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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒ Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Burrows-Wheeler Aligner v0.7.12, Picard (v1.134), Genome Analysis Toolkit v3.6, MuTect (v1.1.7), Strelka (v2.9.2), GATK (v4.0.7.0) FACETS (v0.5.6)
Data analysis	OncoKB (downloaded on 28th June, 2018), PureCN, SOCRATES, PINDEL, deconstructSigs (v1.8.0), PyClone (v0.13.1), GraphPad Prism 6, R v3.4.2, strata 13.1 custom scripts (reported in methods): Shannon Index (ref 30), Position Specific Error Model (PSEM) (ref 48), Large-scale transitions (LST) (ref 25), identification of bilallelic loss of function mutations was done as in ref 26, identification of neoantigens was performed as reported in ref 54, 55. All codes and scripts are available on https://github.com/gustaveroussy/mBC_WES_Fabrice_Andre_2019

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

raw data are available at EGAS00001003290 , the data and scripts used to generate the figures are accessible at https://github.com/gustaveroussy/mBC_WES_Fabrice_Andre_2019
Tumor biopsies and blood for constitutional DNA were collected and were labeled with an anonymous study ID. A second step of anonymisation was done by assigning a new number in the shared databases.

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	617 metastatics breasts cancers samples from 6 precision medicine trials. With alpha=5% (2-sided) and 1537 patients (617 mBC and 920 eBC), it's possible to detect a difference between groups of 3.7% supposing an incidence in the eBC group of 5% (i.e 5% vs 8.7%) with a power of 80%. This shows that the study has the statistical power to detect new drivers or drivers enriched in mBC. 26 samples of circulating DNA from MONALEESA trials: this represent all patients presenting a RB1 mutation in the MONALEESA program. It was not planned to run statistical tests on these patients, but only describe their PFS. 4 metastatic breast cancer samples from RUBY trial: this represent all responders from RUBY trial available at the time of 1st revision (october 2018) for which no germline mutation was observed. No statistical analyses were planned to be done on these four samples, only the description of the genomic landscape of outlier responders
Data exclusions	no data were excluded from the analysis
Replication	we did not run in vivo or in vitro experiments, only analyses of human genomic data. The present study does not include a validation or a replication set. In order to avoid false positive results by statistical hazard, we have adjusted for multiple hypothesis testings.
Randomization	In the RUBY trial, all patients were allocated to experimental group (Fig 3e). In MONALEESA trial, patients were randomized between endocrine therapy and endocrine therapy + CDK4 inhibitor (Fig 2G). In SAFIR01, SAFIR02, MOSCATO, MATCH-R, PERMED, SHIVA trials; all trials and the experimental and control arms (when it exists) were merged in a single cohort of 617 patients. Outcome of this cohort was not analysed according to arm of treatment, but according to mutational profile. For this latter analysis, comparison was also done with an early breast cancer cohort (TCGA).
Blinding	MONALEESA was double blinded for patients and investigators.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☐	☒ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Unique biological materials

Policy information about availability of materials

Obtaining unique materials	samples are available on request. please send project summary to fandre@igr.fr

Human research participants

Policy information about studies involving human research participants

Population characteristics	Patients were selected for the current analyses if they fulfilled the following criteria: a. presenting a mBC, b. biopsy prospectively done in the metastatic setting, c. >30% tumor cells in the tumor biopsy, d. good genomic DNA quality (Genomic Quality Number > 7 using Fragment Analyzer from AATI), e. blood sample available for the sequencing of normal DNA. Supplementary Table describes the population and co-variates In addition, we included 26 patients from MONALEESA 2,3,7 trials that present an RB1 mutation detected by ctDNA. These patients were all presenting a metastatic breast cancer with expression of estrogen receptor and lack of Her2. They received maximum of one line of therapy for the metastatic breast cancer. 4 patients from RUBY trial. All these patients present with metastatic breast cancer, without germline mutation for BRCA1/2, at least one line of chemotherapy, no Her2 overexpression and with a genomic instability identified on SNP6 arrays.
Recruitment	In all trials, patients were recruited by investigators from local centers. There is no bias of recruitment in these centers since patients are not prescreened for molecular analyses before entering in the study, except for the 4 patients analyzed from RUBY trial. Patients presenting a mBC were selected from six prospective precision medicine trials. SAFIR-01, MOSCATO, SHIVA have already been reported. SAFIR-02 (NCT: 02299999), PERMED-01 (NCT: 02342158), MATCH-R (NCT: 02517892) are ongoing trials. In each of these trials, a biopsy was obtained prospectively and frozen sample was stored. In addition, we analysed plasma samples from three randomized trials (monaleesa 2, 3, 7) and one phase II trial (RUBY).