

Année de publication : 2020

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Antoine Vasseur, Nicolas Kiavue, François-Clément Bidard, Jean-Yves Pierga, Luc Cabel (2020 Dec 8)

**Clinical utility of circulating tumor cells: an update.**

*Molecular oncology* : [DOI : 10.1002/1878-0261.12869](https://doi.org/10.1002/1878-0261.12869)

**Résumé**

The prognostic role of circulating tumor cells (CTCs) has been clearly demonstrated in many types of cancer. However, their roles in diagnostic and treatment strategies remain to be defined. In this review, we present an overview of the current clinical validity of CTCs in non-metastatic and metastatic cancer, and the main studies or concepts investigating the clinical utility of CTCs. In particular, we focus on breast-, lung-, colorectal- and prostate cancer. Two major topics concerning the clinical utility of CTC are discussed: treatment based on CTC count or CTC variations; and treatment based on the molecular characteristics of CTCs. Although some of these studies are inconclusive, many are still ongoing, and their results could help to define the role of CTCs in the management of cancers. A summary of published or ongoing phase II-III trials is also presented.

François-Clément Bidard, William Jacot, Nicolas Kiavue, Sylvain Dureau, Amir Kadi, Etienne Brain, Thomas Bachelot, Hugues Bourgeois, Anthony Gonçalves, Sylvain Ladoire, Hervé Naman, Florence Dalenc, Joseph Gligorov, Marc Espié, George Emile, Jean-Marc Ferrero, Delphine Loirat, Sophie Frank, Luc Cabel, Véronique Diéras, Laure Cayrefourcq, Cécile Simondi, Frédérique Berger, Catherine Alix-Panabières, Jean-Yves Pierga (2020 Nov 5)

**Efficacy of Circulating Tumor Cell Count-Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: The STIC CTC Randomized Clinical Trial.**

*JAMA oncology* : [DOI : 10.1001/jamaoncol.2020.5660](https://doi.org/10.1001/jamaoncol.2020.5660)

**Résumé**

The choice between chemotherapy and endocrine therapy as first-line treatment for hormone receptor-positive, ERBB2 (also known as HER2)-negative metastatic breast cancer is usually based on the presence of clinical features associated with a poor prognosis. In this setting, a high circulating tumor cell (CTC) count ( $\geq 5$  CTCs/7.5 mL) is a strong adverse prognostic factor for overall survival and progression-free survival (PFS).

Luc Cabel, Dan Rosenblum, Florence Lerebours, Etienne Brain, Delphine Loirat, Mattias Bergqvist, Paul Cottu, Anne Donnadiou, Anne Bethune, Nicolas Kiavue, Manuel Rodrigues, Jean-Yves Pierga, Marie-Laure Tanguy, François-Clément Bidard (2020 Sep 15)

**Plasma thymidine kinase 1 activity and outcome of ER+ HER2- metastatic breast cancer patients treated with palbociclib and endocrine therapy.**

*Breast cancer research : BCR : 98 : DOI : [10.1186/s13058-020-01334-2](https://doi.org/10.1186/s13058-020-01334-2)*

**Résumé**

Previous cohort studies have reported plasma TK1 activity (pTKa) as a potential prognostic biomarker in estrogen receptor-positive (ER+) HER2-negative (HER2-) metastatic breast cancer (MBC). In this prospective study, we report here the prognostic impact of pTKa in ER+/HER2- MBC patients treated with endocrine therapy and CDK4/6 inhibitor.

Afroditi Nanou, Leonie Laura Zeune, Francois-Clement Bidard, Jean-Yves Pierga, Leonardus Wendelinus Mathias Marie Terstappen (2020 Aug 14)

**HER2 expression on tumor-derived extracellular vesicles and circulating tumor cells in metastatic breast cancer.**

*Breast cancer research : BCR : 86 : DOI : [10.1186/s13058-020-01323-5](https://doi.org/10.1186/s13058-020-01323-5)*

**Résumé**

Tumor-derived extracellular vesicles (tdEVs) and circulating tumor cells (CTCs) in the blood of metastatic cancer patients associate with poor outcomes. In this study, we explored the human epidermal growth factor receptor 2 (HER2) expression on CTCs and tdEVs of metastatic breast cancer patients.

Mark Jesus M Magbanua, Laura H Hendrix, Terry Hyslop, William T Barry, Eric P Winer, Clifford Hudis, Deborah Toppmeyer, Lisa Anne Carey, Ann H Partridge, Jean-Yves Pierga, Tanja Fehm, José Vidal-Martínez, Dimitrios Mavroudis, Jose A Garcia-Saenz, Justin Stebbing, Paola Gazzaniga, Luis Manso, Rita Zamarchi, María Luisa Antelo, Leticia De Mattos-Arruda, Daniele Generali, Carlos Caldas, Elisabetta Munzone, Luc Dirix, Amy L Delson, Harold Burstein, Misbah Qadir, Cynthia Ma, Janet H Scott, François-Clément Bidard, John W Park, Hope S Rugo (2020 Aug 10)

**Serial analysis of circulating tumor cells in metastatic breast cancer receiving first-line chemotherapy.**

*Journal of the National Cancer Institute : DOI : [djaa113](https://doi.org/10.1186/djaa113)*

**Résumé**

We examined the prognostic significance of circulating tumor cell (CTC) dynamics during treatment in metastatic breast cancer (MBC) patients receiving first-line chemotherapy.

William Jacot, Martine Mazel, Caroline Mollevi, Stéphane Poudroux, Véronique D'Hondt, Laure Cayrefourcq, Céline Bourcier, Florence Boissiere-Michot, Fella Berrabah, Evelyne Lopez-Crapez,

François-Clément Bidard, Marie Viala, Thierry Maudelonde, Séverine Guiu, Catherine Alix-Panabières (2020 Jul 27)

**Clinical Correlations of Programmed Cell Death Ligand 1 Status in Liquid and Standard Biopsies in Breast Cancer.**

*Clinical chemistry* : 1093-1101 : [DOI : 10.1093/clinchem/hvaa121](https://doi.org/10.1093/clinchem/hvaa121)

**Résumé**

Data regarding the prognostic value of programmed cell death ligand 1 (PD-L1) expression on circulating tumor cells (CTCs) are lacking. However, CTCs could represent an alternative approach to serial biopsies, allowing real-time monitoring of cancer phenotype.

Marcela Carausu, Samia Melaabi, Jean-Yves Pierga, François-Clément Bidard, Luc Cabel (2020 May 13)

**Mutation Detection and Dynamics in Meningeal Carcinomatosis in Breast Cancer.**

*Journal of breast cancer* : 218-223 : [DOI : 10.4048/jbc.2020.23.e4](https://doi.org/10.4048/jbc.2020.23.e4)

**Résumé**

mutation is frequently encountered in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC), especially after aromatase inhibitor (AI) therapy, as a mechanism of resistance to endocrine therapy. Circulating tumor DNA-based detection of mutation in plasma has been demonstrated as a prognostic and predictive factor for poor outcomes in subsequent AI therapy. In this case report, for the first time, we describe the detection of mutation (p.Tyr537Ser) only in the cerebrospinal fluid (CSF) and not in the plasma of a patient with isolated leptomeningeal progression who was treated with AI for HR-positive, HER2-negative MBC (bone metastasis only). Circulating tumor DNA levels also appeared to be correlated with clinical evolution. We suggest that in the presence of isolated leptomeningeal metastasis and when tamoxifen or AI has been prescribed for HR-positive MBC, CSF should be screened for mutations to potentially adjust systemic treatment.

Ryan J O Dowling, Kevin Kalinsky, Daniel F Hayes, Francois-Clement Bidard, David W Cescon, Sarat Chandarlapaty, Joseph O Deasy, Mitch Dowsett, Robert J Gray, N Lynn Henry, Funda Meric-Bernstam, Jane Perlmutter, George W Sledge, Scott V Bratman, Lisa A Carey, Martin C Chang, Angela DeMichele, Marguerite Ennis, Katarzyna J Jerzak, Larissa A Korde, Ana Elisa Lohmann, Eleftherios P Mamounas, Wendy R Parulekar, Meredith M Regan, Daniel Schramek, Vuk Stambolic, Mangesh A Thorat, Timothy J Whelan, Antonio C Wolff, Jim R Woodgett, Joseph A Sparano, Pamela J Goodwin (2020 Apr 28)

**Toronto Workshop on Late Recurrence in Estrogen Receptor-Positive Breast**

**Cancer: Part 1: Late Recurrence: Current Understanding, Clinical Considerations.**

*JNCI cancer spectrum* : pkz050 : [DOI : 10.1093/jncics/pkz050](https://doi.org/10.1093/jncics/pkz050)

**Résumé**

Disease recurrence (locoregional, distant) exerts a significant clinical impact on the survival of estrogen receptor-positive breast cancer patients. Many of these recurrences occur late, more than 5 years after original diagnosis, and represent a major obstacle to the effective treatment of this disease. Indeed, methods to identify patients at risk of late recurrence and therapeutic strategies designed to avert or treat these recurrences are lacking. Therefore, an international workshop was convened in Toronto, Canada, in February 2018 to review the current understanding of late recurrence and to identify critical issues that require future study. In this article, the major issues surrounding late recurrence are defined and current approaches that may be applicable to this challenge are discussed. Specifically, diagnostic tests with potential utility in late-recurrence prediction are described as well as a variety of patient-related factors that may influence recurrence risk. Clinical and therapeutic approaches are also reviewed, with a focus on patient surveillance and the implementation of extended endocrine therapy in the context of late-recurrence prevention. Understanding and treating late recurrence in estrogen receptor-positive breast cancer is a major unmet clinical need. A concerted effort of basic and clinical research is required to confront late recurrence and improve disease management and patient survival.

Ryan J O Dowling, Joseph A Sparano, Pamela J Goodwin, Francois-Clement Bidard, David W Cescon, Sarat Chandarlapaty, Joseph O Deasy, Mitch Dowsett, Robert J Gray, N Lynn Henry, Funda Meric-Bernstam, Jane Perlmutter, George W Sledge, Mangesh A Thorat, Scott V Bratman, Lisa A Carey, Martin C Chang, Angela DeMichele, Marguerite Ennis, Katarzyna J Jerzak, Larissa A Korde, Ana Elisa Lohmann, Eleftherios P Mamounas, Wendy R Parulekar, Meredith M Regan, Daniel Schramek, Vuk Stambolic, Timothy J Whelan, Antonio C Wolff, Jim R Woodgett, Kevin Kalinsky, Daniel F Hayes (2020 Apr 28)

**Toronto Workshop on Late Recurrence in Estrogen Receptor-Positive Breast Cancer: Part 2: Approaches to Predict and Identify Late Recurrence, Research Directions.**

*JNCI cancer spectrum* : pkz049 : [DOI : 10.1093/jncics/pkz049](https://doi.org/10.1093/jncics/pkz049)

**Résumé**

Late disease recurrence (more than 5 years after initial diagnosis) represents a clinical challenge in the treatment and management of estrogen receptor-positive breast cancer (BC). An international workshop was convened in Toronto, Canada, in February 2018 to review the current understanding of late recurrence and to identify critical issues that require future study. The underlying biological causes of late recurrence are complex, with the processes governing cancer cell dormancy, including immunosurveillance, cell proliferation, angiogenesis, and cellular stemness, being integral to disease progression.

These critical processes are described herein as well as their role in influencing risk of recurrence. Moreover, observational and interventional clinical trials are proposed, with a focus on methods to identify patients at risk of recurrence and possible strategies to combat this in patients with estrogen receptor-positive BC. Because the problem of late BC recurrence of great importance, recent advances in disease detection and patient monitoring should be incorporated into novel clinical trials to evaluate approaches to enhance patient management. Indeed, future research on these issues is planned and will offer new options for effective late recurrence treatment and prevention strategies.

Alexandre Eeckhoutte, Alexandre Houy, Elodie Manié, Manon Reverdy, Ivan Bièche, Elisabetta Marangoni, Oumou Goundiam, Anne Vincent-Salomon, Dominique Stoppa-Lyonnet, François-Clément Bidard, Marc-Henri Stern, Tatiana Popova (2020 Apr 22)

**ShallowHRD: detection of homologous recombination deficiency from shallow whole genome sequencing.**

*Bioinformatics (Oxford, England)* : 3888-3889 : [DOI : 10.1093/bioinformatics/btaa261](https://doi.org/10.1093/bioinformatics/btaa261)

### Résumé

We introduce shallowHRD, a software tool to evaluate tumor homologous recombination deficiency (HRD) based on whole genome sequencing (WGS) at low coverage (shallow WGS or sWGS; ~1X coverage). The tool, based on mining copy number alterations profile, implements a fast and straightforward procedure that shows 87.5% sensitivity and 90.5% specificity for HRD detection. shallowHRD could be instrumental in predicting response to poly(ADP-ribose) polymerase inhibitors, to which HRD tumors are selectively sensitive. shallowHRD displays efficiency comparable to most state-of-art approaches, is cost-effective, generates low-storable outputs and is also suitable for fixed-formalin paraffin embedded tissues.

Amanda Bortolini Silveira, François-Clément Bidard, Amélie Kasperek, Samia Melaabi, Marie-Laure Tanguy, Manuel Rodrigues, Guillaume Bataillon, Luc Cabel, Bruno Buecher, Jean-Yves Pierga, Charlotte Proudhon, Marc-Henri Stern (2020 Mar 17)

**High-Accuracy Determination of Microsatellite Instability Compatible with Liquid Biopsies.**

*Clinical chemistry* : 606-613 : [DOI : 10.1093/clinchem/hvaa013](https://doi.org/10.1093/clinchem/hvaa013)

### Résumé

Microsatellite instability (MSI) has recently emerged as a predictive pan-tumor biomarker of immunotherapy efficacy, stimulating the development of diagnostic tools compatible with large-scale screening of patients. In this context, noninvasive detection of MSI from circulating tumor DNA stands as a promising diagnostic and posttreatment monitoring tool.

Emmanuelle Jeannot, Lauren Darrigues, Marc Michel, Marc-Henri Stern, Jean-Yves Pierga, Aurore Rampanou, Samia Melaabi, Camille Benoist, Ivan Bièche, Anne Vincent-Salomon, Radouane El Ayachy, Aurélien Noret, Nicolas Epailard, Luc Cabel, François-Clément Bidard, Charlotte Proudhon (2020 Feb 12)

**A single droplet digital PCR for ESR1 activating mutations detection in plasma.**

*Oncogene* : 2987-2995 : [DOI : 10.1038/s41388-020-1174-y](https://doi.org/10.1038/s41388-020-1174-y)

### Résumé

Activating mutations in the estrogen receptor 1 (ESR1) gene confer resistance to aromatase inhibitors (AI), and may be targeted by selective estrogen receptor downregulators. We designed a multiplex droplet digital PCR (ddPCR), which combines a drop-off assay, targeting the clustered hotspot mutations found in exon 8, with an unconventional assay interrogating the E380Q mutation in exon 5. We assessed its sensitivity in vitro using synthetic oligonucleotides, harboring E380Q, L536R, Y537C, Y537N, Y537S, or D538G mutations. Further validation was performed on plasma samples from a prospective study and compared with next generation sequencing (NGS) data. The multiplex ESR1-ddPCR showed a high sensitivity with a limit of detection ranging from 0.07 to 0.19% in mutant allele frequency. The screening of plasma samples from patients with AI-resistant metastatic breast cancer identified ESR1 mutations in 29% of them, all mutations being confirmed by NGS. In addition, this test identifies patients harboring polyclonal alterations. Furthermore, the monitoring of circulating tumor DNA using this technique during treatment follow-up predicts the clinical benefit of palbociclib-fulvestrant. The multiplex ESR1-ddPCR detects, in a single reaction, the most frequent ESR1 activating mutations with good sensitivity. This method allows real-time liquid biopsy for ESR1 mutation monitoring in large cohorts of patients.

Diana Bello Roufai, François-Clément Bidard (2020 Feb 5)

**Impact of circulating tumor DNA early detection and serial monitoring in the management of stage I to III colorectal cancer.**

*Annals of translational medicine* : S315 : [DOI : 10.21037/atm.2019.10.30](https://doi.org/10.21037/atm.2019.10.30)

### Résumé

**Année de publication : 2019**

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Antoine Vasseur, Luc Cabel, Olivier Tredan, Marion Chevrier, Coraline Dubot, Véronique Lorgis, William Jacot, Anthony Goncalves, Marc Debled, Christelle Levy, Jean-Marc Ferrero, Christelle Jouannaud, Elisabeth Luporsi, Marie-Ange Mouret-Reynier, Florence Dalenc, Jerome Lemonnier, Alexia Savignoni, Marie-Laure Tanguy, Francois-Clement Bidard, Jean-Yves Pierga (2019 Nov 28)

**Prognostic value of CEC count in HER2-negative metastatic breast cancer patients treated with bevacizumab and chemotherapy: a prospective validation**

**study (UCBG COMET).**

*Angiogenesis* : 193-202 : [DOI : 10.1007/s10456-019-09697-7](https://doi.org/10.1007/s10456-019-09697-7)

**Résumé**

Proof of concept studies has reported that circulating endothelial cell (CEC) count may be associated with the outcome of HER2-negative metastatic breast cancer (mBC) patients treated by chemotherapy and the anti-VEGF antibody bevacizumab. We report the results obtained in an independent prospective validation cohort (COMET study, NCT01745757).

William Jacot, Paul Cottu, Frederique Berger, Coraline Dubot, Laurence Venat-Bouvet, Alain Lortholary, Hugues Bourgeois, Marc Bollet, Veronique Servent, Elisabeth Luporsi, Marc Espié, Severine Guiu, Veronique D'Hondt, Veronique Dieras, Marie-Paule Sablin, Etienne Brain, Souhir Neffati, Jean-Yves Pierga, Francois-Clement Bidard (2019 Nov 16)

**Actionability of HER2-amplified circulating tumor cells in HER2-negative metastatic breast cancer: the CirCe T-DM1 trial.**

*Breast cancer research : BCR* : 121 : [DOI : 10.1186/s13058-019-1215-z](https://doi.org/10.1186/s13058-019-1215-z)

**Résumé**

In this prospective phase 2 trial, we assessed the efficacy of trastuzumab-emtansine (T-DM1) in HER2-negative metastatic breast cancer (MBC) patients with HER2-positive CTC.