



**HAL**  
open science

## **Quantitative cell-free DNA markers for prediction of early progression in patients undergoing immunotherapy**

Linh Nguyen Phuong, Laurent Greillier, Caroline Gaudy, Jean-Laurent Deville, Jean-Charles Garcia, Frédéric Fina, Sébastien Salas, Sébastien Benzekry

### ► **To cite this version:**

Linh Nguyen Phuong, Laurent Greillier, Caroline Gaudy, Jean-Laurent Deville, Jean-Charles Garcia, et al. Quantitative cell-free DNA markers for prediction of early progression in patients undergoing immunotherapy. Summer School AI4Health, Jul 2023, Paris, France. <hal-04388821>

**HAL Id: hal-04388821**

**<https://inria.hal.science/hal-04388821v1>**

Submitted on 11 Jan 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

# Quantitative cell-free DNA (cfDNA) markers for prediction of early progression in patients undergoing immunotherapy

Linh Nguyen Phuong<sup>1</sup>, Laurent Greillier<sup>1, 2</sup>, Caroline Gaudy<sup>2</sup>, Jean-Laurent Deville<sup>2</sup>, Jean-Charles Garcia<sup>4</sup>, Frédéric Fina<sup>3, 4</sup>, Sébastien Salas<sup>1, 2</sup>, Sébastien Benzekry<sup>1</sup>

<sup>1</sup> COMputational pharmacology and clinical Oncology Team, Inria Sophia Antipolis - Méditerranée, Cancer Research Center of Marseille, Inserm, CNRS, Aix Marseille University, Marseille, France.  
<sup>2</sup> Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique - Hôpitaux de Marseille, Aix Marseille University, Marseille, France.  
<sup>3</sup> ADELIS, Labège, France  
<sup>4</sup> Id-Solutions, Grabels, France

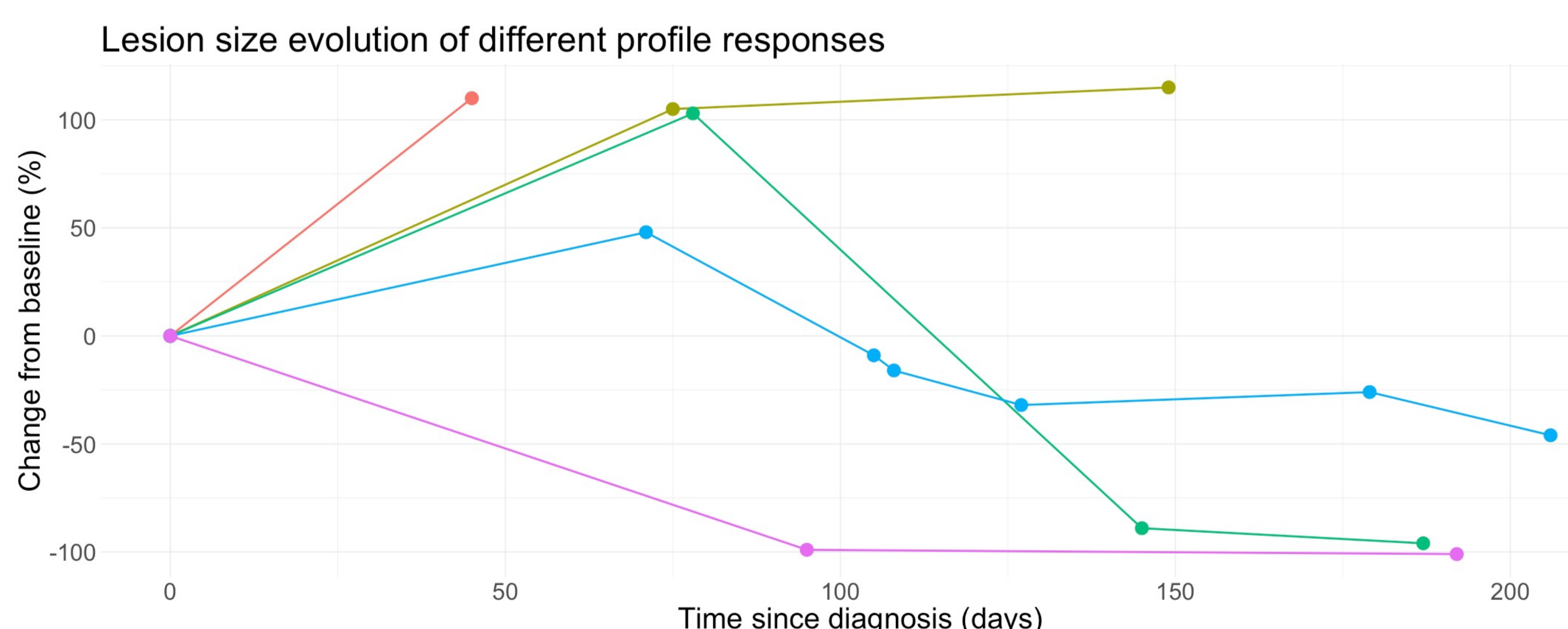
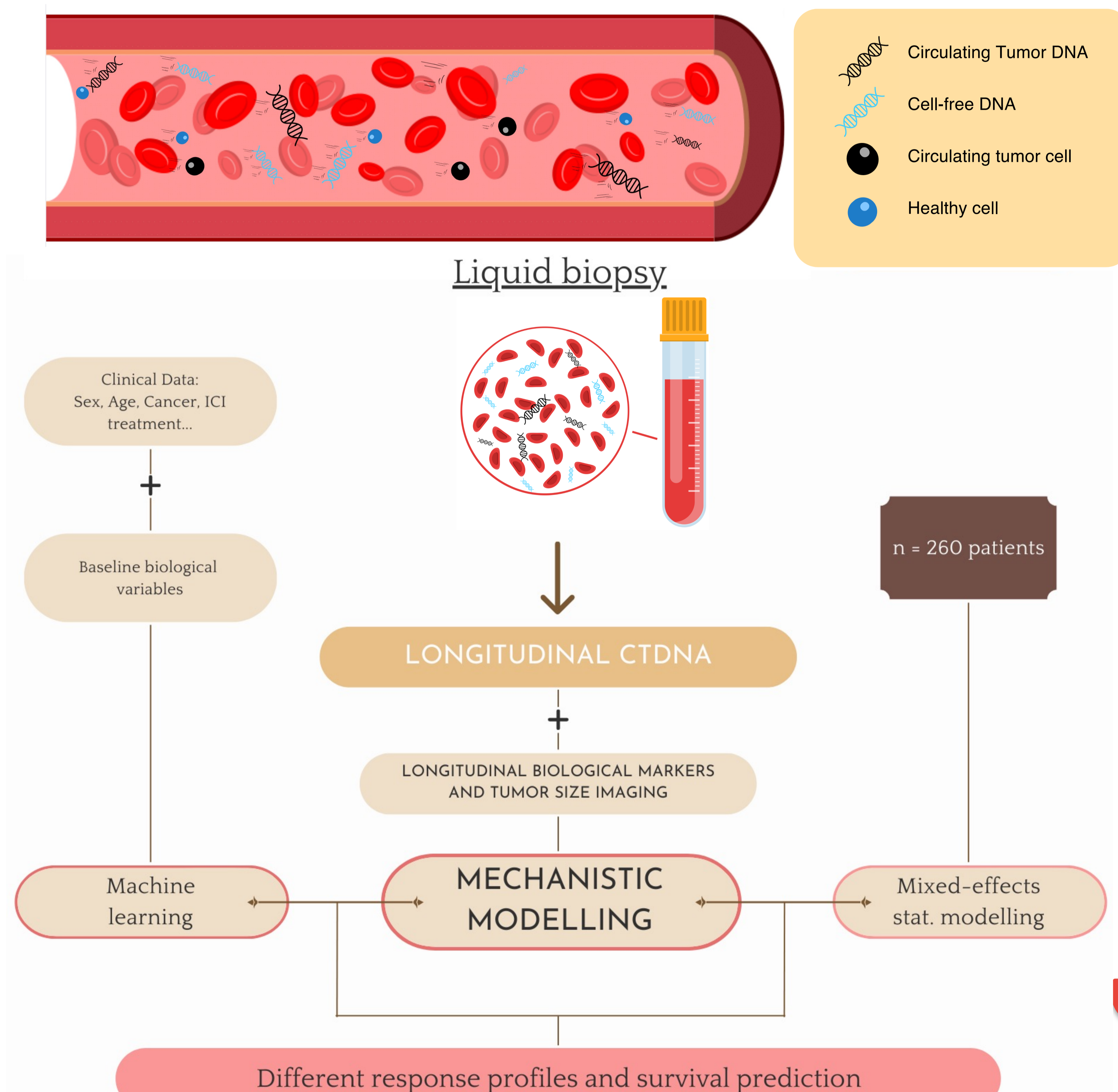
## BACKGROUND

A major current issue in immuno-oncology is to early predict the response of immunotherapy for cancer patients, ideally before the first imaging exam. Circulating DNA available from liquid biopsies are a promising and non-invasive surrogate to imaging to early assess response during treatment.

## OBJECTIVES

The ongoing **SchISM** (Size CfDNA Immunotherapies Signature Monitoring) clinical study proposes an innovative approach based on patented cfDNA quantification methods, providing concentration and size profile fluctuations of plasmatic circulating DNA for early therapeutic management of immune checkpoint inhibitors treated patients.

The objective is to model real-time variations in concentration and size of cfDNA to early predict response and survival following immunotherapy for five cancer types, using a novel, patented, standardized and innovative technology provided by our partners, **ID-solutions** and **Adelis**. Final purpose will be to propose a new predictive method to suggest more suitable treatment to patient, such as chemotherapy.



## REFERENCES

- Diehl F, Schmidt K, Choti MA, Romans K, Goodman S, Li M, et al. Circulating mutant DNA to assess tumor dynamics. *Nat Med.* 2008;14(9):985-90.18670422
- Moding, et al. « Circulating Tumor DNA Dynamics Predict Benefit from Consolidation Immunotherapy in Locally Advanced Non-Small Cell Lung Cancer ». *Nature cancer* 1, no 2 (février 2020): 176-83.
- Moding, et al. « Circulating Tumor DNA Dynamics Predict Benefit from Consolidation Immunotherapy in Locally Advanced Non-Small Cell Lung Cancer ». *Nature cancer* 1, no 2 (février 2020): 176-83. Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med.* 2013;368(13):1199-209.23484797
- Benzekry, S. Artificial intelligence and mechanistic modeling for clinical decision making in oncology. *Clinical pharmacology and therapeutics* (2020)
- Benzekry S et al. Pharmacometrics modeling coupled with machine learning for early prediction of overall survival following atezolizumab monotherapy in non-small cell lung cancer. *WCOP*, 2022.

## CFDNA

**cell-free DNA** : non-encapsulated fragments of DNA released, during apoptosis, necrosis or lysis, in body fluids as blood, urine, cerebrospinal fluid, saliva. Its half-life turn around 15 min, making its monitoring more representative of the real-time present quantities.

**circulating tumor DNA (ctDNA)** : portion of circulating cell-free DNA originating from tumor cells. By the detection of specific cancer mutations, studies found correlations between concentration of ctDNA and some outcomes of interest, such as progression-free survival, clinical benefit, radiographic response. Problems are :

- Finding tumor-specific mutations in cfDNA is expensive;
- Only 80% of patients harbor a genomic alteration that can be used as a biomarker target.

Current study aims to **focus on measuring global cfDNA**.

## DATA

- 260 patients** starting an **anti-PD-L1/P1**, currently 180 included, with :
    - Melanoma
    - Head and neck squamous cell carcinoma
    - Urothelial bladder carcinoma
    - Clear cell kidney cancer
    - Non-small cell bronchial cancer
  - Clinical variables :
    - Comorbidities
    - Anterior anti-cancer treatments
    - Genetic mutations
    - Previous cancer treatment
    - Tumor size imaging**
  - Classical biological markers
  - cfDNA variables**, collected **every two treatments** infusion (~ every 2 weeks) before first imaging :
    - concentration**
    - size distribution**
  - Outcomes :
    - Progression at first imaging after first immunotherapy cure
    - Progression-free survival
    - Overall survival at 3 years
- Response :**
- Hyper-progression
  - Progression
  - Pseudo progression
  - Response
  - Stable disease

## METHODS

### Survival analysis

- Kaplan-Meier estimator**
- Proportional hazard Cox regression**

### Longitudinal modeling

- Mechanistic modeling**  
Dynamic system of differential equations
- Non-linear mixed effects modeling**

### Machine Learning

- Statistical analysis :**
  - univariate and multivariate logistic regression**
- ML :**
  - logistic regression
  - random forest
  - single layer neural network
  - naïve Bayes
  - k-nearest neighbors
  - support vector models
  - decision tree