospective study that tracks non-small-cell lung cancer (NSCLC) tumor evolution over time, enabling a detailed exploration of metastatic evolution. Here, we report the longitudinal primary-metastasis dissemination and divergence timing analysis of the completed TRACERx cohort.

Methods

Multi-region lung primary and metastatic lesions were subjected to whole-exome sequencing. We constructed phylogenetic trees to classify metastatic dissemination and divergence timing. We categorized metastases as monoclonal if seeded by a single clone or polyclonal otherwise. We classified metastases as late diverging if all primary clonal mutations were present in the metastatic tumor and early diverging otherwise.

Results

Data from the TRACERx primary-metastasis cohort suggest that early intrathoracic metastatic divergence present at primary surgery indicates a higher relapse risk. The cohort contains 249 patients with paired primary-metastasis samples including over 440 metastatic samples passing quality control. The metastatic samples include 353 lymph node (LN) metastases (primary surgery and relapse), 47 non-LN thoracic metastases as well as 49 extrathoracic metastases. 75% of the metastasis samples were monoclonal, comprising almost all extrathoracic metastases. While LN metastases were also largely monoclonal, intrathoracic LNs at primary surgery were more enriched in polyclonal metastases compared to recurrence/progression LNs. In 18% of patients, metastases diverged early from the primary tumor before the last clonal sweep. In patients with LN metastases at primary surgery, early diverging LN metastases were enriched in patients who later relapsed compared to patients who did not, translating to significantly shorter disease-free survival. These findings may be driven by differences in immune evasion and other metastatic driver events.

Conclusions

In the TRACERx primary-metastasis cohort we identify early metastatic divergence at primary surgery as a marker of disease relapse, highlighting the potential of classifying early tumor evolution to guide recurrence risk stratification.

Clinical trial identification

NCT01888601.

Legal entity responsible for the study

UCL and TRACERx Consortium.

Funding

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Disclosure

A.A. Azizi: Financial Interests, Personal, Other, Consulting: WHYZE Health, Nxera Pharma. M. Al Bakir: Financial Interests, Speaker, Consultant, Advisor: Achilles Therapeutics. M. Jamal-Hanjani: Financial Interests, Personal, Invited Speaker, Invited speaker honorarium: Oslo Cancer Cluster, Astex Pharmaceutical; Financial Interests, Personal, Invited Speaker, Speaker honorarium: Pfizer, Bristol Myers Squibb; Financial

Interests, Personal, Advisory Board, Cancer cachexia research advisory board: Pfizer; Financial Interests, Personal, Other, Consultancy meeting - one off: Astex; Financial Interests, Personal, Other, Speaker honoraria: Genentech; Financial Interests, Personal, Other, Co-Chair of the Scientific Evaluation Committee - honorarium received: Spanish Association Against Cancer; Non-Financial Interests, Advisory Role, Scientific Advisory Board and Steering Committee member: Achilles Therapeutics; Non-Financial Interests, Other, Scientific Review Committee Member: AACR CORE Grants Scheme; Other, I am named as co-inventor on patent PCT/US2017/028013 relating to methods for lung cancer detection: Patent; Other, GB priority patent application (GB2400424.4) with title: Treatment and Prevention of Lung Cancer: Patent. C. Swanton: Financial Interests, Personal, Invited Speaker, Activity took place in 2016: Pfizer; 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, AdBoard - 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 and is Chair of the Clinical Advisory Group/Board: 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: CiCOR (formerly Roche Innovation Centre Shanghai); Financial Interests, Personal, Advisory Board, Adboard member 2022, 2023, 2024 and 2025: 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; 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, Trial Chair, Chief Investigator for the MeRmaid 1 and 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, Principal Investigator, Chief Investigator for MeRmaid 1 and 2 clinical trials: AstraZeneca; Non-Financial Interests, Member of Board of Directors, From 2019-2022: AACR; Non-Financial Interests, Other, Board of Directors: AACR; Non-Financial Interests, Advisory Role, EACR Advisory Council member: EACR. All other authors have declared no conflicts of interest.