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# **Mechanistic Modeling of Joint Circulating Cell-free DNA Concentration-Tumor Size Kinetics under Immune-Checkpoint Inhibitors in Advanced Cancer**

Linh Nguyen Phuong, Frederic Fina, Romain Zakrajsek, Lucie Della-Negra, Pascale Tomasini, Jean-Laurent Deville, Laurent Greillier, Caroline Gaudy-Marqueste, Audrey Boutonnet, Frédéric Ginot, et al.

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# Mechanistic Modeling of Joint Circulating Cell-free DNA Concentration—Tumor Size Kinetics under Immune-Checkpoint Inhibitors in Advanced Cancer

*L. Nguyen Phuong, F. Fina, R. Zakrajsek, L. Della Negra, P. Tomasini, J.-L. Deville, L. Greillier, C.*

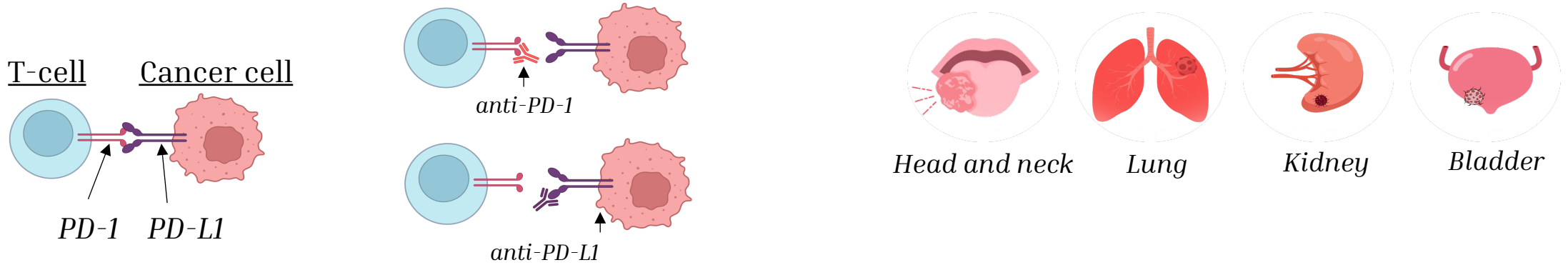
*Gaudy-Marqueste, A. Boutonnet, F. Ginot, J.-C. Garcia, S. Salas, S. Benzekry*



Size  
Cell-free DNA  
Immunotherapy  
Signature  
Monitoring

# Immunotherapy in oncology : how to predict progression?

- 2011+ : FDA approval of immune-checkpoint inhibitors (ICI) targeting PD-1
- 20-40 % long-term response<sup>1</sup>

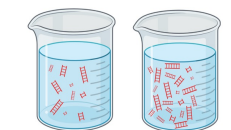


**PREDICTING PROGRESSION?**

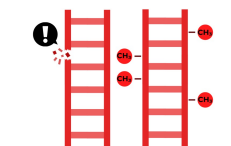
Gold standard biomarkers: PD-L1 expression (+ TMB)

New biomarker: liquid biopsy<sup>2</sup> → Circulating cell-free DNA (**cfDNA**)

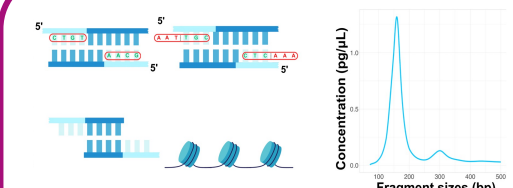
- ✓ Half-life: 15min-2h
- ✓ Systemic
- ✓ Non-invasive
- ✓ Cost-effective



Concentration<sup>3</sup>



Mutations



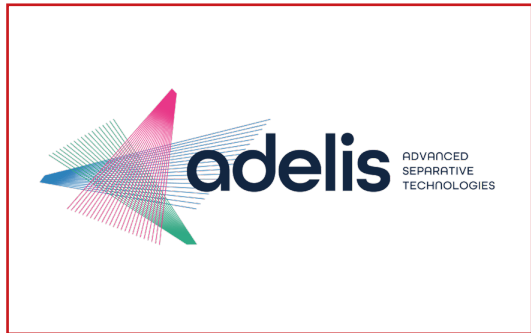
Fragmentome

<sup>1</sup>Gilberto De Castro et al., J Clin Oncol, 2022; Sharma et al., Cell, 2017

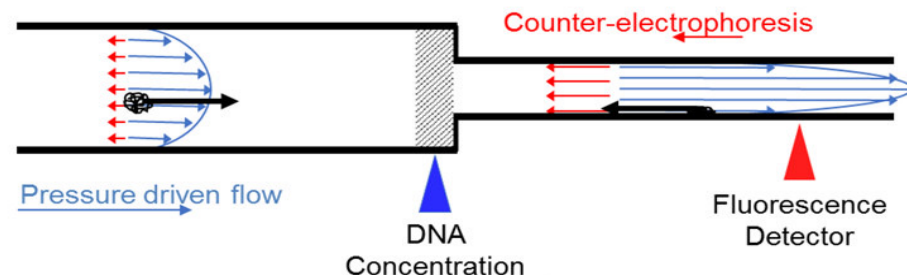
<sup>3</sup>Ribba et al., Front Pharmacol, 2023

<sup>2</sup>Siravegna et al., Nat Rev Clin Oncol, 2017

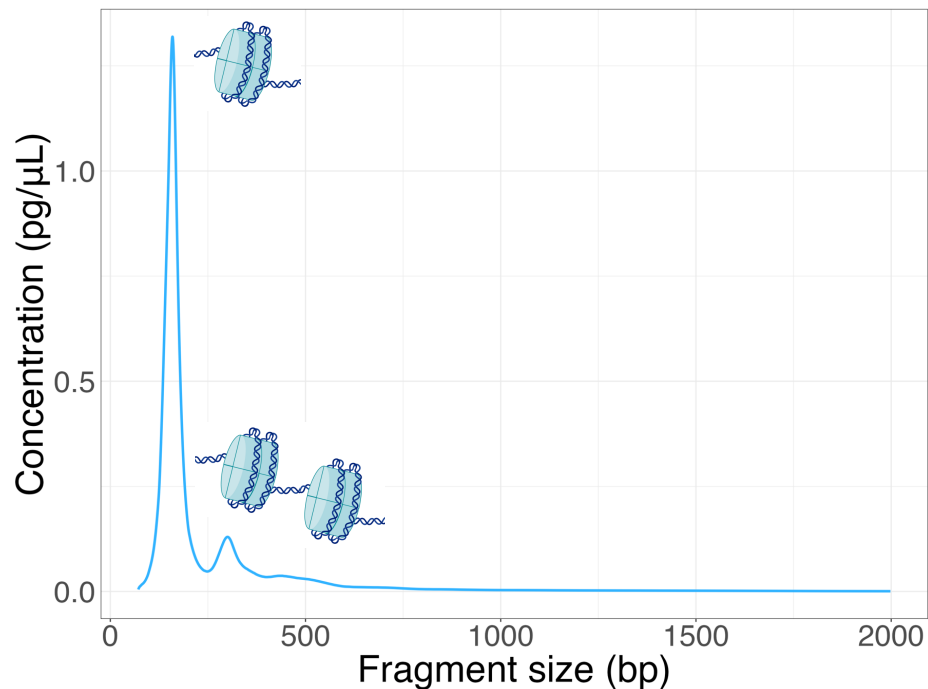
# CfDNA size profile as a promising biological marker



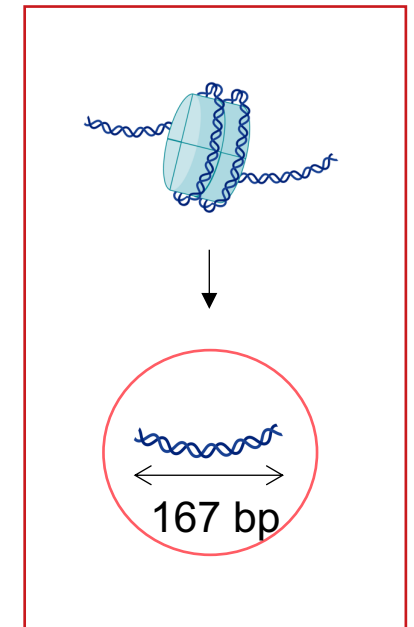
μLAS technology:



- Independent of genome position
- No need of prior DNA extraction
- Only needs 1 μL of plasma
- Cost-effective ~ 15€/sample
- 2 bp - accuracy on fragments sizes



- Apoptosis
- Necrosis
- Active secretion



## Objectives



Size  
Cell-free DNA  
Immunotherapy  
Signature  
Monitoring

Develop a **mechanistic model** of the **joint cfDNA – tumor kinetics (TK)** in advanced cancer patients undergoing ICI

Assess pre-treatment **cfDNA size profiles** and **early, on-treatment, model-based parameters** as predictors of immunotherapy resistance

# SChISM: Size CfDNA Immunotherapy Signature Response

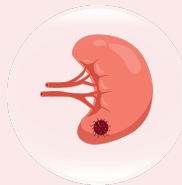
126 patients



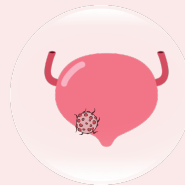
Head and neck (HNSCC)



Lung (NSCLC)

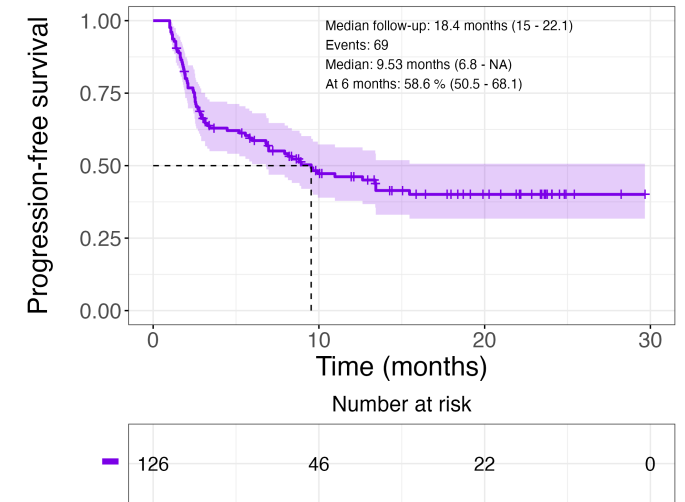
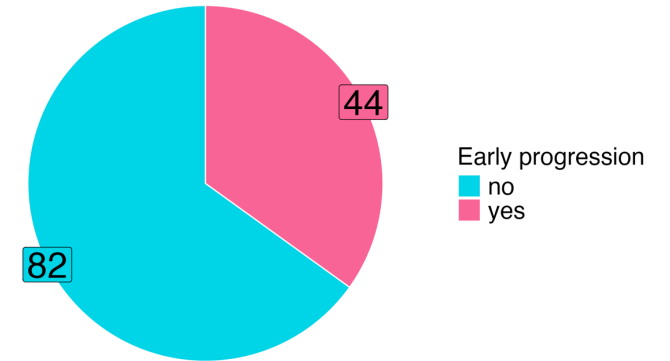
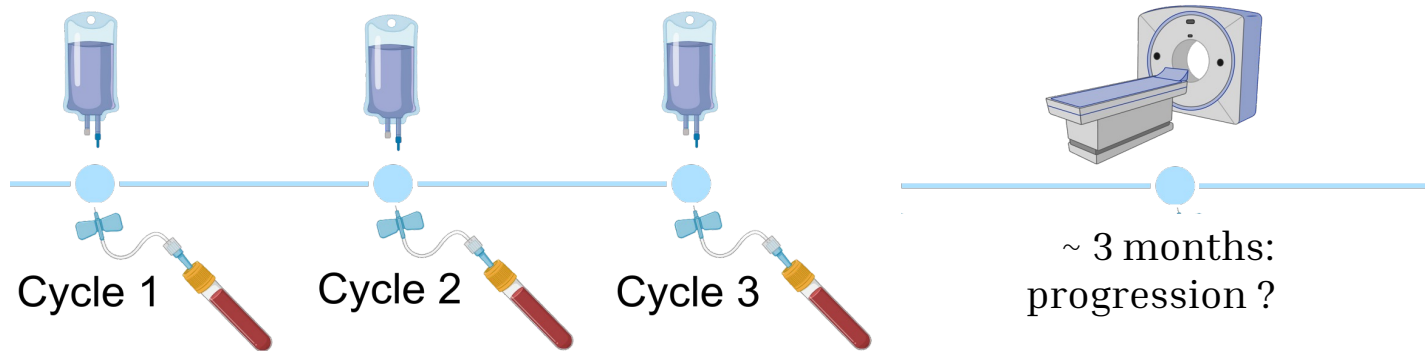


Kidney (ccRCC)



Bladder (UC)

ICI



- Outcomes:
  - Early progression (EP)
  - Progression-free survival (PFS)

# SChISM: Size CfDNA Immunotherapy Signature Response

## Clinical variables

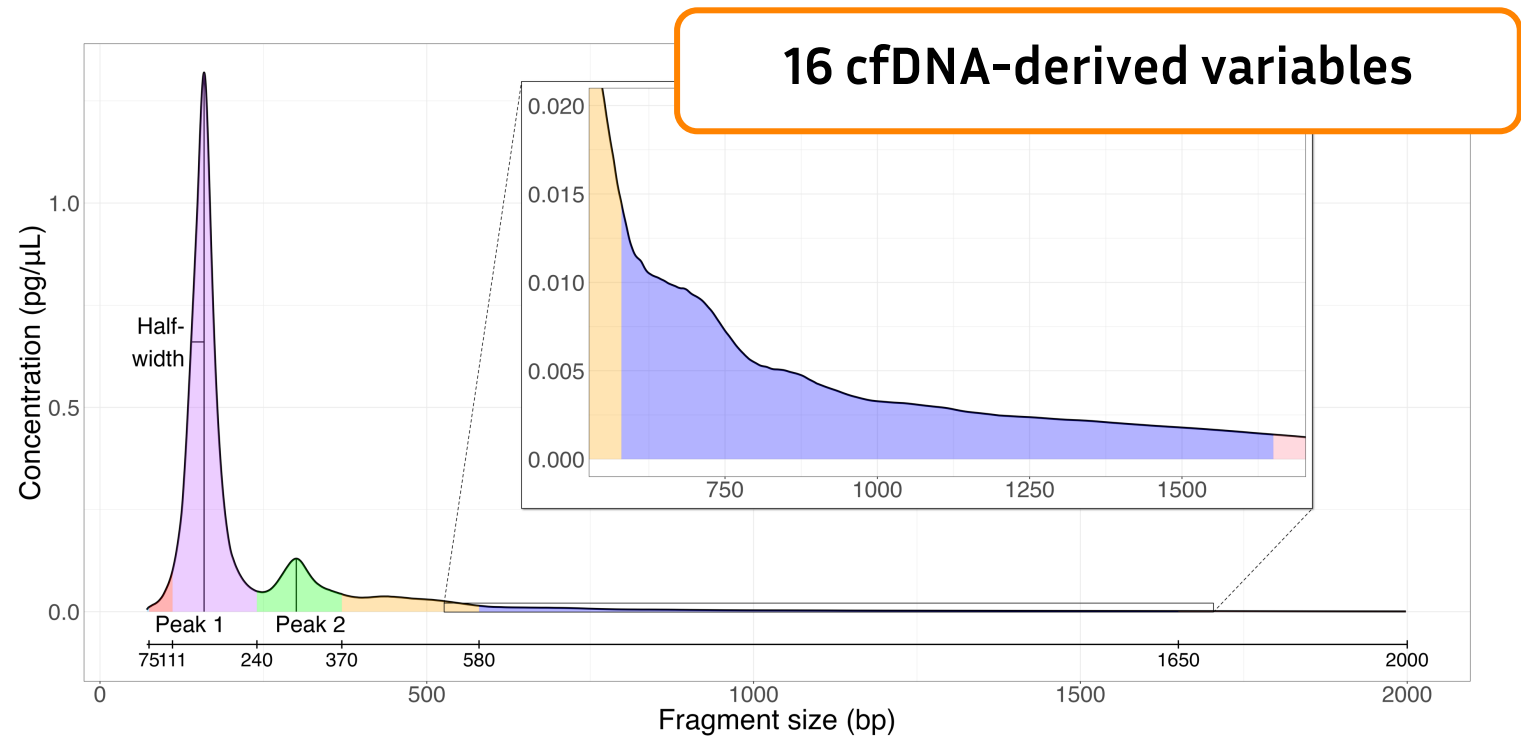
Age, tumor type, sex, Eastern Cooperative Oncology Group (ECOG)

## Biological variables

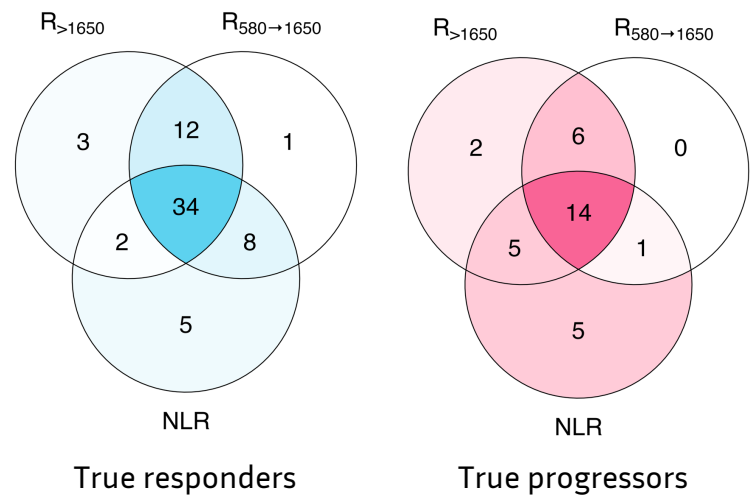
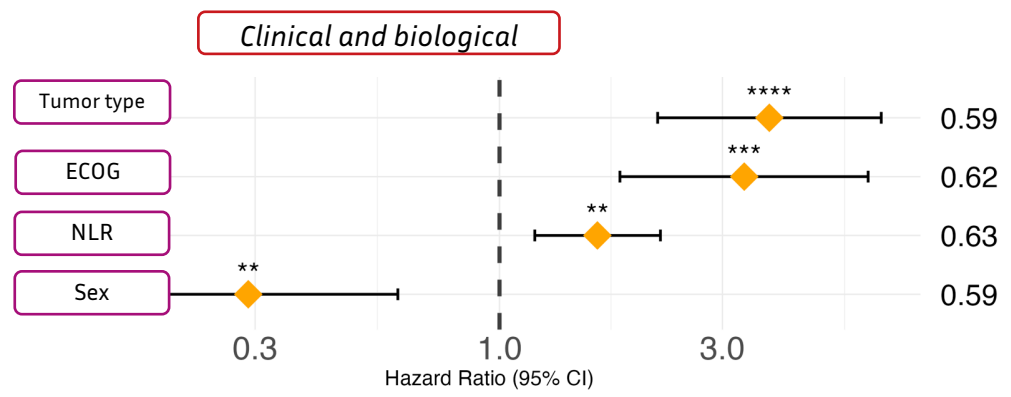
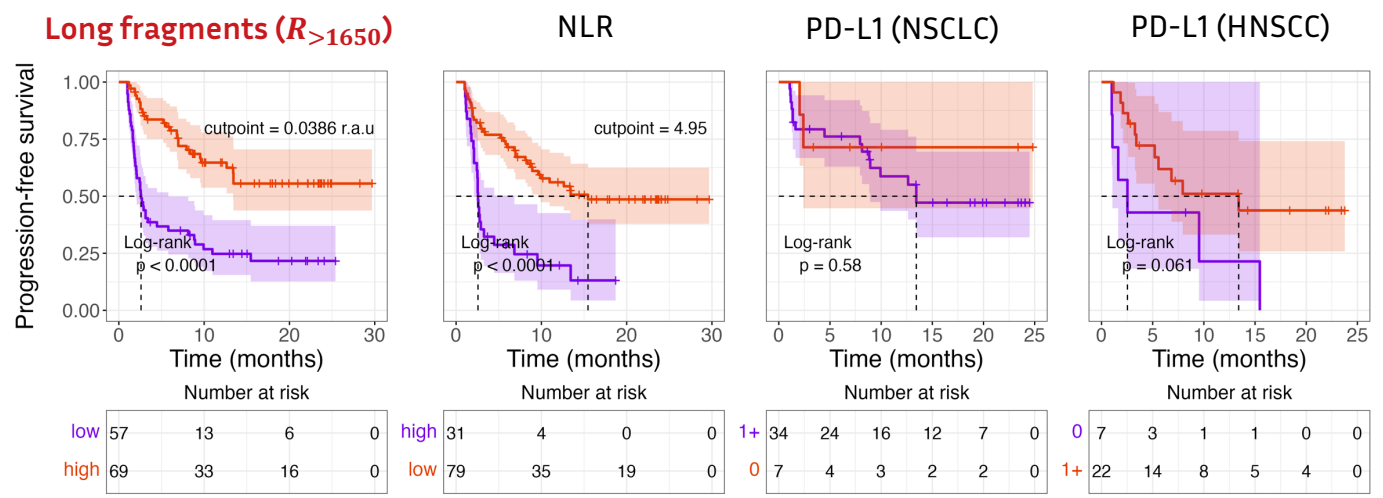
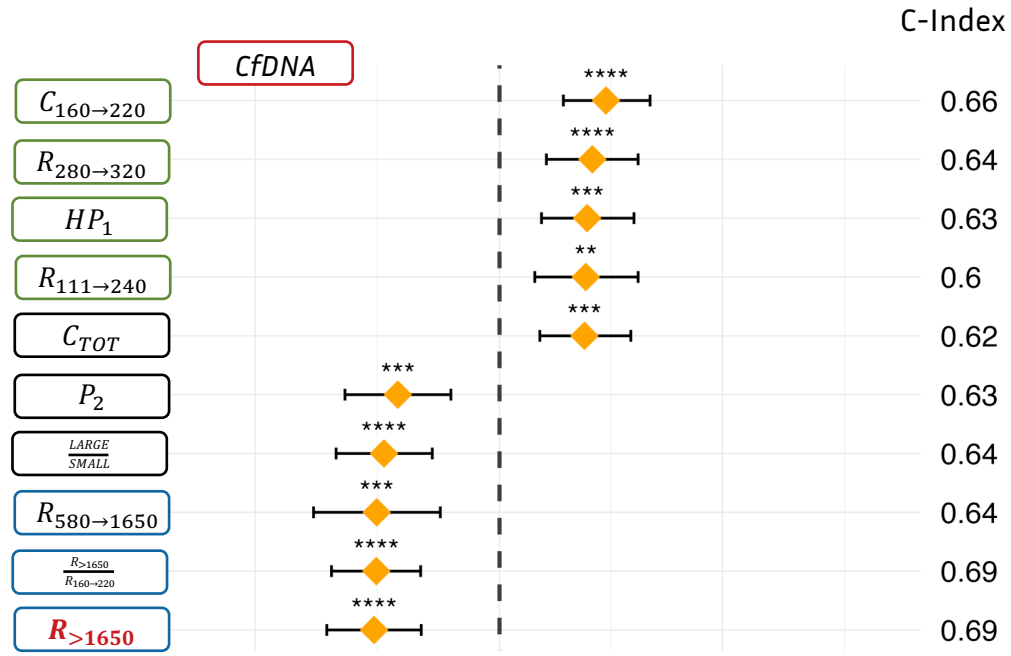
Neutrophil to lymphocyte ratio (*NLR*)  
Lactate dehydrogenase level (*LDH*)

## CfDNA variables

Total concentration (pg/μL)  $C_{TOT}$   
Location of the peaks (bp)  $P_1, P_2$   
Height of the peaks (pg/μL)  $HP_1, HP_2$   
Half-width of first peak  $HW_1$   
Absolute concentrations (pg/μL):  $C_{a \rightarrow b}$   
Relative concentrations  $R_{a \rightarrow b}$  (over  $C_{TOT}$ )

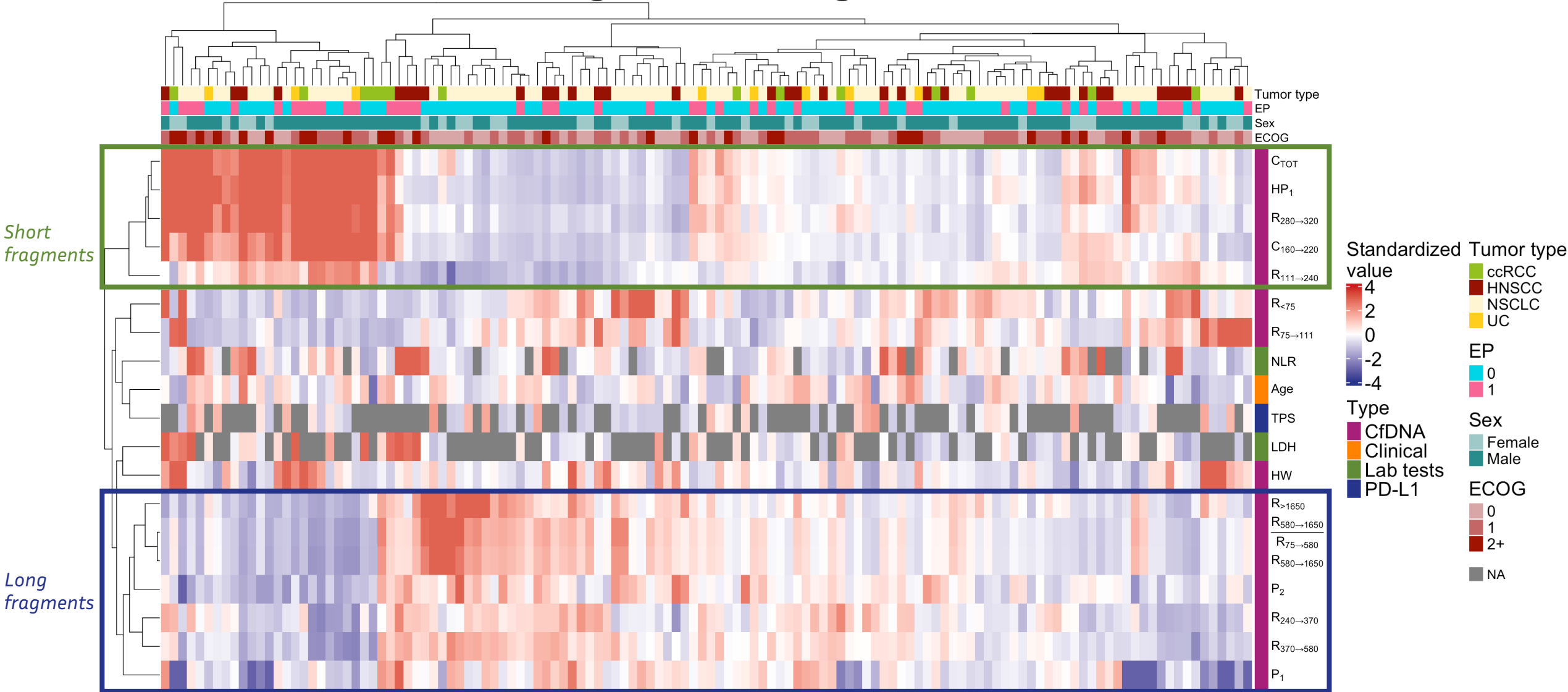


# High proportion of long fragments at baseline is associated with response

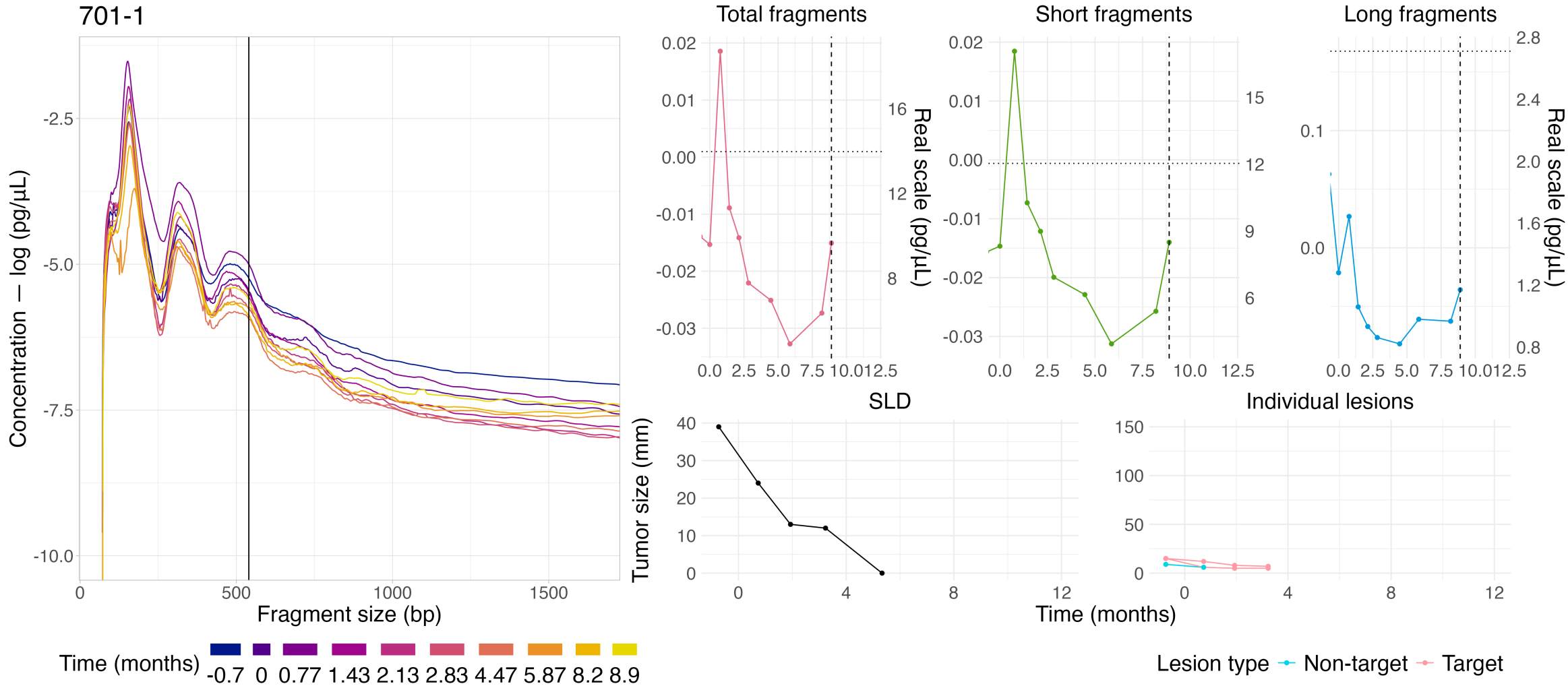


- Multi-cancer  $R_{>1650}$ :
  - AUC test: **0.74** [0.65–0.83]
  - PPV test: **0.56** [0.45–0.68]
- Multi-cancer PD-L1<sup>1</sup>:
  - AUC: **0.65**
  - PPV: **0.34**
- Multi-cancer TMB<sup>1</sup>:
  - AUC: **0.69**
  - PPV: **0.42**

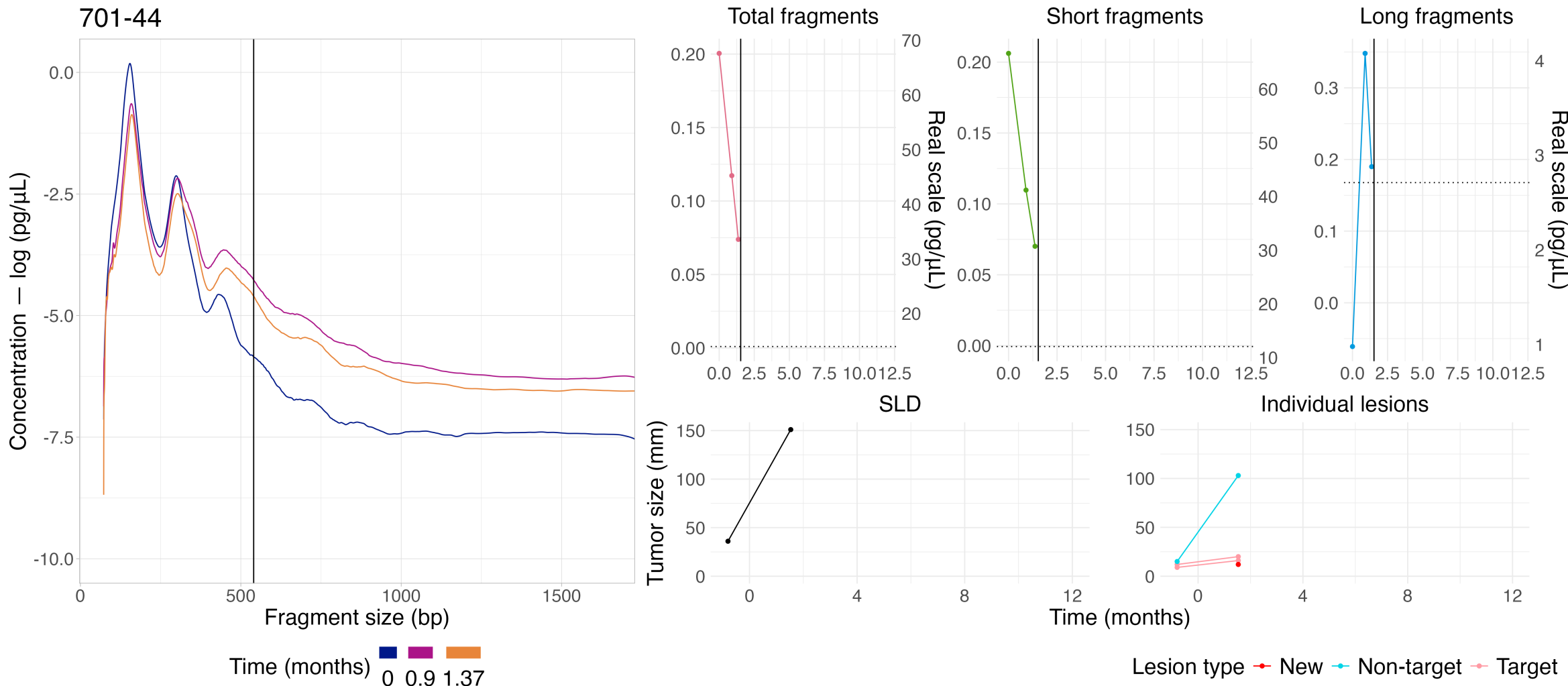
# Patients cluster according to their fragment size distribution



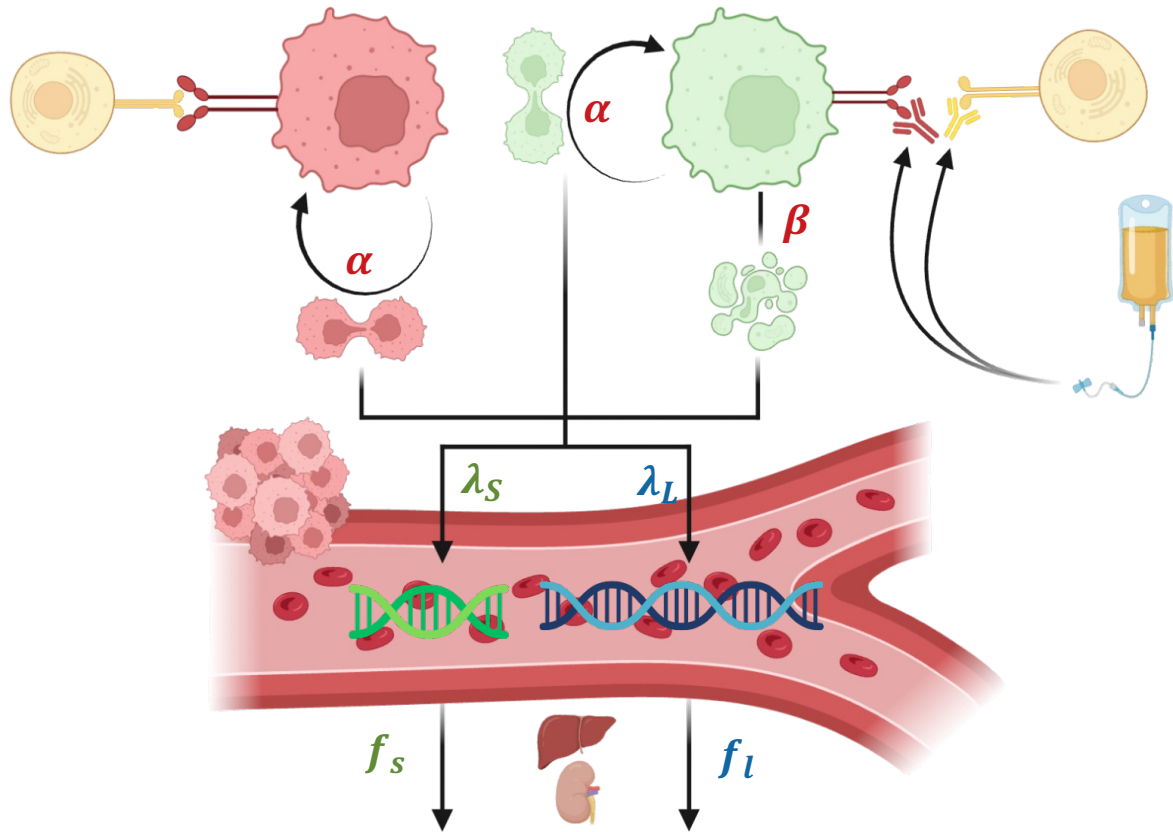
# Short and long fragments showed different kinetics



# Short and long fragments showed different kinetics



# Joint modeling of tumor and size-dependent cfDNA kinetics



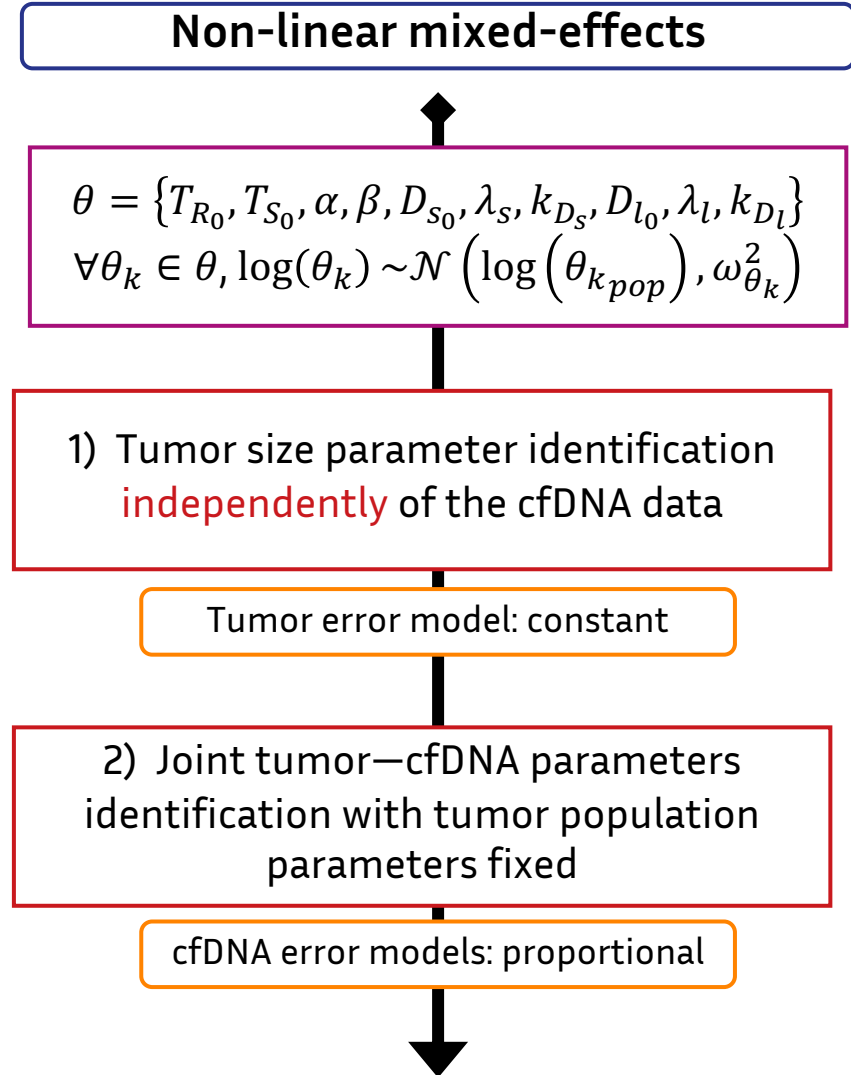
1. Tumor cells (Sum of Largest Diameters, SLD,  $T$ ) comprise two sub-populations: treatment-**resistant** cells  $T_R$  and treatment-**sensitive**  $T_S$  ones.
2. Short fragments  $D_S$  (540-75) bp) are **proportionally** released through:
  - $T$  **growth**, through **active secretion** during **proliferation**
  - $T_S$  **death** through **apoptosis**
3. Long fragments  $D_L$  (1650-540) bp) are **proportionally** released through:
  - $T$  **growth**, through **active secretion** and/or **necrosis** of the tumor microenvironment
  - $T_S$  **death** through **necrosis**
4. CfDNA is **cleared** from the circulation by liver and kidneys, **depending on fragment size**  $f_s(D_S)$ ,  $f_l(D_L)$ .

$$\begin{cases} \frac{dT_R}{dt} = \alpha \cdot T_R \\ \frac{dT_S}{dt} = \begin{cases} \alpha \cdot T_S & \text{if } t < 0 \\ (\alpha - \beta) \cdot T_S & \text{if } t \geq 0 \end{cases} \\ T = T_R + T_S \\ \frac{dD_S}{dt} = \lambda_s \cdot (\alpha \cdot T + \beta \cdot T_S) - f_s(D_S) \\ \frac{dD_L}{dt} = \lambda_l \cdot (\alpha \cdot T + \beta \cdot T_S) - f_l(D_L) \end{cases}$$

Initial conditions:

$$\begin{cases} T_S(t = 0) = T_{S0} \\ T_R(t = 0) = T_{R0} \\ D_S(t = 0) = D_{S0} \\ D_L(t = 0) = D_{L0} \end{cases}$$

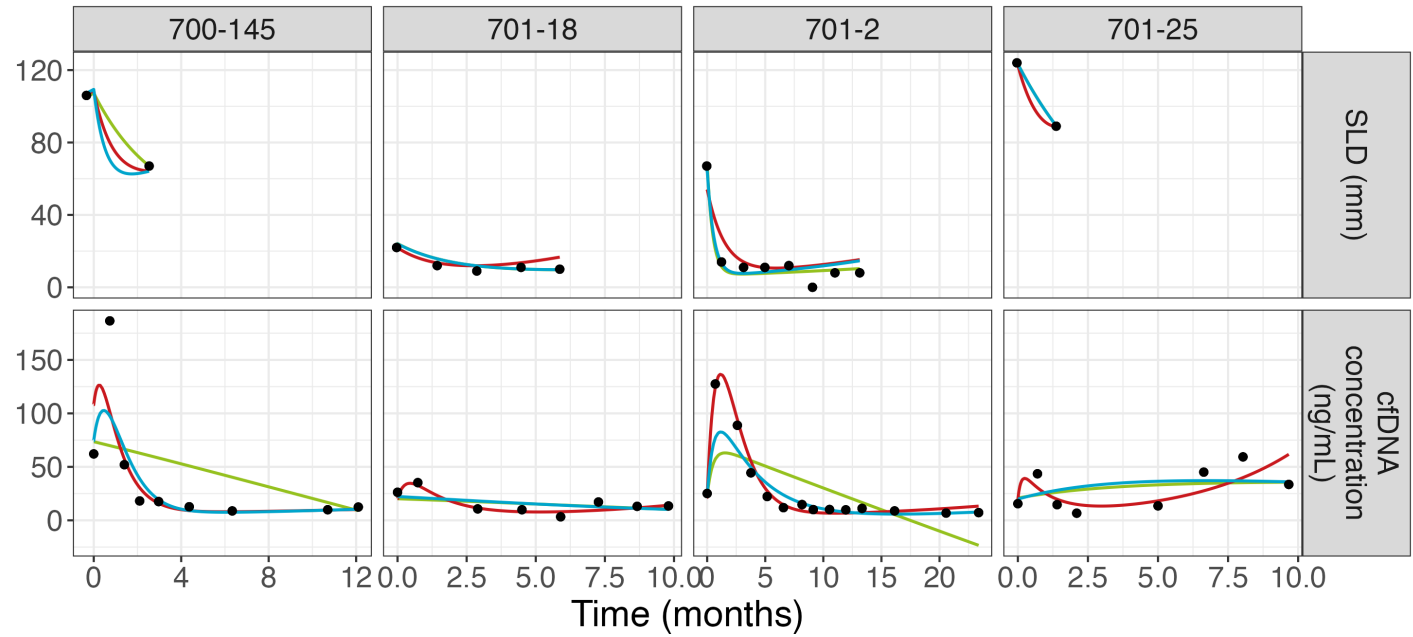
# Population approach



n = 109

Number of samples per patient	
	median (min-max)
Tumor imaging	2 (1–10)
cfDNA samples	7 (1–20)

Best clearance function: **linear**



Clearance — constant — linear — saturated

$$\begin{cases} \frac{dD_s}{dt} = \lambda_s \cdot (\alpha \cdot T + \beta \cdot T_S) - k_{D_s} \cdot D_s \\ \frac{dD_l}{dt} = \lambda_l \cdot (\alpha \cdot T + \beta \cdot T_S) - k_{D_l} \cdot D_l \end{cases}$$

# Model diagnostics

## TK model

VALUE	C.V. (%)	STOCHASTIC APPROXIMATION	
		S.E.	R.S.E.(%)

### FIXED EFFECTS

$\alpha_{pop}$	0.065	0.015	23
$\beta_{pop}$	0.36	0.045	12
$TR_{0pop}$	7.9	1.7	22
$TS_{0pop}$	43	4.1	9.7

### STANDARD DEVIATION OF THE RANDOM EFFECTS

$\omega_{\alpha_{pop}}$	0.9	110	0.13	14
$\omega_{\beta_{pop}}$	0.83	99	0.12	14
$\omega_{TR_{0pop}}$	0.88	110	0.15	17
$\omega_{TS_{0pop}}$	0.86	100	0.073	8.5

### ERROR MODEL PARAMETERS

$\alpha$	8.7	0.74	8.5
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Correlation of the estimates  
 $\in [-0.12, 0.44]$

Condition number = 4.74

## Joint model

VALUE	C.V. (%)	STOCHASTIC APPROXIMATION	
		S.E.	R.S.E.(%)

### FIXED EFFECTS

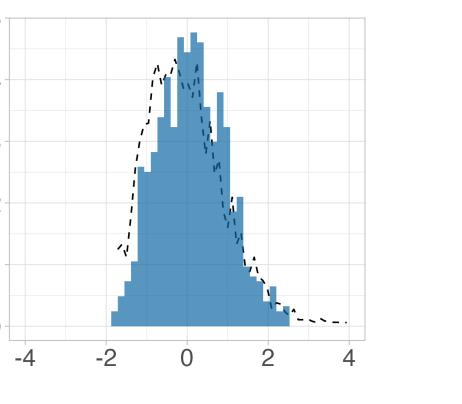
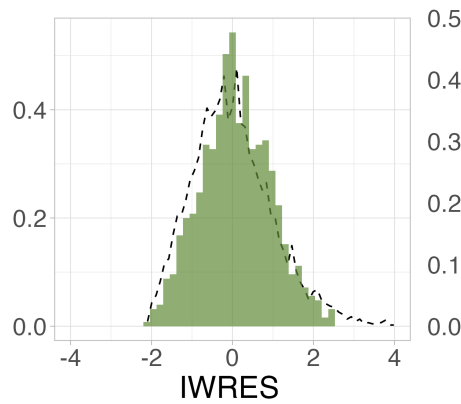
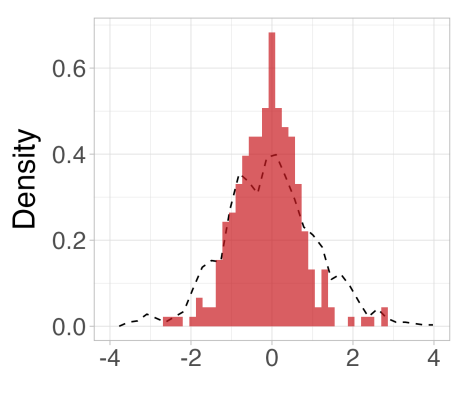
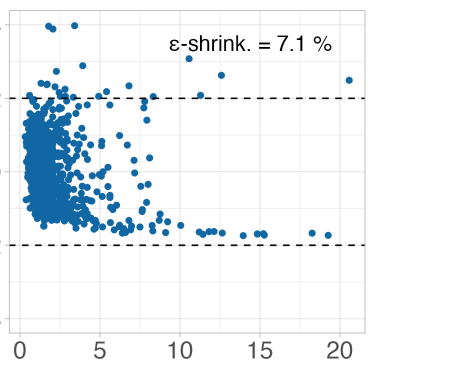
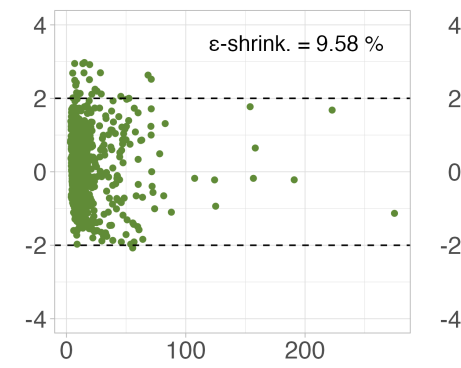
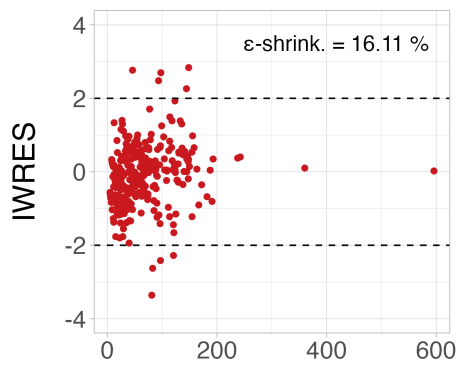
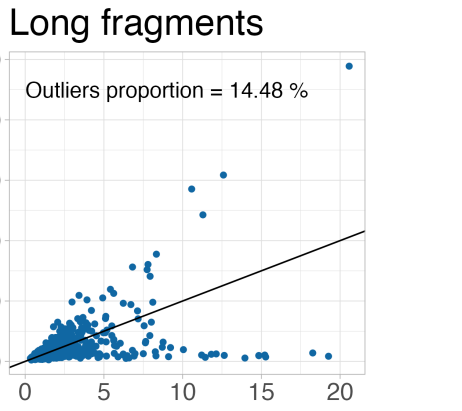
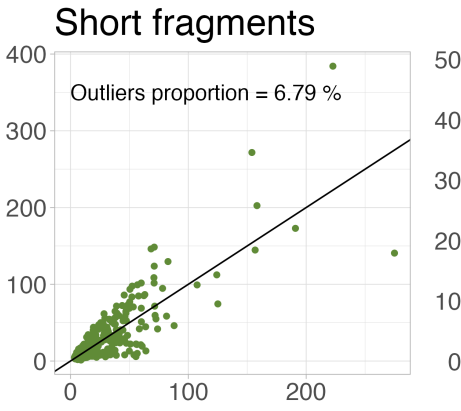
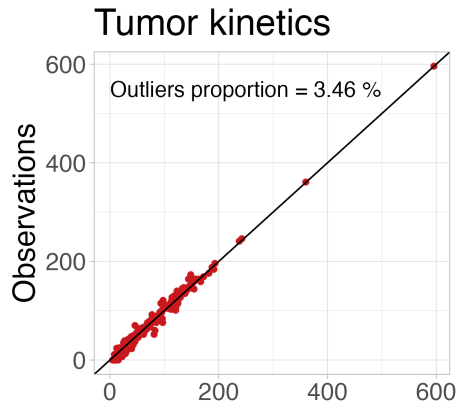
$D_{s0pop}$	11	0.94	8.9
$D_{l0pop}$	1.4	0.1	7.4
$\lambda_{spop}$	0.38	0.047	12
$\lambda_{lpop}$	0.086	0.013	15
$k_{D_{spop}}$	0.29	0.038	13
$k_{D_{lpop}}$	0.53	0.089	17

### STANDARD DEVIATION OF THE RANDOM EFFECTS

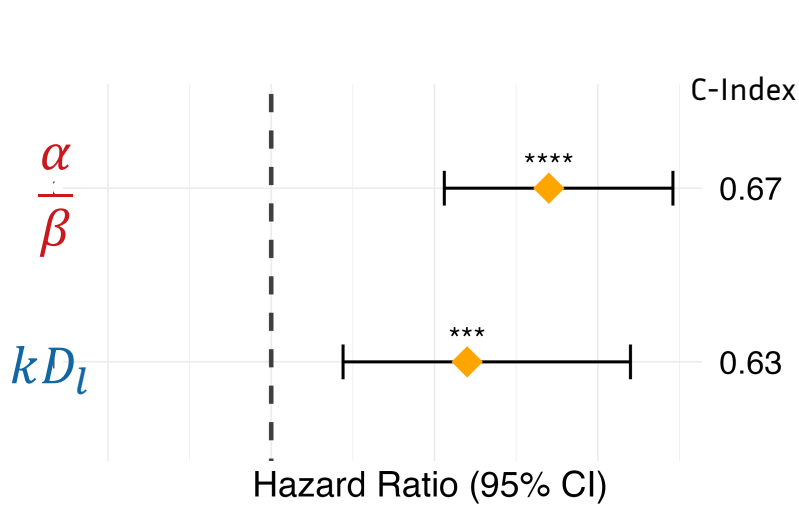
$\omega_{D_{s0pop}}$	0.71	82	0.07	9.9
$\omega_{D_{l0pop}}$	0.51	54	0.062	12
$\omega_{\lambda_{spop}}$	0.94	120	0.095	10
$\omega_{\lambda_{lpop}}$	0.96	120	0.094	9.8
$\omega_{k_{D_{spop}}}$	0.95	120	0.11	11
$\omega_{k_{D_{lpop}}}$	1.2	170	0.12	11

### ERROR MODEL PARAMETERS

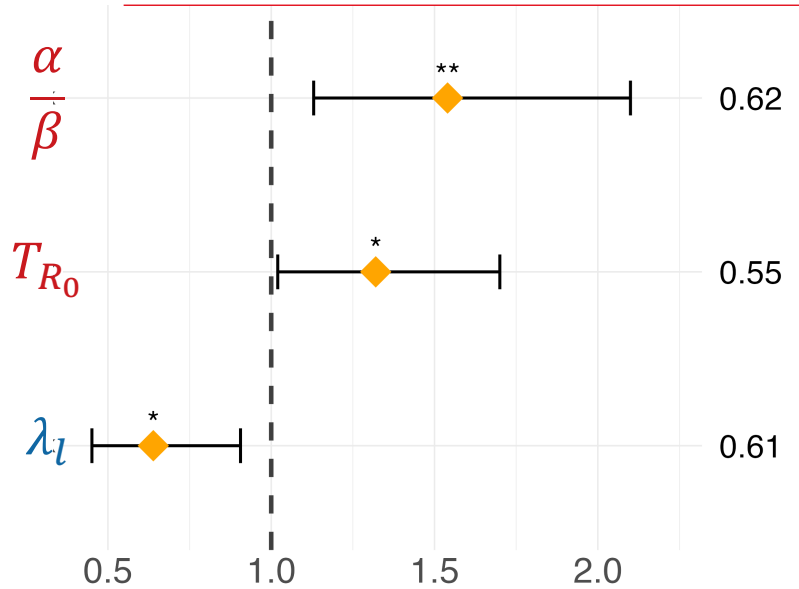
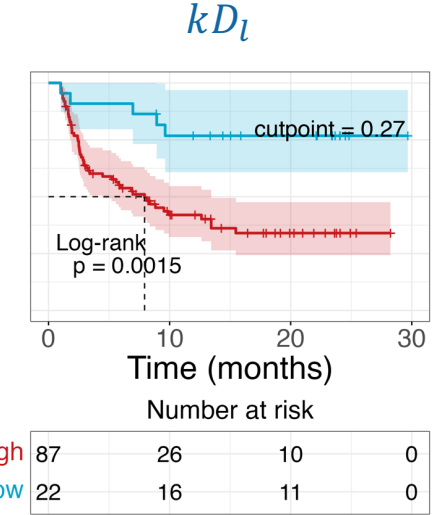
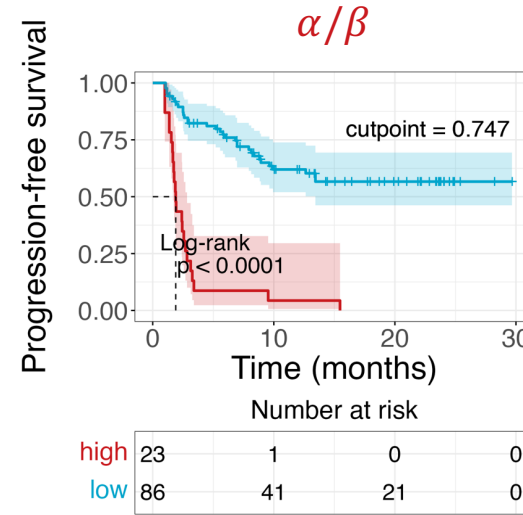
$b_{SHORT}$	0.43	0.013	3
$a_{TK}$	8.7		
$b_{LONG}$	0.55	0.018	3.2



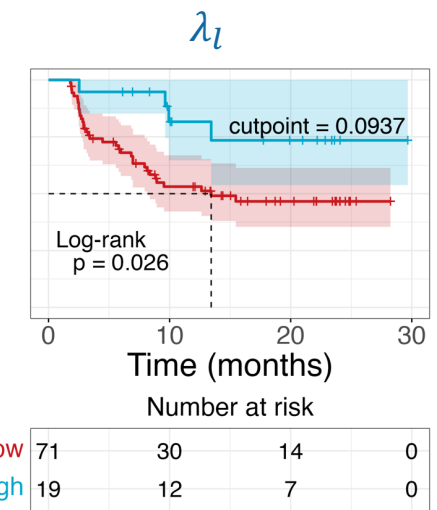
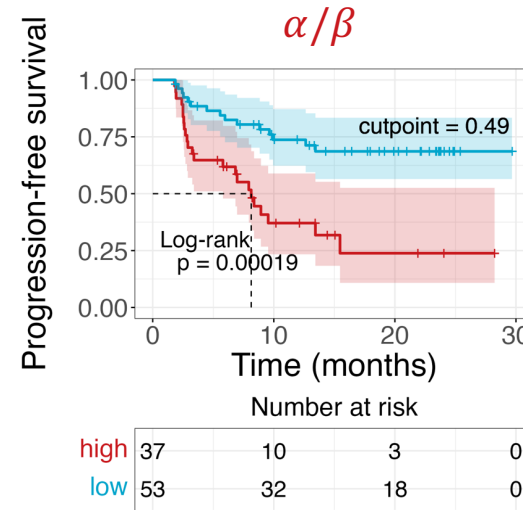
# Parameters of the dynamic modeling are predictive of the PFS



Full kinetics  
(n = 109)



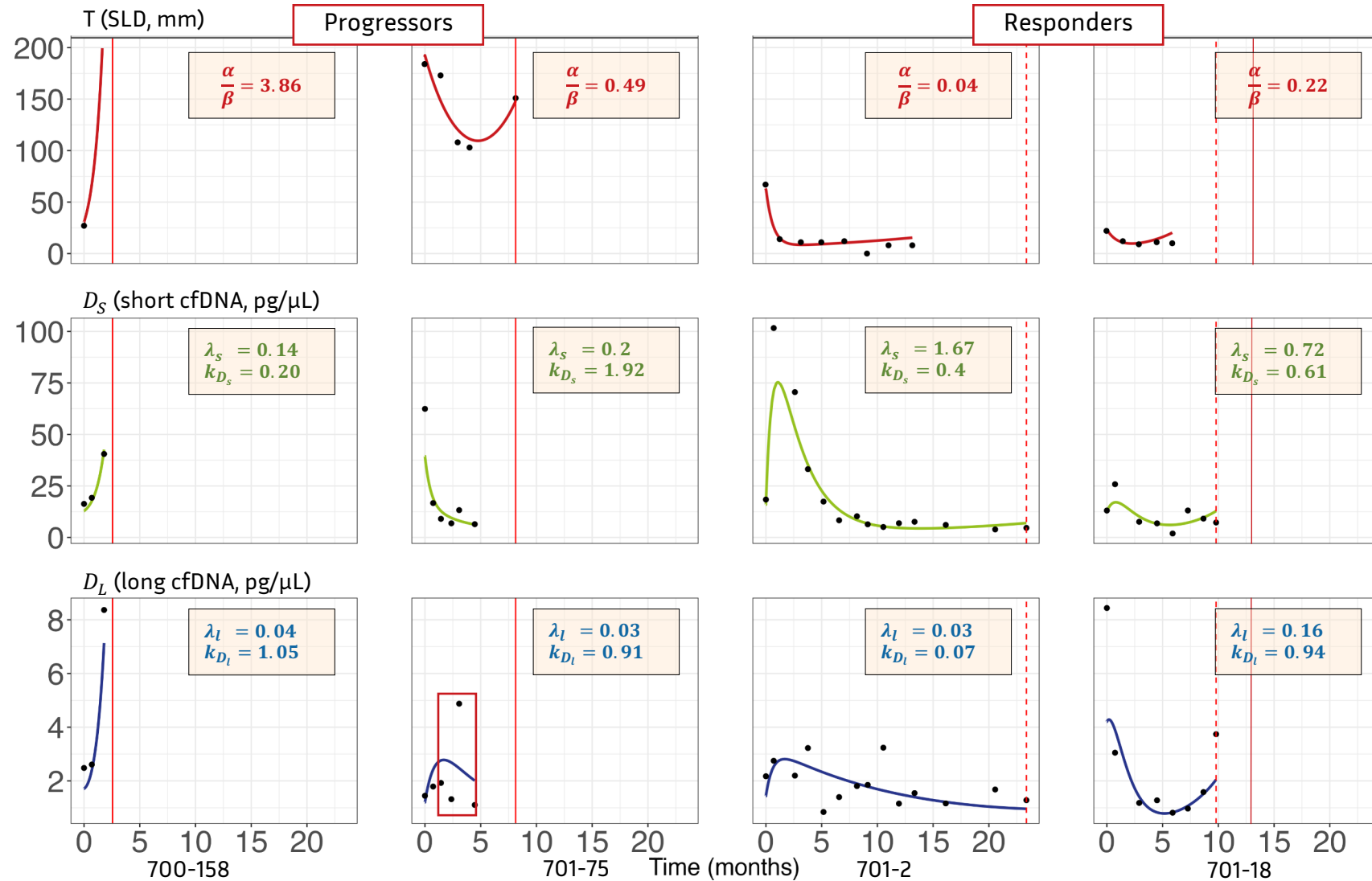
Early-on treatment  
(6 weeks, n = 90)



# The model describes different size-dependent cfDNA kinetics

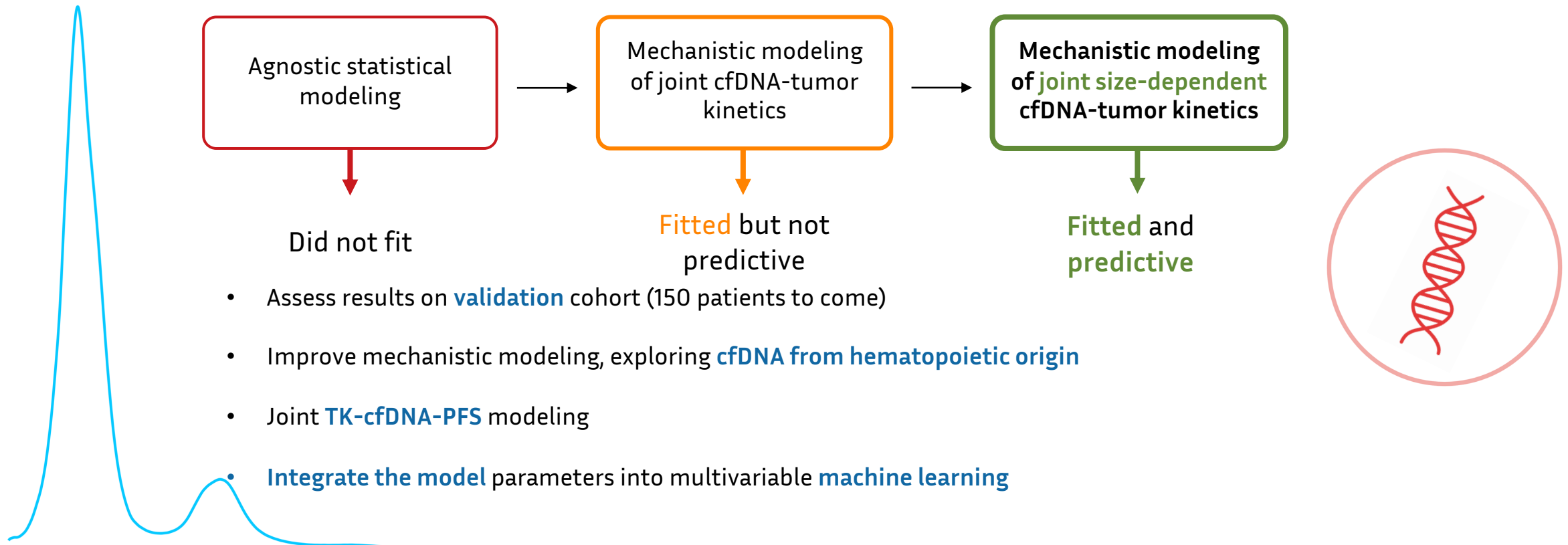
## PFS

- Censored Progression
- Observed data



# Conclusions and perspectives

- ICI-treated patients **with lower fragmentation** of cfDNA **before** treatment tend to **respond better** and to have **longer PFS**.
- Mechanistic modeling offers biological insights to explain the **interplay between cfDNA and tumor kinetics**.



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[team.inria.fr/compo/](http://team.inria.fr/compo/)

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# Thanks for your attention!