# Designing Evolutionary Treatment for Metastatic Non-Small Cell Lung Cancer

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Joint work with:

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CATMo 2020

# Outline

1. Cancer Treatment as a Stackelberg Evolutionary Game (SEG)
2. SEG Application to Treatment of Metastatic Non-Small Cell Lung Cancer with Immune Checkpoint Inhibition
   - Data
   - Questions
   - Approach to Address One of These Questions
   - Interesting Observations
   - Results
3. Conclusions & Future Research
4. Discussion Points

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Salvioli, PhD thesis 2020; Salvioli et al, PLOS One, in press; Cunningham et al, JTB 2018, PLOS One 2020, Stankova et al, JAMA Onc 2019,...

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**What is the minimal knowledge necessary?**

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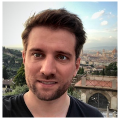
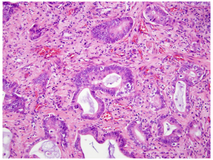


- Stage 4, anti-PD1 drug Atezolizumab (MPDL3280A)
- Tumor diameter over time, typically few time points
- In our dataset typically 2 or 3 metastases per patient



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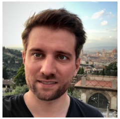

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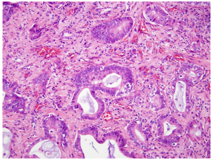

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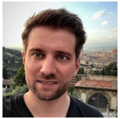

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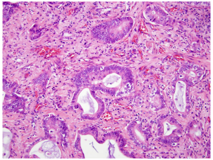

## Our questions:


1. Based on the initial tumor volume proxy and its trend, can we predict how its volume will change in the future?
2. Would adaptive immunotherapy work in cases where tumor keeps growing when treated in the standard way?

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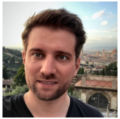

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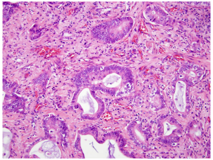

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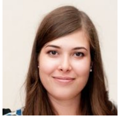
## Our modelling approach to answer question 2:




- Fitting the data into minimalistic G-function model
- Optimizing the treatment for cases with tumor growing

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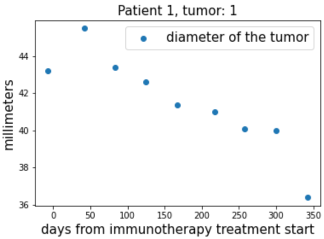
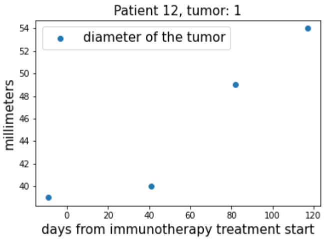
# 2. SEG Application to Treatment of Metastatic NSCLC

**Example of data**:




- All patients treated with the same immune checkpoint inhibition
- Treatment starts between the first and second data points

Are these different trends a result of treatment-induced resistance and other patient- and tumor-specific factors?

# 2. SEG Application to Treatment of Metastatic NSCLC

**NSCLC model details** (Vincent and Brown (2005)):

$$\dot{x} = x\,G(m,u,x)$$

$$\dot{u} = \sigma \frac{\partial G(m,u,x)}{\partial u}$$

$$G(m,u,x) = r(u)\left(1 - \frac{x}{K}\right) - \frac{m}{k + b\,u} - d$$

| symbol & range | meaning |
|---|---|
| $m \in \{0,1\}$ | treatment (on or off) |
| $u \in [0,1]$ | rate of treatment-induced resistance |
| $K > 0$ | carrying capacity |
| $x \in [0,K]$ | cancer cell population |
| $G(m,u,x)$ | fitness-generating function |
| $r_{\max} > 0$ | maximal growth rate |
| $d > 0$ | natural death rate |
| $\sigma \geq 0$ | evolutionary speed |
| $k > 0$ | innate resistance |
| $b > 0$ | effect of $u$ |

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Three different forms of $r(u)$ considered:

- Quadratic cost of resistance: $r(u) = r_{\max}(1 - u^2)$
- Linear cost of resistance: $r(u) = r_{\max}(1 - u)$
- No cost of resistance : $r(u) = r_{\max}$

# 2. SEG Application to Treatment of Metastatic NSCLC

**Fitting the model (also for predictions)**:

- The population of cancer cells is estimated from the diameter.
- Distinguishing 6 groups of tumors: 3 according to initial volume and 2 according to initial trend.
- Fix $K$, $b$ and $\sigma$ per group, estimate $r_{\max}$, $k$ and $u(0)$ per patient, $d$ fixed to 0.01.

| | Small | Medium | Large |
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| Increasing | $K = 0.1$<br>$b = 100$<br>$\sigma = 0.01$ | $K = 2$<br>$b = 150$<br>$\sigma = 0.01$ | $K = 2$<br>$b = 0.9$<br>$\sigma = 0.05$ |
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Jakob Nikolas Kather: "There is no cost of
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# 2. SEG Application to Treatment of Metastatic NSCLC

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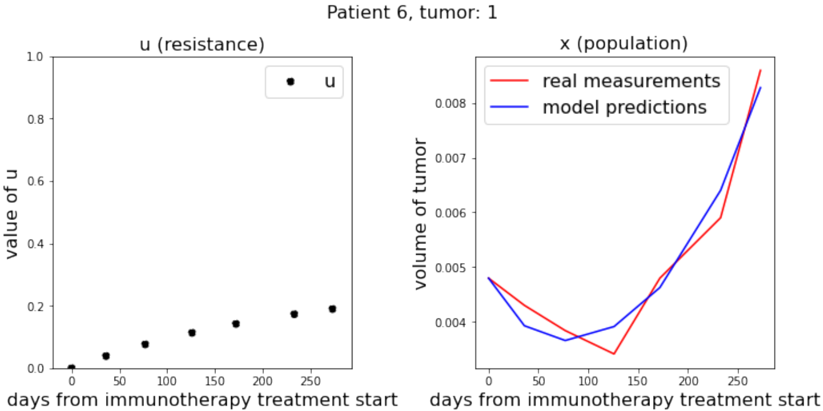
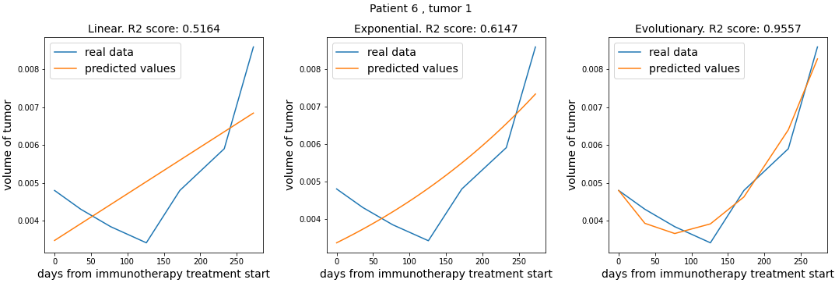


# 2. SEG Application to Treatment of Metastatic NSCLC

**Comparison with linear and exponential models**:

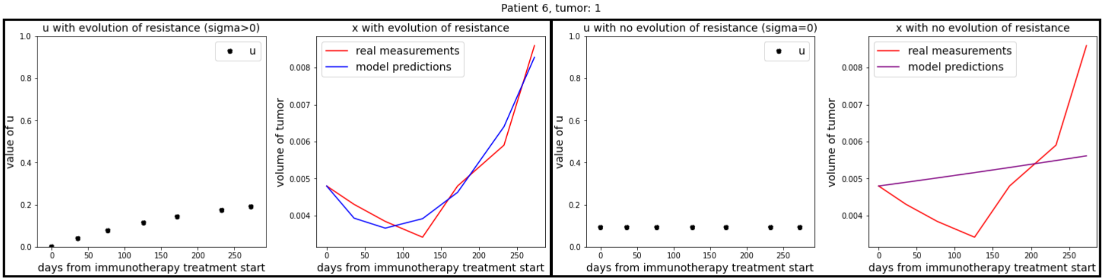
- Mean of the R2-scores: 0.59, 0.72, 0.80 for linear, exponential and evolutionary models, respectively.




*Linear, exponential and evolutionary model with quadratic cost of resistance*

# 2. SEG Application to Treatment of Metastatic NSCLC

**Evolution of treatment-induced resistance only plays an important role in tumors that exhibit a rapid change of trend.**




*Evolutionary model with quadratic cost of resistance with and without evolution of resistance*

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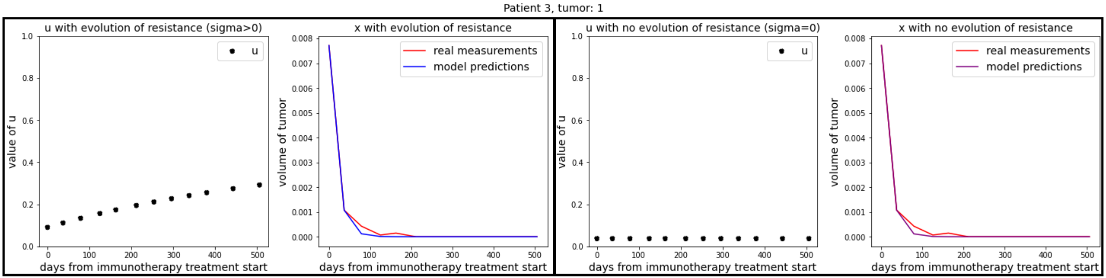


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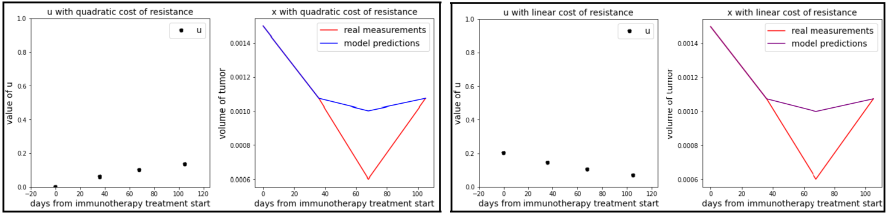
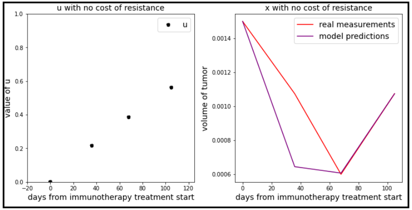
# 2. SEG Application to Treatment of Metastatic NSCLC

## Comparison of the different forms of $r(u)$:




*Quadratic and linear cost of resistance*




*No cost of resistance*

# 2. SEG Application to Treatment of Metastatic NSCLC

## Optimization

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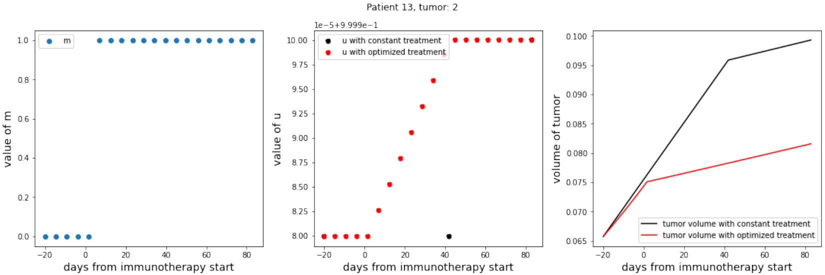
Preliminary results:

- With linear and/or quadratic cost of resistance, the best is to always treat or not treat at all
- With no cost of resistance, sometimes it is the best to switch between no and standard treatment. We do not understand yet when precisely.
- With the objective $\min\, x(T)$, we can never stop the growth, we can only slow it down

# 2. SEG Application to Treatment of Metastatic NSCLC

## Optimization - preliminary results:



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- Our model has better predictive capabilities than linear/exponential models used until now

# 4. Discussion Points/Questions for You

- Does resistance to immune checkpoint inhibition in NSCLC carry a cost?
- If yes, is there any way how to estimate it from other measurements (For other projects/cancers, we are exploring whether genomics and histopathology can help us to answer such questions, but here we know too little)?
- What other information can be useful here?
- Would a model with immune cells as active players be a better choice here?

# Thank you !

02/12/2020

Marie Skłodowska-Curie Actions

Evolutionary Game Theory & Population Dynamics: From Theory to Applications

fully funded

## 15 Early Stage Researcher positions as part of the H2020 MSCA ETN project EvoGamesPlus

Intended starting date: July - September 2021

15 different EU hosts + 15 different partners where secondments take place (incl. Moffitt, Cancer Research UK, but also with Yannick at Université Paris Dauphine!)

Check the details on www.evogamesplus.eu and/or @EvoGamesPlus!