SUPPLEMENTARY MATERIAL & METHODS

Cellularity assessment

The tumor cellularity is performed on the FFPE and the frozen specimens. The most representative FFPE bloc of the metastasis is recorded in order to facilitate any further molecular analyses based on the nucleic acids extracted from this bloc.

The respective percentage of tumor cells, the percentage of in situ versus invasive lesions, of lymphoid infiltrates, of (myo)-fibroblasts and the existence of necrosis areas are taken into account.

Macrodissection is performed if necessary to enrich the tumor samples with tumoral cells before nucleic acid extraction.

Immunohistochemistry of PTEN

The genomic loss or a deletion of PTEN has been validated using immunohistochemistry. The monoclonal antibody specific of the PTEN amino acids 321 to 336 has been used (Zymed® laboratories). Internal control was a positive expression of PTEN in the stromal fibroblasts. A normal prostate tissue was used for an external control in every manipulation. Interpretation of the staining determined the percentage of tumoral positive cells, the intensity of the staining on a three-tiered scale (form 1 to 3) as well as the good quality of the external control and the presence of the internal control.

CGH array

DNA was extracted according to a standard phenol/chloroform method using Phase Lock Gel Light (Eppendorf, Hamburg, Germany). The quantity and quality of the obtained DNA were estimated in 2 steps. Firstly, a Nanodrop spectrophotometer was used to assess gDNA purity (for optimal labeling yield, samples should have A260/A280 ≥ 1.8 and A260/A230 ≥ 1.9). Then, a Qubit dsDNA BR Assay Kit was used to measure the double-stranded DNA concentration.

For each sample having good quality and sufficient quantity, 700 to 1000 ng of tumor DNA and reference DNA were labeled, purified and cohybridized in equal quantity to Agilent Microarrays (Agilent Technologies, Santa Clara, USA) over 12 to 24 hours. Arrays were washed and scanned according to the manufacturer's protocols (Agilent, cat. No: G4884A).

Images were acquired on a SureScanMicroarray Scanner using the CytoScan Software V.2.7, then analysed on CytoGenomics Software V.2.7. Profiles were validated as interpretable when they obtained good quality reports based on the classical parameters for aCGH such as the sex mismatch dynamics between the control and the tested sample, standard deviation of the Log2(R) around zero, and thickness of the smoothing signal. For each profile, tumoral cells content was taken into account to evaluate the alterations of interest and adapt the proposed Log2(R) threshold for focal Amplification (<10Mb >6-8 copies in a diploid context), Hemizygous losses (1 copie) and Homozygous losses (no copy at all)

Microsatellite instability analysis

DNA was extracted from macro-dissected FFPE tumor sections using Macherey-Nagel Tissue DNA extraction Kit and quantified using a QubitdsDNA BR Assay Kit (cat. No: Q32850). MSI analysis was performed with MSI Analysis System (Promega) consisting of mononucleotide repeats BAT-25, BAT-26, NR-21, NR-24, MONO-27 (and pentanucleotide repeats Penta C and Penta D for sample identification).

For detection of MSI, 10 ng of DNA was amplified with 1x primer mix, 1x Gold STR Buffer (Promega), and 0.5U Amplitaq Gold DNA Polymerase (ThermoFischer) in a GeneAmp PCR System 9700 Thermocycler (Applied Biosystems) following manufacturer's recommended amplification conditions for the MSI Analysis System. PCR products were denatured in deionized formamide with Internal Lane Standard 600 (Promega) for allele sizing and analyzed on a 3130xl Genetic Analyzer using GeneMapper 4.0 Software (Applied Biosystems). Samples were classified as MSI-High (MSI-H) when two or more markers out of a panel of five were unstable and MSI stable when there were no unstable markers.

NGS panel

Theranostic NGS panel is a custom targeted Generead DNAseq panel (Qiagen) including *AKT1, ALK, BRAF, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, HRAS, KIT, KRAS, MAP2K1, MAP2K2, MET, NOTCH1, NRAS, PDGFRA, PIK3CA* and *ROS1* genes.

For each sample, DNA libraries were prepared using Generead DNAseq panel PCR kit (Qiagen). Targeted NGS was performed using Illumina Miseq technology according to the manufacturer's instructions (Illumina, San Diago, CA, USA). Sequence data were aligned to the human reference genome (hg19) using Bowtie2 algorithm. The single nucleotide variants (SNVs) and indels were called using GATK Unified Genotyper with default parameters. Known variants found in dbsnp129 and dbsnp137 with a variant allele frequency (VAF) superior to 1% (1000g or ESP6500) were removed. Filtered retained variants must have a total coverage depth of greater than or equal to 300 reads and VAF of at least 1%.

Supplementary Table 1: Molecular alterations and classes of drugs received by the 45 patients included in clinical trials

Tumor location	Molecular alterations	Class of drug	Best overall response (CR/PR/SD/PD selon RECIST)
Ovary	KRAS mutation	RAF inhibitor	NE
Ovary	AKT2 amplification	mTOR inhibitor	PD
Ovary	PTEN loss	mTOR inhibitor	SD
Ovary	KRAS mutation	RAF inhibitor	NA
Ovary	PIK3R2	mTOR inhibitor	PD
Ovary	PTEN loss	mTOR inhibitor	PD
Ovary	RICTOR amplification	mTOR inhibitor	SD
Ovary	PTEN deletion	mTOR inhibitor	PR
Ovary	PTEN deletion	mTOR inhibitor	NA
Ovary	KRAS mutation	RAF inhibitor	PD
Ovary	PIK3CA amplification	mTOR inhibitor	SD
Ovary	KRAS mutation	RAFinhibitor	PD
Breast	PIK3CA mutation	mTOR inhibitor	PD
Breast	PIK3CA mutation	mTOR inhibitor	PD
Breast	FGFR amplification	mTOR inhibitor	PD
Breast	PIK3CA mutation	mTOR inhibitor	PR
Breast	HRAS mutation	RAF inhibitor	PD
Breast	NOTCH2 amplification	NOTCH inhibitor	PD
Colorectal	AKT2 amplification	mTOR inhibitor	NE
Colorectal	KRAS mutation	RAF inhibitor	PD
Colorectal	PIK3CA mutation	mTOR inhibitor	SD
Colorectal	FBXW7 mutation	NOTCH inhibitor	SD
Colorectal	PTEN loss	mTOR inhibitor	PR
Colorectal	NRAS mutation	RAFinhibitor	SF
Cervix	PIK3CA mutation	mTOR inhibitor	SD
Cervix	PIK3CA mutation	mTOR inhibitor	CR
Cervix	PTEN mutation	mTOR inhibitor	PD
Cervix	KRAS mutation	RAF inhibitor	SF
Prostate	PTEN mutation	mTOR inhibitor	PD
Prostate	KIT mutation	KIT inhibitor	PD
Prostate	PTEN deletion	mTOR inhibitor	PD
Uterus	KDR/VEGFR2, PDGFRA and KIT amplification	VEGFR2 inhibitor	PD
Uterus	KRAS mutation	RAF inhibitor	SD
Uterus	PIK3CA mutation and PTEN loss	mTOR inhibitor	PD
Pancreas	KRAS mutation	RAF inhibitor	SF
Pancreas	KRAS mutation	RAF inhibitor	NA

Urothelial	KDR mutation	VEGFR2 inhibitor	SD
Urothelial	PTEN Loss	mTOR inhibitor	PD
Bone	PIK3CA mutation	mTOR inhibitor	PD
Brain	NOTCH4 mutation	NOTCH inhibitor	PD
Head and neck	PIK3CA mutation and PTEN loss	PI3K inhibitor	PD
Liver	KRAS mutation	RAF inhibitor	SD
Lung	STK11 incativation	mTOR inhibitor	SD
Skin	PTEN loss	mTOR inhibitor	PD
Unknown	PTEN deletion	mTOR inhibitor	PD

NA = not available; NE = not evaluable; CR = complete response, PR = partial response; SD = stable disease, PD = progressive disease; SF = screen failed (patient not treated)