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School of Pharmacy

Using Biomarker Change and Treatment Adherence to Predict Risk of Relapse among Chronic Myeloid Leukemia Patients Who are in Remission

J. Felipe Montano-Campos
fmontano@uw.edu

Twitter: *@JFelipeMCampos*

UNIVERSITY of WASHINGTON

The team!

Aasthaa Bansal, PhD

CHOICE Institute, University of Washington

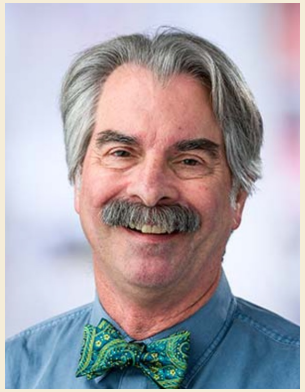
KAISER PERMANENTE®

Eric C Haupt, ScM

Kaiser Permanente Southern California

Erin Hahn, PhD

Kaiser Permanente Bernard J. Tyson School of Medicine

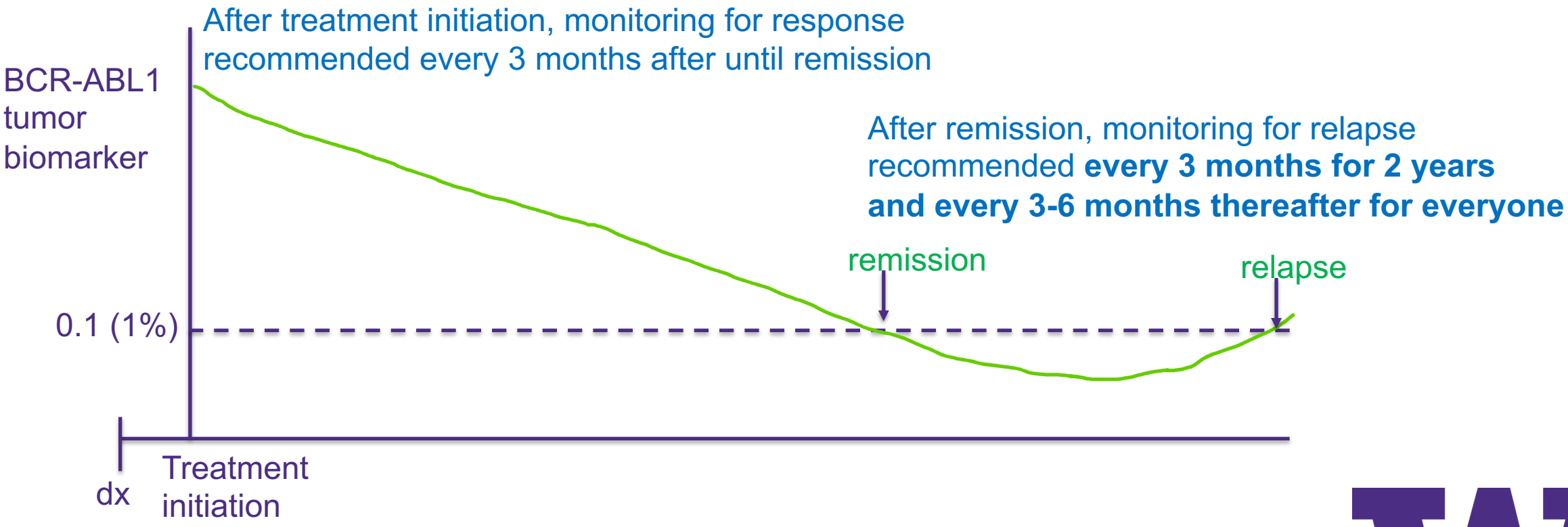


Jerald Radich, MD

Fred Hutchinson Cancer Research Center

UNIVERSITY of WASHINGTON

Clinical guidelines in CML



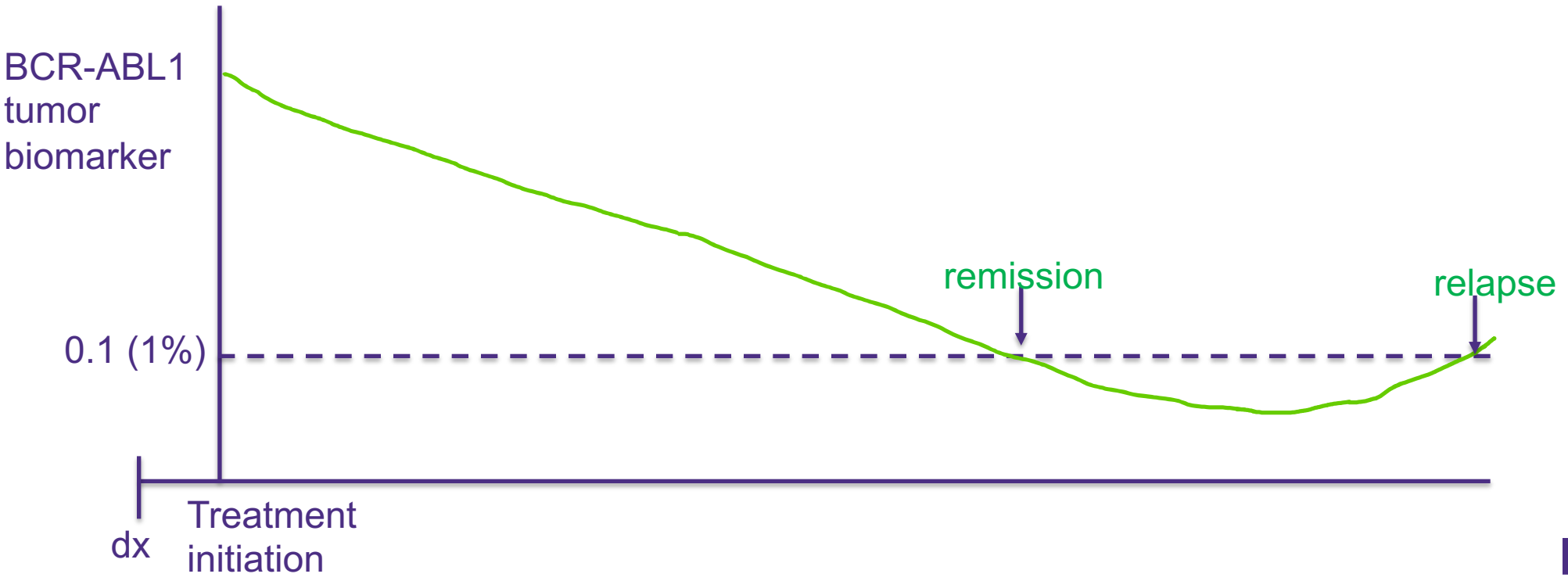
But there is heterogeneity in risk of relapse

Heterogeneity among patients with respect to:

- Response to treatment
- Adherence to treatment
- Other disease factors

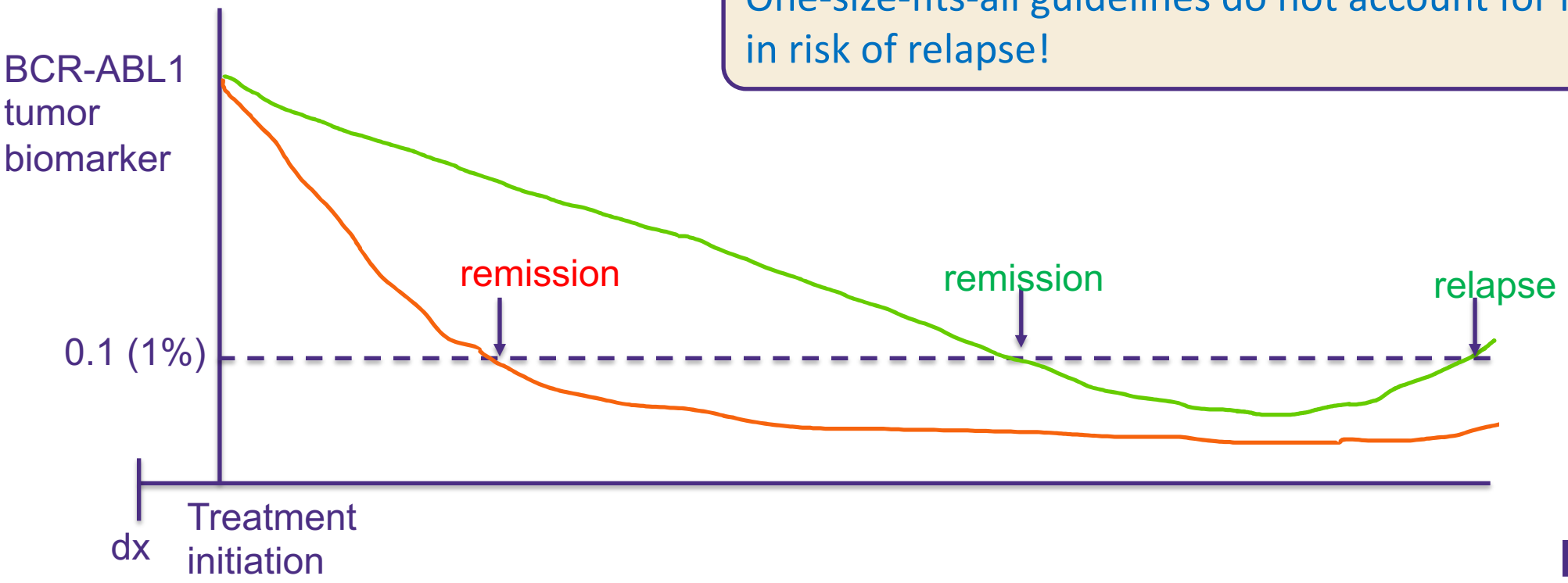
Heterogeneity in Risk of Relapse

Slower biomarker response to treatment can mean higher risk of relapse



Quicker biomarker response to treatment can mean lower risk of relapse

One-size-fits-all guidelines do not account for heterogeneity in risk of relapse!



Furthermore, adherence affects relapse risk

Adherence is highly associated with prognosis, but there are no risk models to date in CML that have incorporated adherence.

Patient adherence to tyrosine kinase inhibitor therapy in chronic myeloid leukemia

Elias J. Jabbour,[1]* Hagop Kantarjian,[1] Lina Eliasson,[2] A. Megan Cornelison,[1] and David Marin[2]

Adherence to BCR-ABL Inhibitors: Issues for CML Therapy

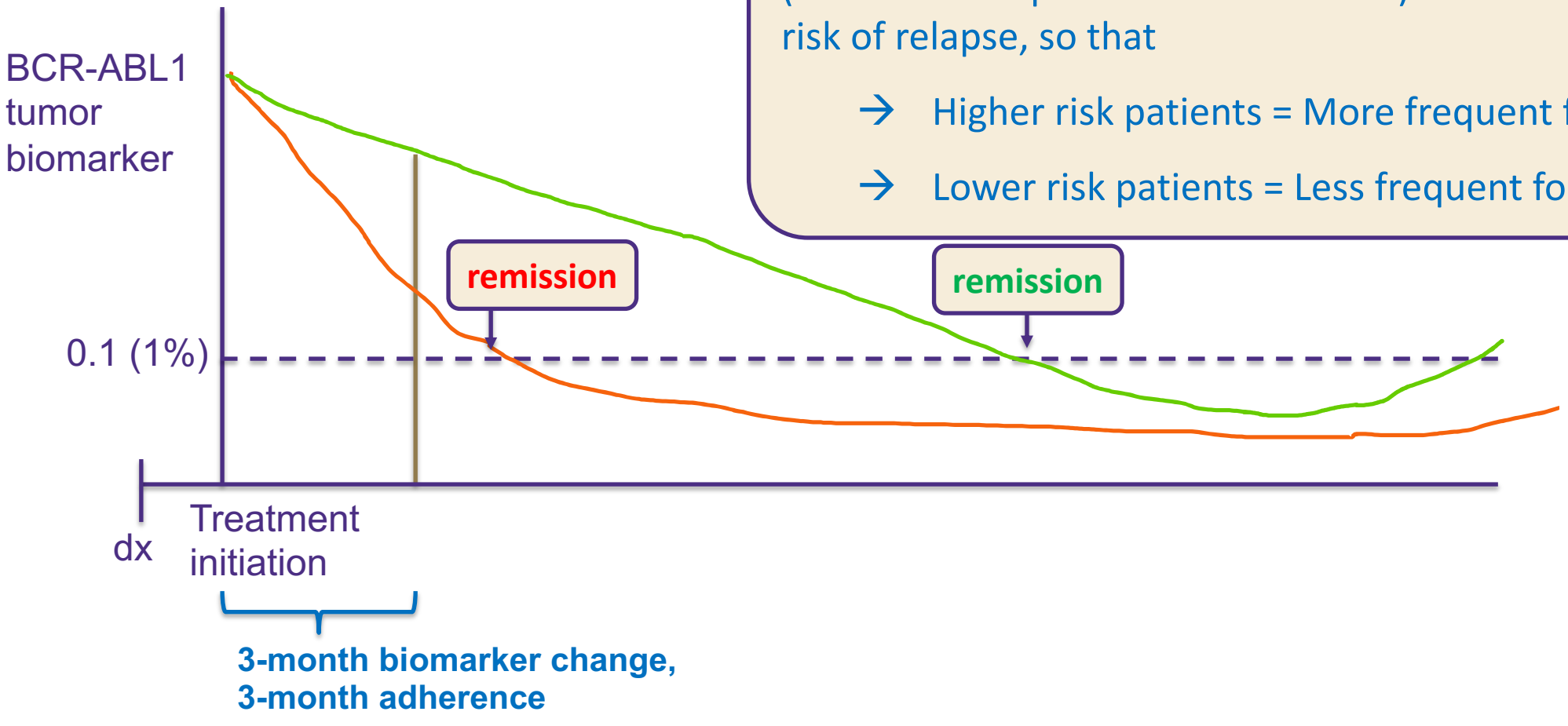
Elias Jabbour,[1] Giuseppe Saglio,[2] Jerald Radich,[3] Hagop Kantarjian[1]

Risk prediction to personalize patient monitoring for relapse

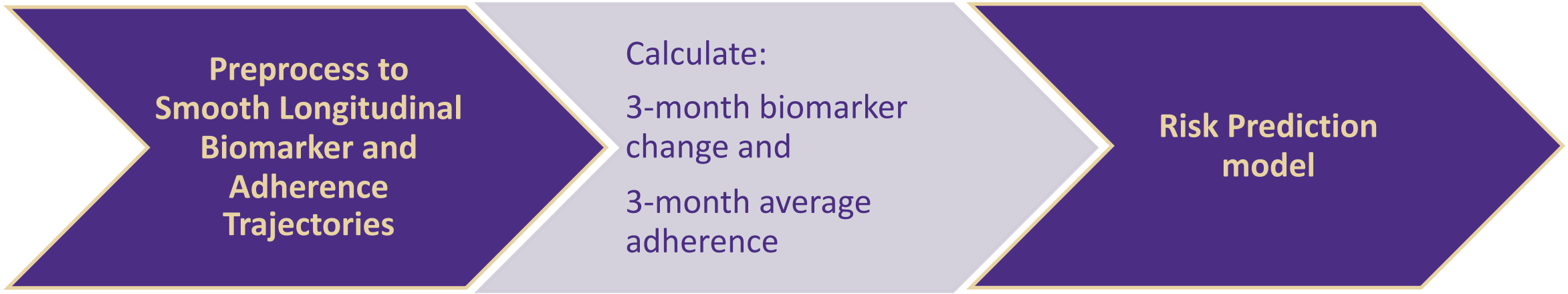
Question: At **remission**, can we use early longitudinal information (biomarker response and adherence) to identify those at higher risk of relapse, so that

→ Higher risk patients = More frequent follow-up

→ Lower risk patients = Less frequent follow-up



A framework for incorporating early biomarker response and adherence to inform risk prediction



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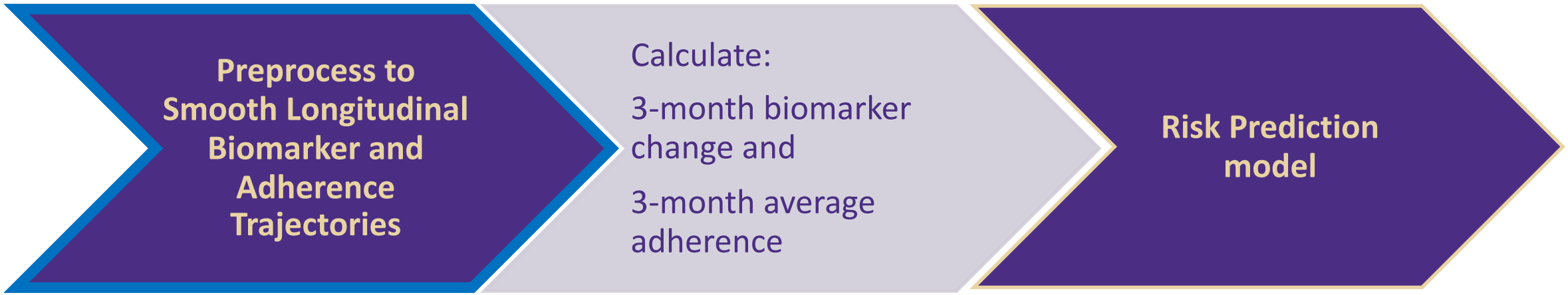


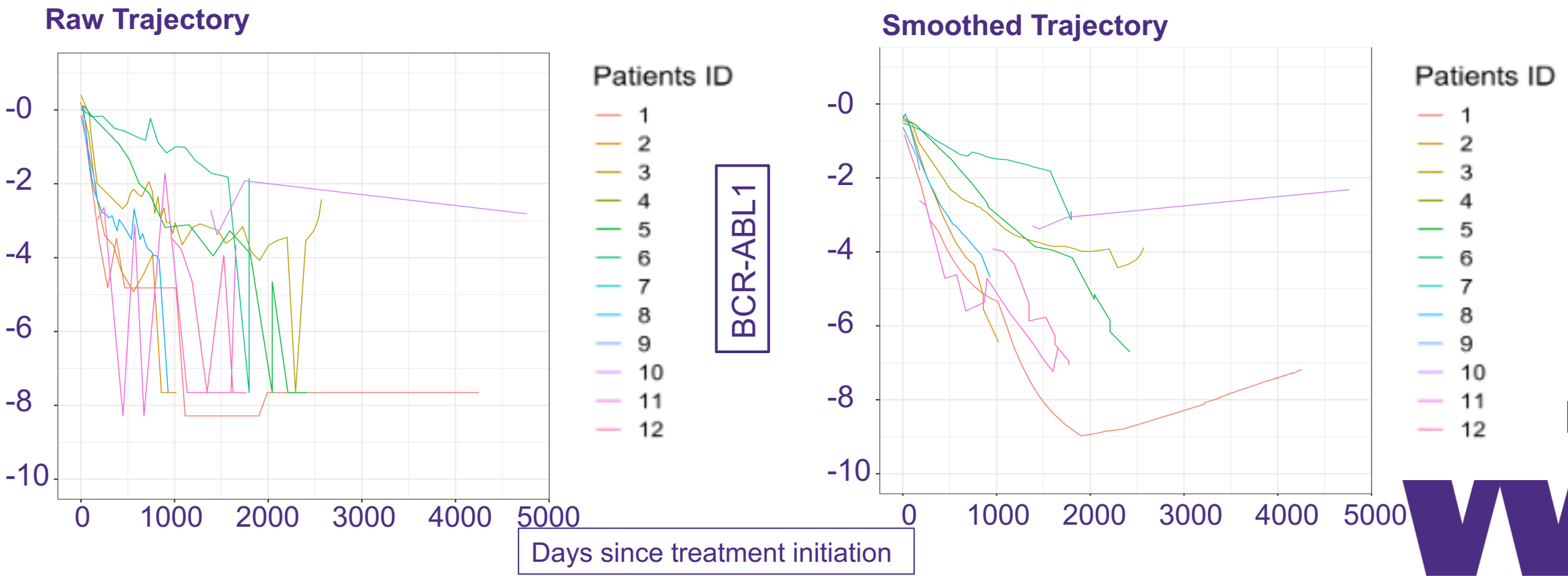
Why do we smooth the data?

1. Biomarker variation due to measurement error often leads to attenuated estimates of biomarker effect on outcomes in a Cox Model (towards zero) (Prentice, 1982).

2. To be able to calculate 3-month change (not everyone had collections at exactly 3 months)

Smoothing longitudinal BCR-ABL1

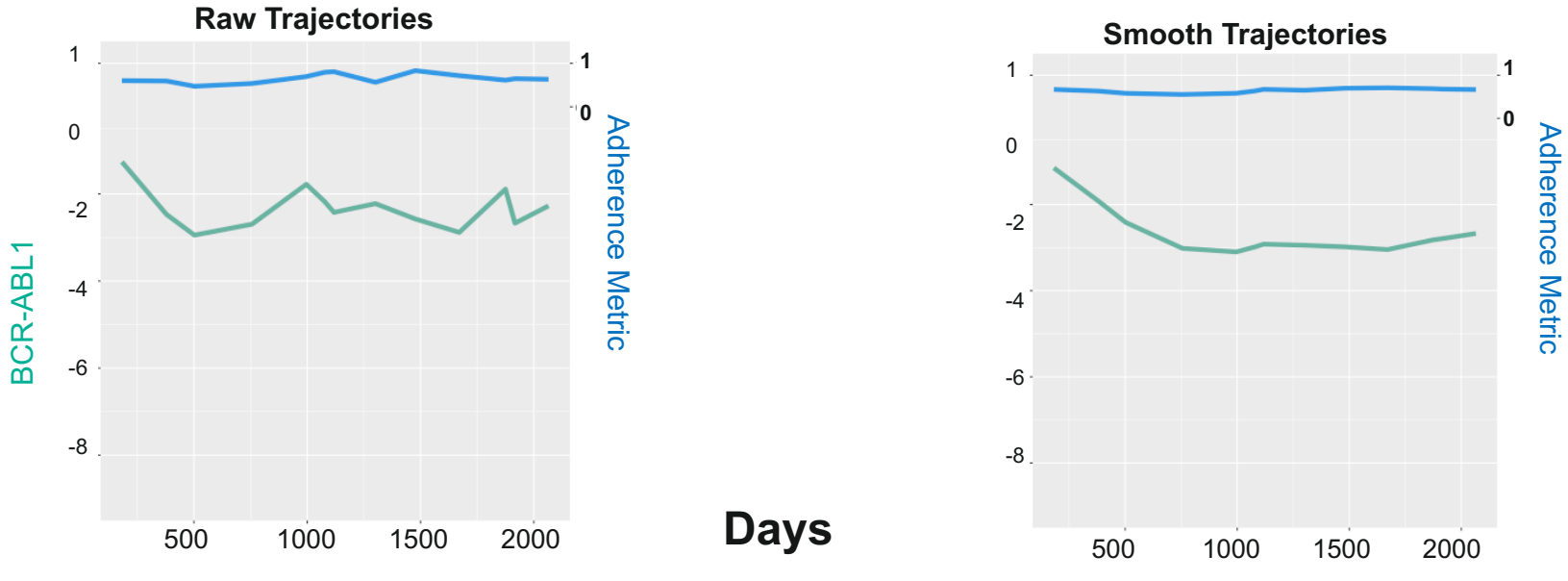
- Collections every three months for most of the patients
- Using a Linear Mixed Effects Model: time (fix and random effect), BMI, gender, age and treatment data



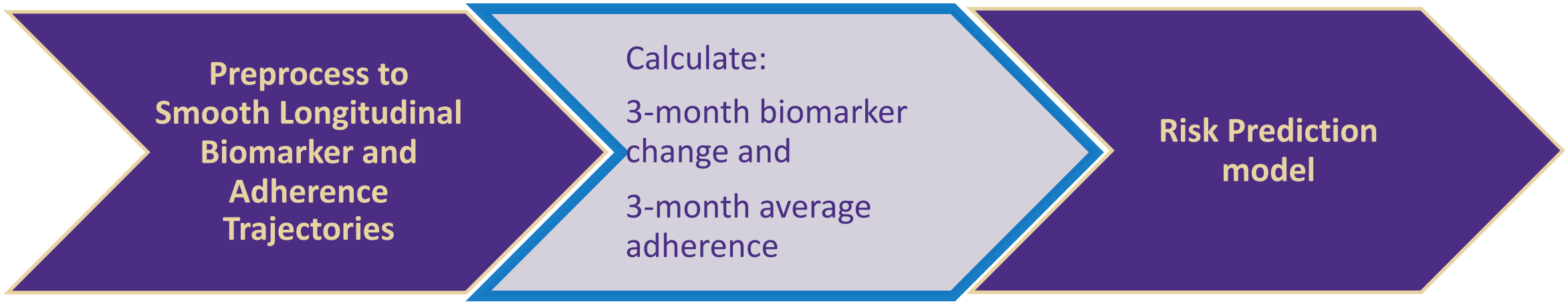
Smoothing longitudinal adherence trajectory

- How do we measure adherence?
  - ❖ For every BCR-ABL1 collection, we calculate adherence in the past 3 months of that collection (using a metric similar to proportion of days covered)
  - ❖ Number between 0 and 1 (where 1 = perfect adherence).

- Smoothing: Using a Linear Mixed Effects Model: time (fix and random effect), BMI, gender, age and treatment data (same as BCR-ABL1 longitudinal adherence)



A framework for incorporating early biomarker response and adherence to inform risk prediction

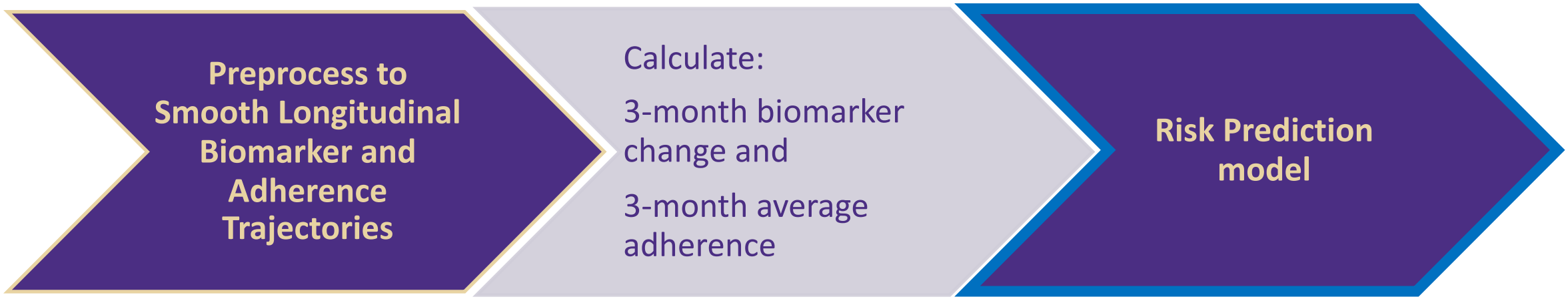


Defining 3-month biomarker change and adherence

Using Smoothed Data:

Variable	Levels	Definition
3-Month Change in the Biomarker Level	Increased Levels 👎	$\Delta > SD/2$
	No Change	Δ within $SD/2$
	Decreased Levels 👍	$\Delta < SD/2$
Adherence Level in the First 3 Months	High Adherence	> 0.80
	Low Adherence	< 0.80

A framework for incorporating early biomarker response and adherence to inform risk prediction



Cohort and descriptive statistics

- We use Electronic Health Records data from an integrated health system
- Final Cohort: 443 Patients
- Diagnosed with CML between 2007-2019 and monitored for relapse after remission

Variable	Descriptive Statistics
Age (Mean (Sd))	53.61 (16)
BMI (Mean (Sd))	29.50 (6.5)
Female (%)	39%
Asian (%)	9.70%
Black (%)	10.40%
White (%)	64.30%
Other (%)	15.60%
Smoking Behavior (%)	
Never	61.18%
Quit	31.82%
Yes	7%
Baseline Treatment (%)	
Imatinib	79.90%
Dasatinib	16.50%
Nilotinib	3.60%

Methods and statistical analysis

Model:	• **Time to event analysis:** Cox Proportional Hazards model • Baseline: When patients entered Remission
Event:	• Relapse **conditional on entering remission** 
Censoring:	• Min(death, membership end, hospice, end of study)
Main Predictors:	• Adherence and change in the BRC-ABL1 values the first 3 months after treatment initiation
Co-Variates:	• Race, sex, BMI, age, smoking behavior, and baseline treatment

Results and performance of the model

Relative to no change in the level of the BCR-ABL1:

- The hazard of relapse was 117% higher in patients with worsened levels
- 17% lower in patients with improved levels

Relative to patients with lower levels of adherence:

- The hazard of relapse was 12% lower for patients with higher medication adherence

Bootstrap AUC:
Mean = 0.88
95% CI (0.64-0.97)

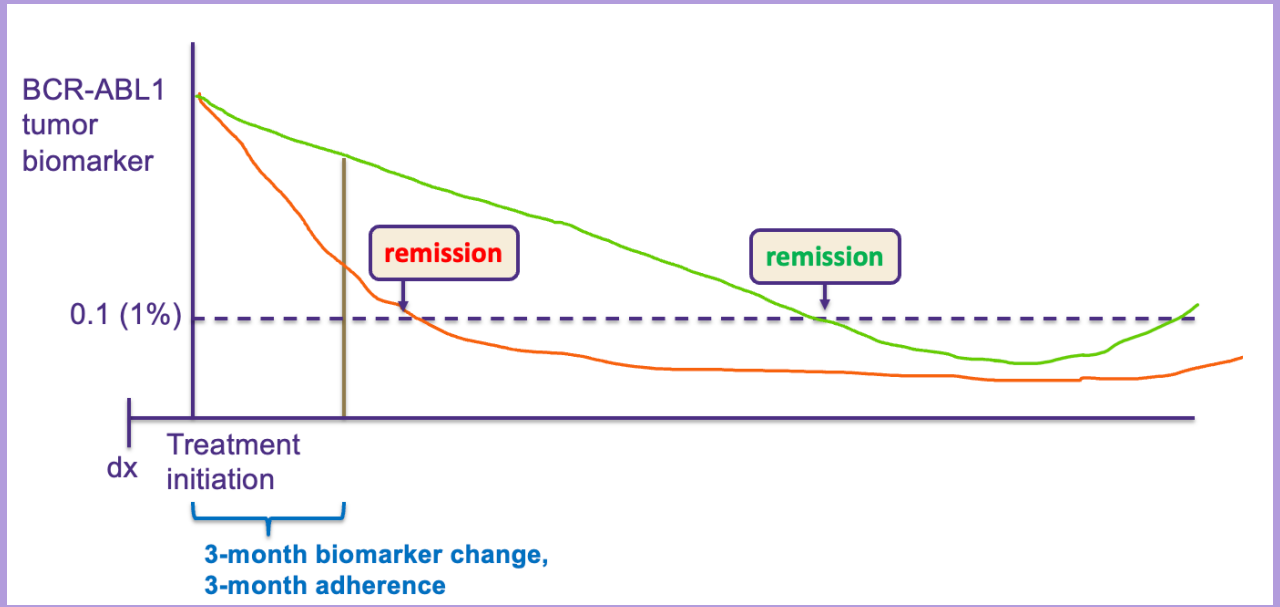
Conclusion and further research

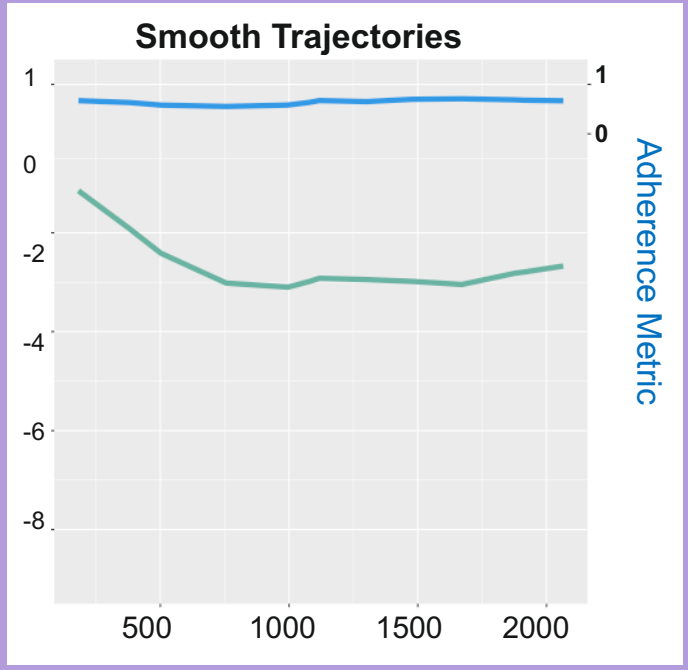
- There is heterogeneity in the risk of relapse after remission among patients diagnosed with CML

- Using longitudinal information on the biomarker trajectory and treatment adherence, we were able to achieve high accuracy in predicting the risk of relapse after remission

- In progress: Updating biomarker change and adherence over time to predict dynamic risk of relapse

Q & A





BE BOUNDLESS

Thank you!

BE BOUNDLESS

Appendix

BE BOUNDLESS

Existing risk models mostly use baseline information and model different outcomes

Existing Risk Models

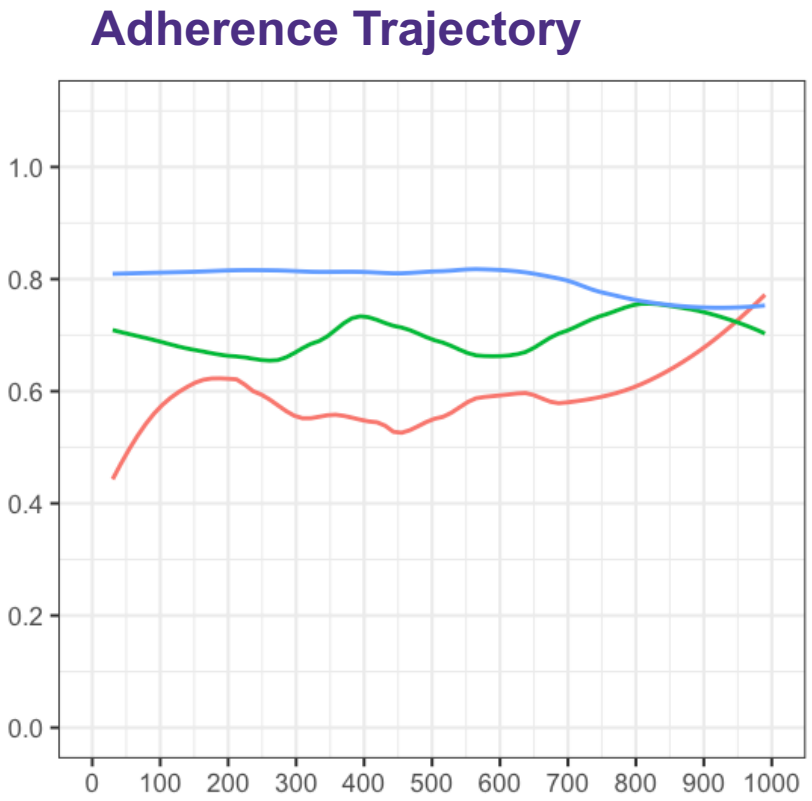
- Age at diagnosis
- Spleen size at diagnosis
- Platelet and blast count at diagnosis
- BCR-ABL1 transcript level at diagnosis
- Time taken for BCR-ABL1 value to halve

→

- Remission
- Survival
- Major Molecular Response

However, patients' early adherence and early biomarker response to treatment are highly correlated with risk of relapse

Adherence trajectory



Category 1: Low adherence in the first three months after tx initiation
Category 2: Med adherence in the first three months after tx initiation
Category 3: High adherence in the first three months after tx initiation

Persistence in the Adherence Behavior

BCR-ABL standardization (log-ratio)

- **Standardization:**

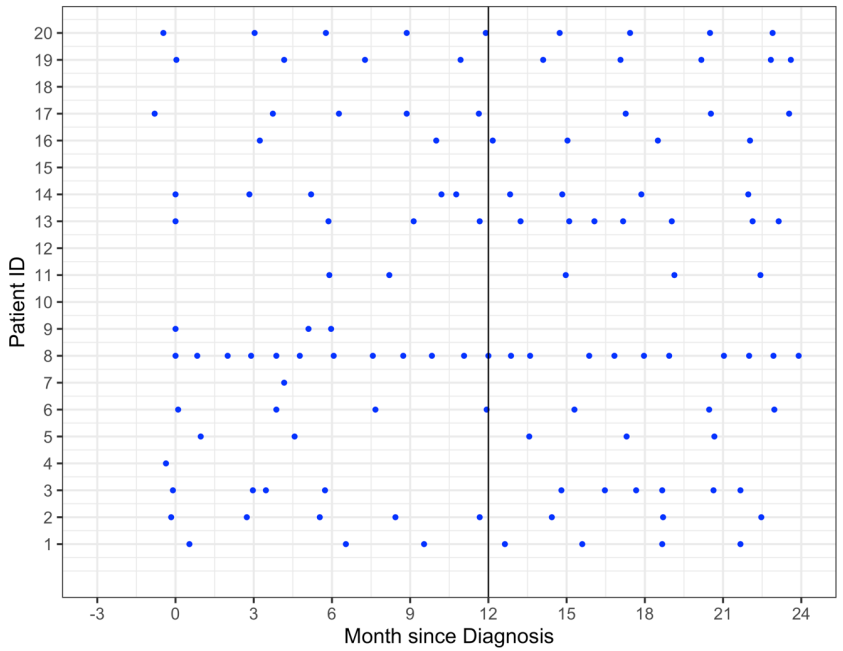
$$BCR-ABLstd_i = log(\frac{BCR-ABL_i}{Median(\overline{BCR-ABL})})$$ where $\overline{BCR-ABL}$ is the baseline value.

We use the median baseline value of the unit measure of the BCR-ABL value.

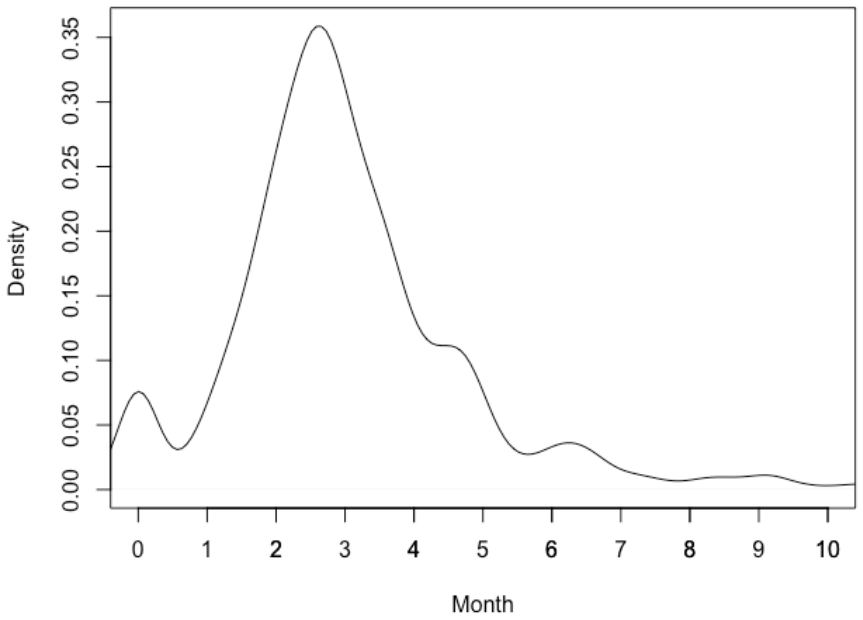
BCR-ABL1 (biomarker) data

> Collections of the BCR-ABL1 biomarker of patients (every 3 months for most of the patients)

Collections



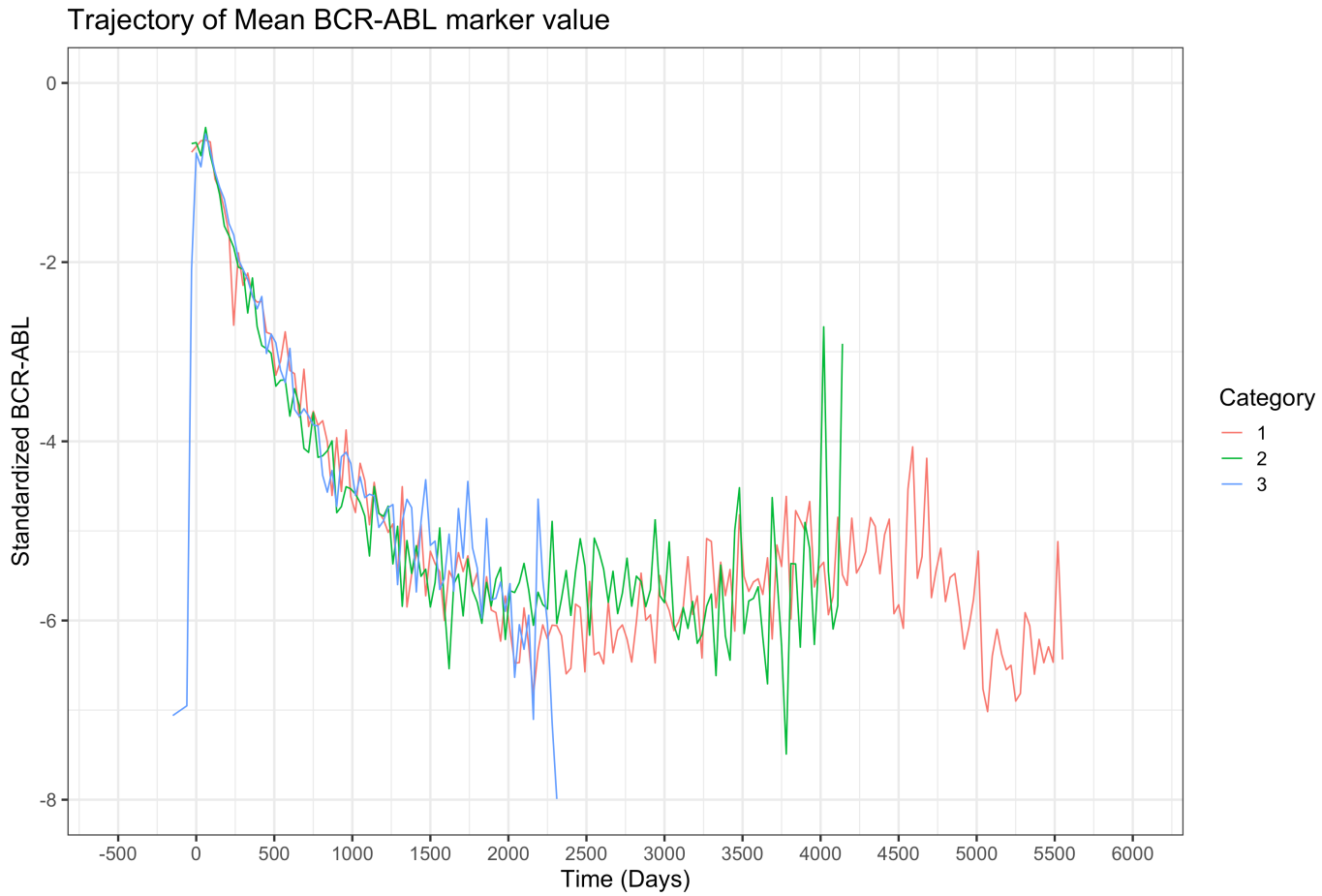
Average time in between collections (Median = 3 Months)



Trajectories: Year of diagnosis

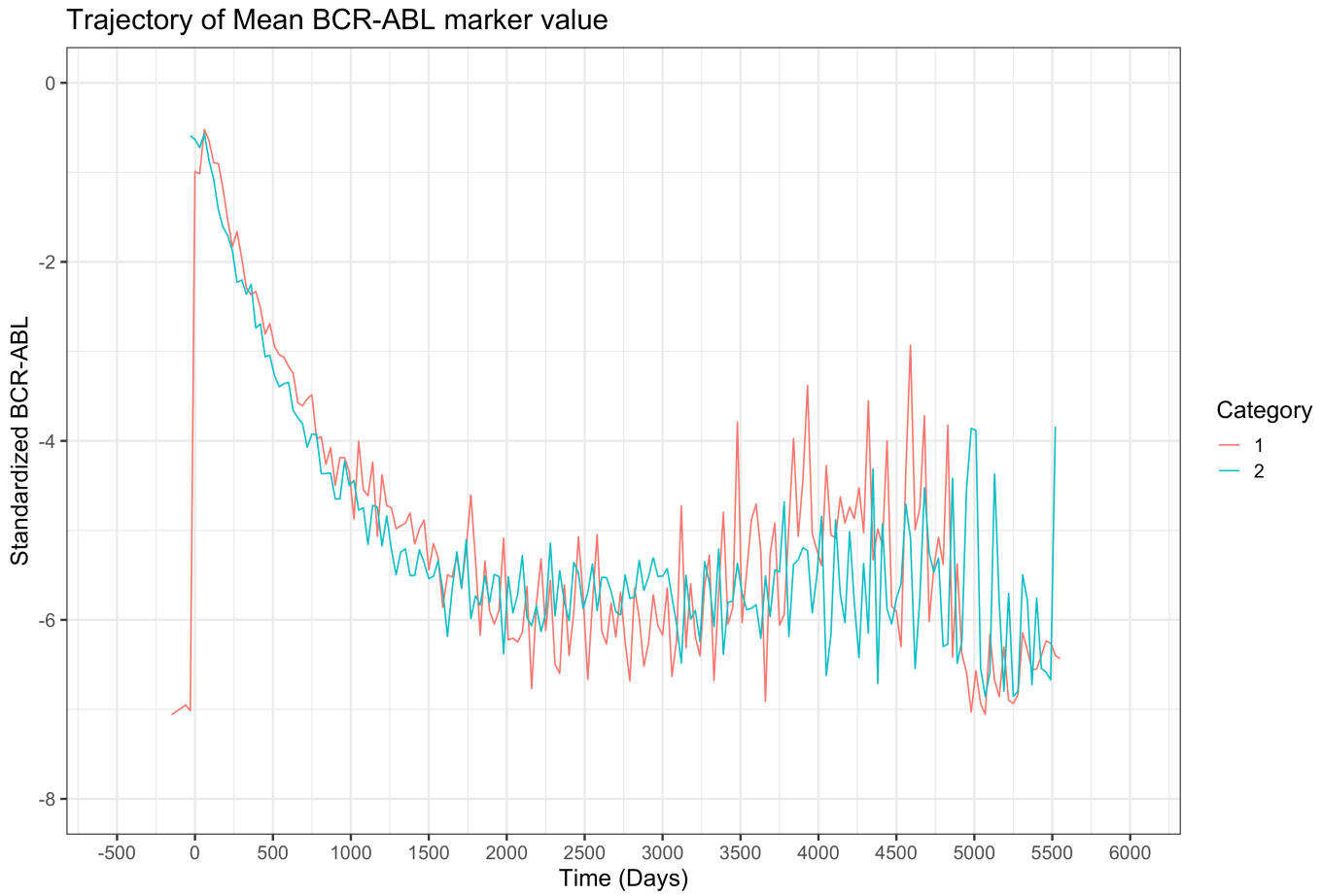
Time unit: 30 days interval using Dx2collect.

Category 1: <2011
Category 2: 2011-2015
Category 3: >2015



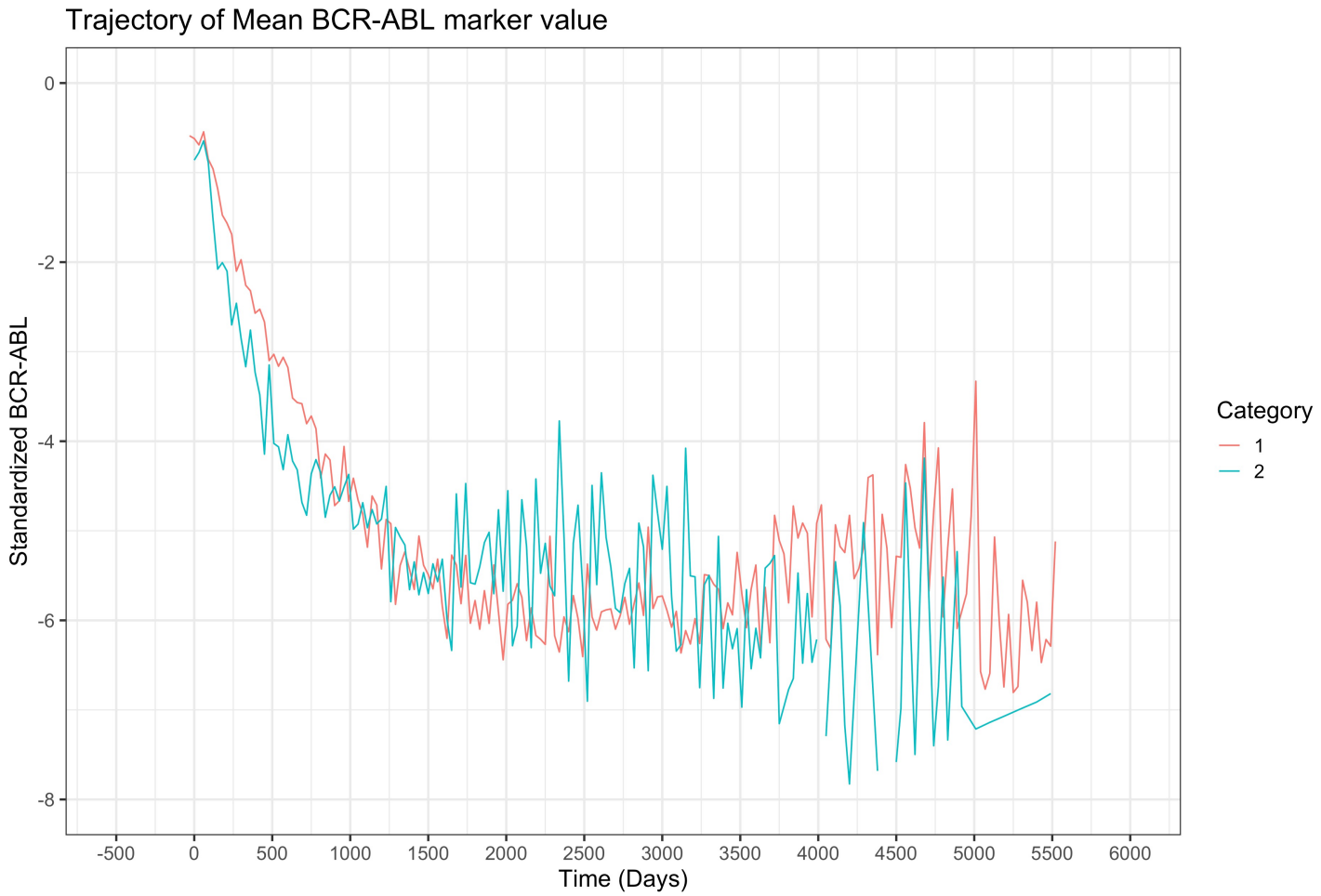
Trajectories: Treatment

Category 1: Ever prescribed Hydroxyurea and Dexamethasone (either with TKI or by themselves)
Category 2: Only TKIs prescribed

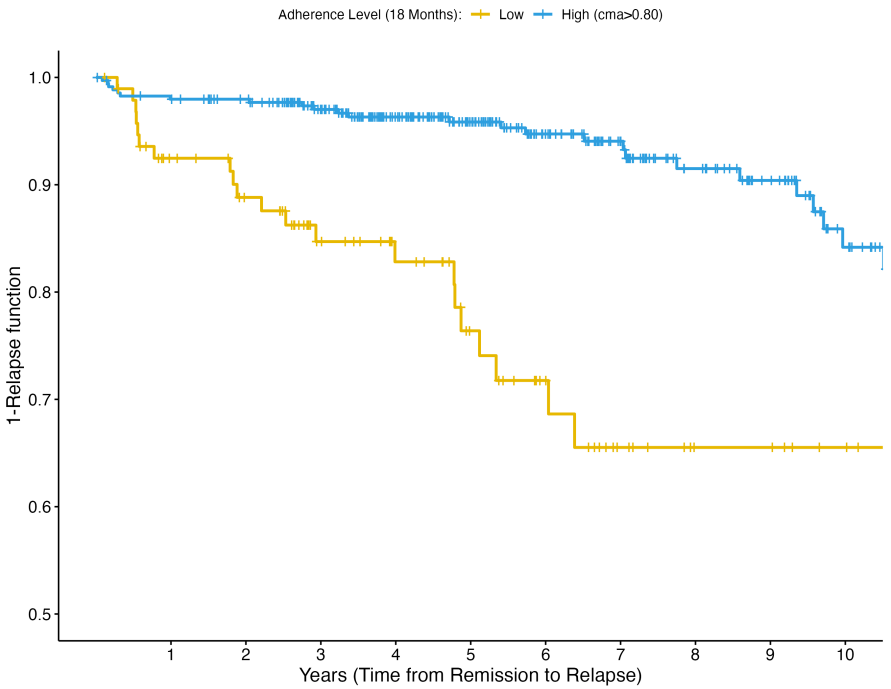


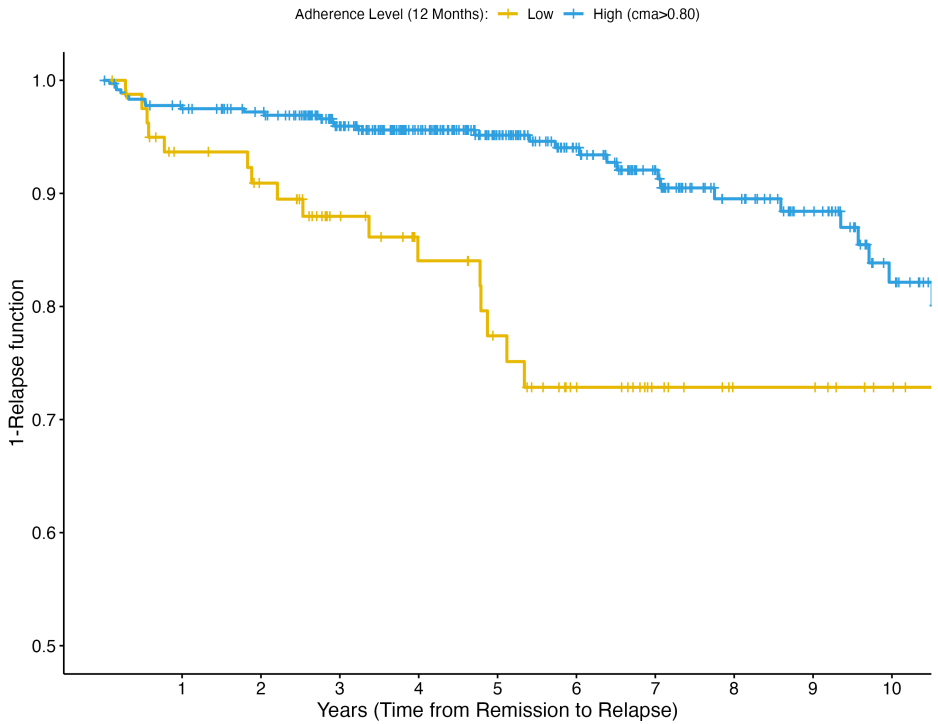
Trajectories: Baseline treatment

Category 1: First Generation
Category 2: Second Generation



Methods and statistical analysis





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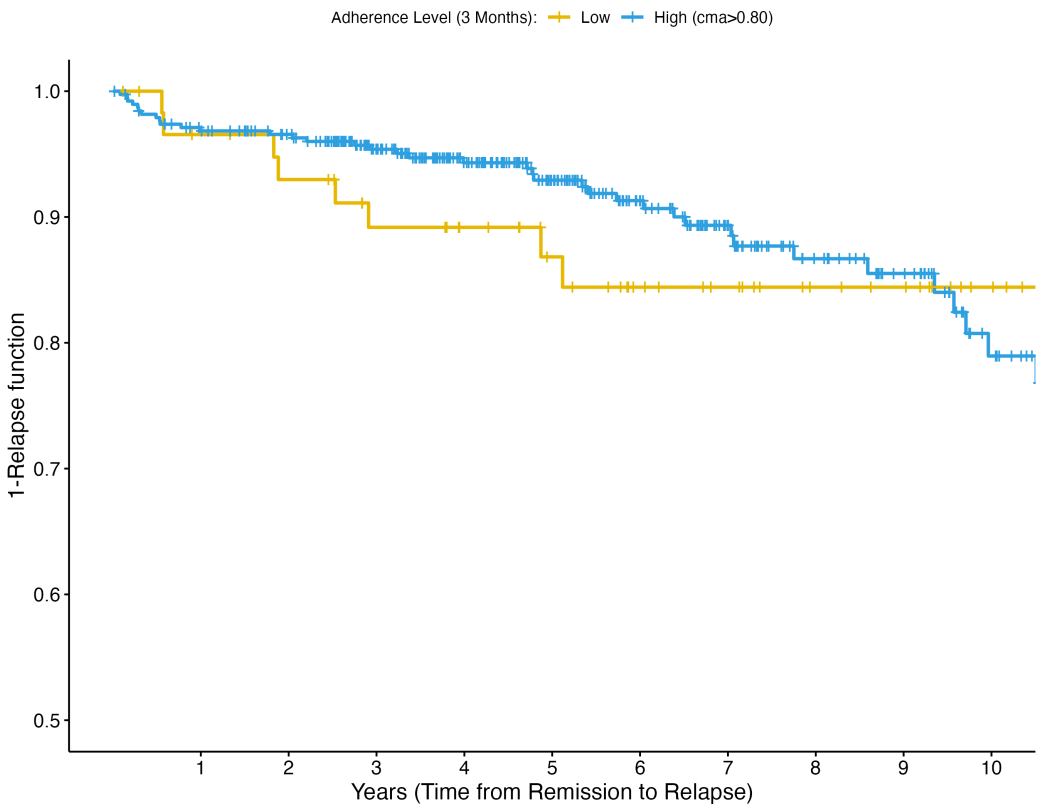

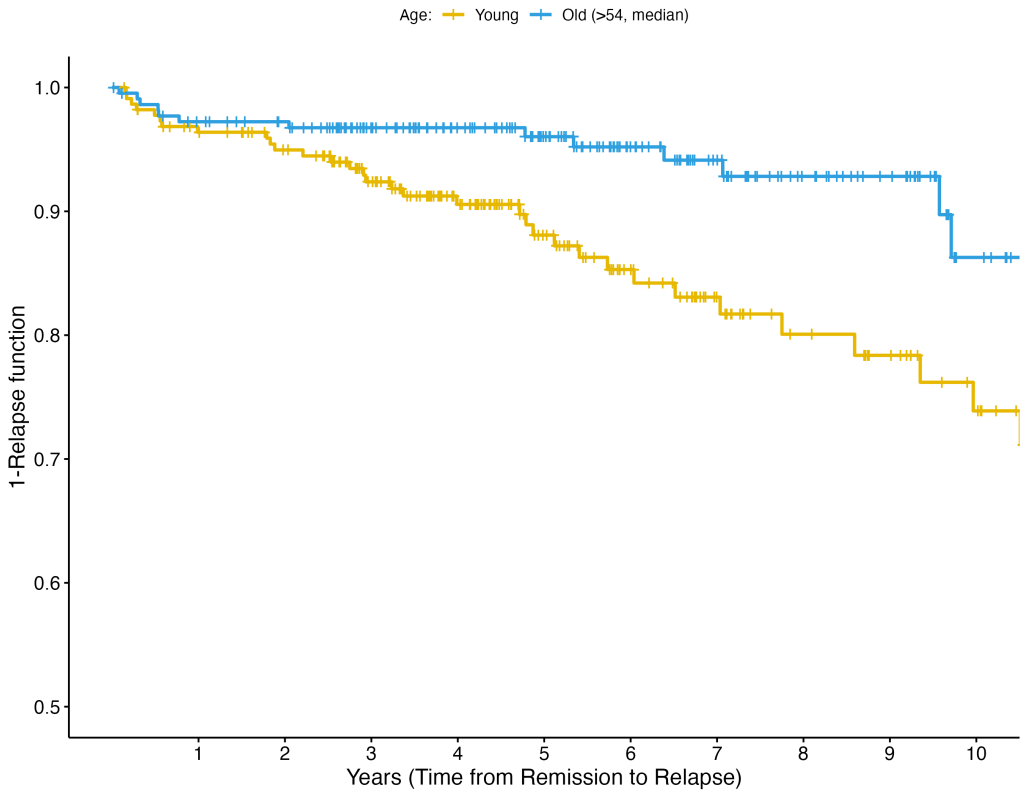

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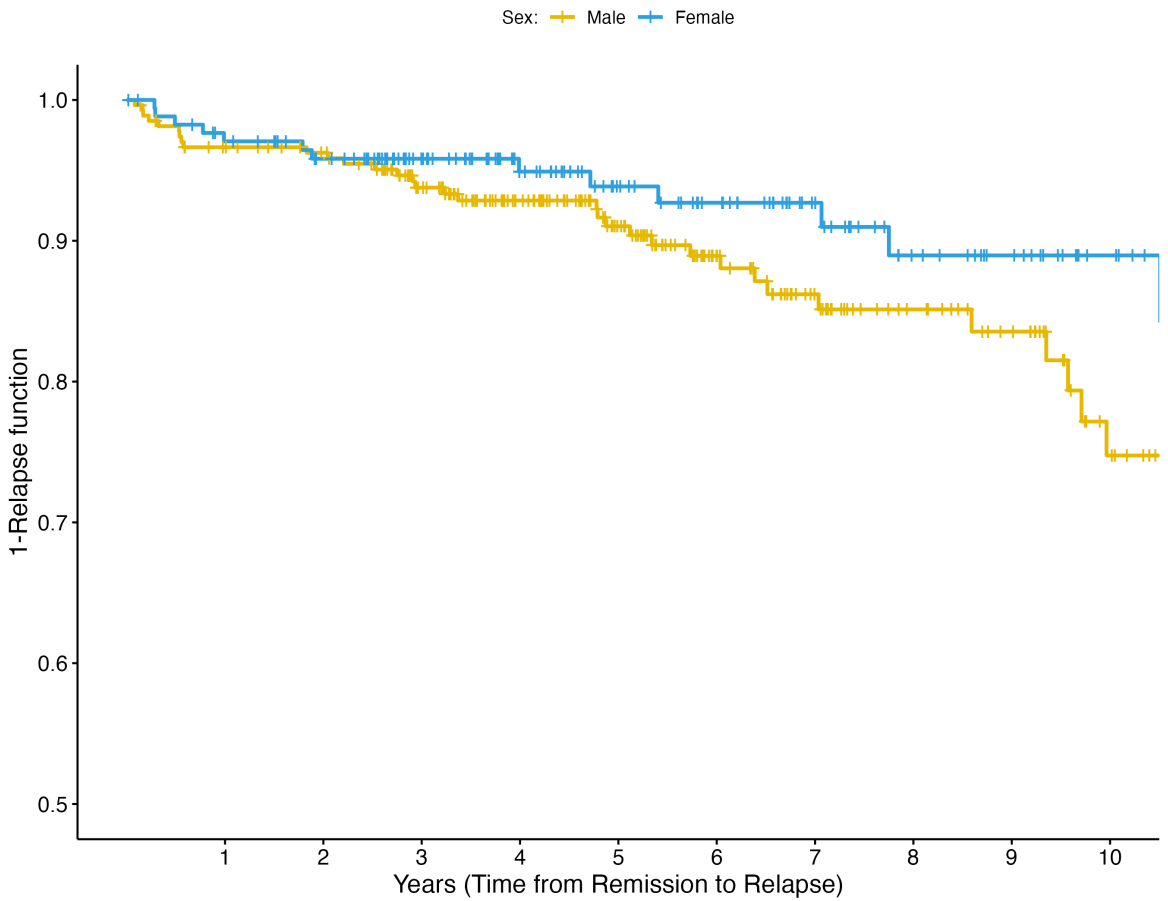
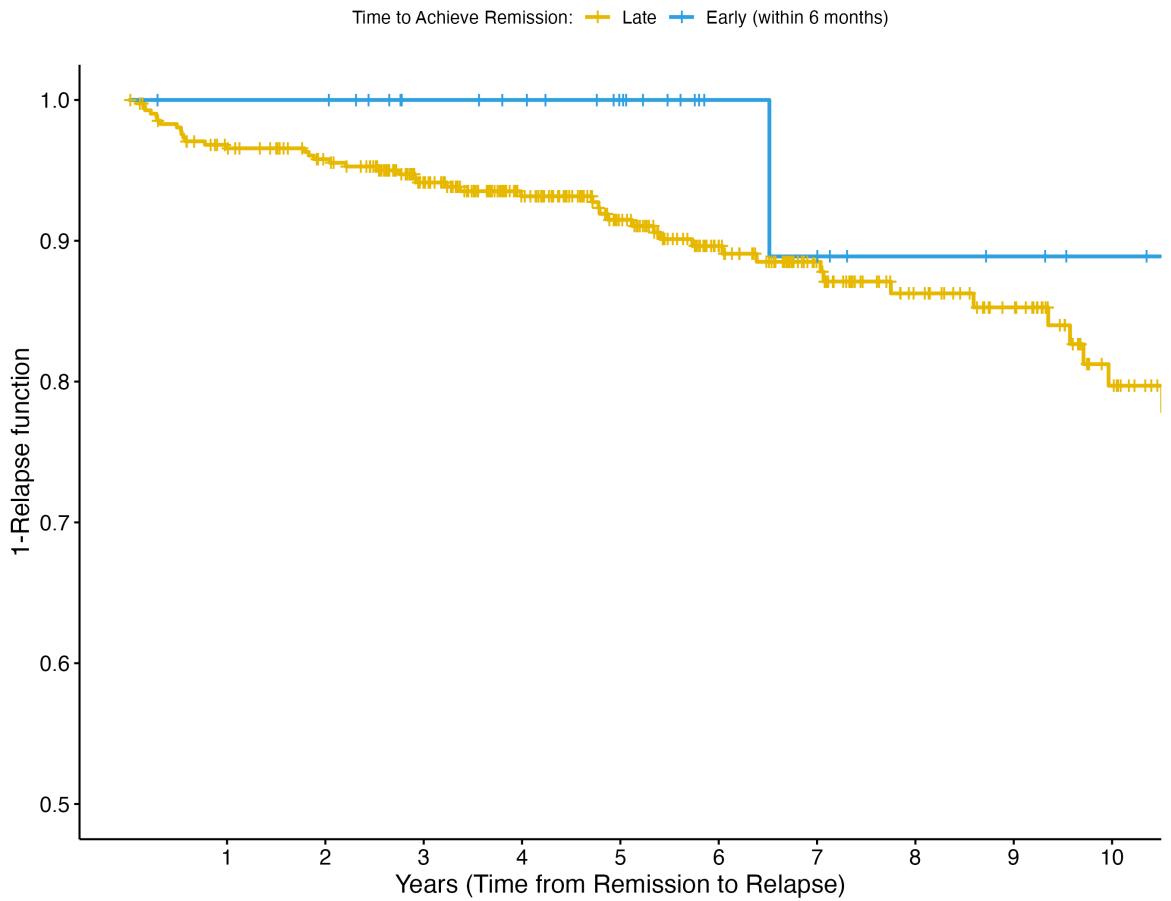
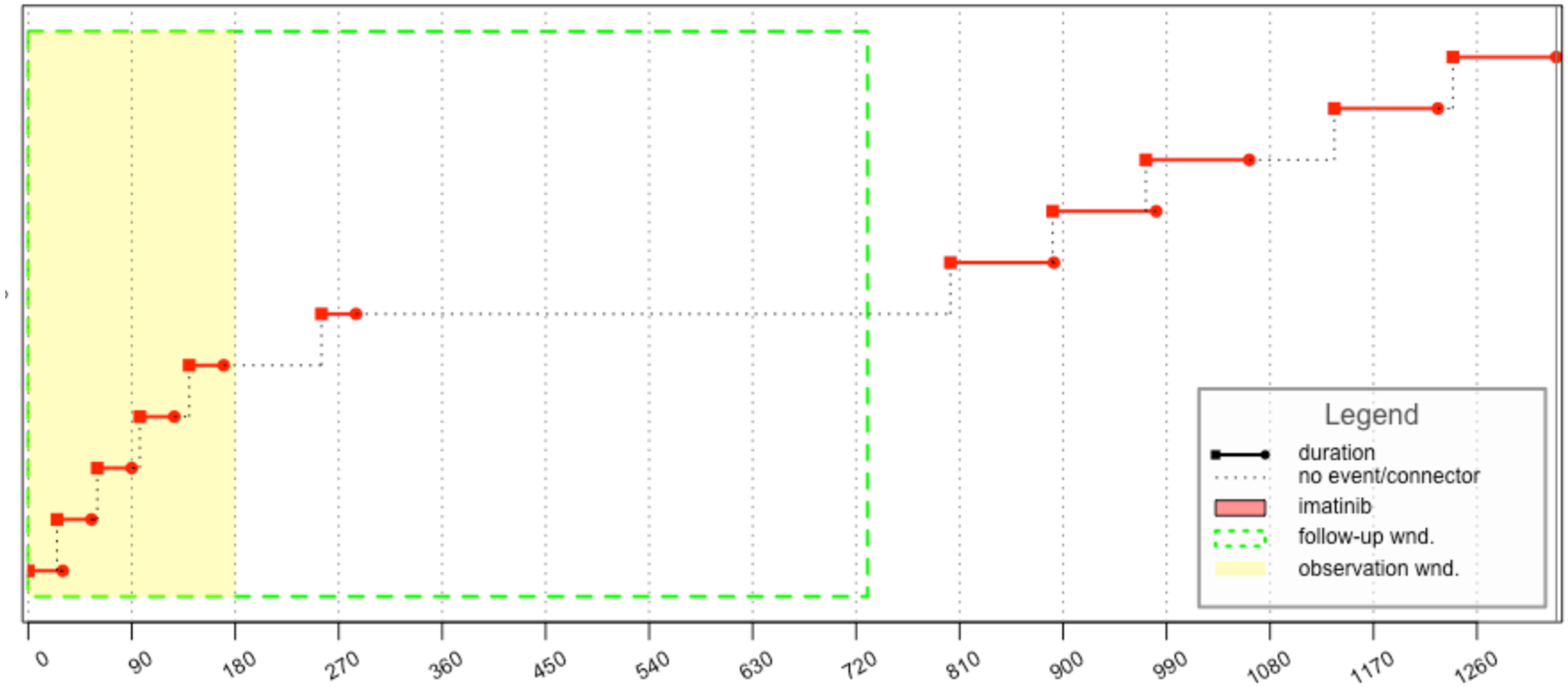




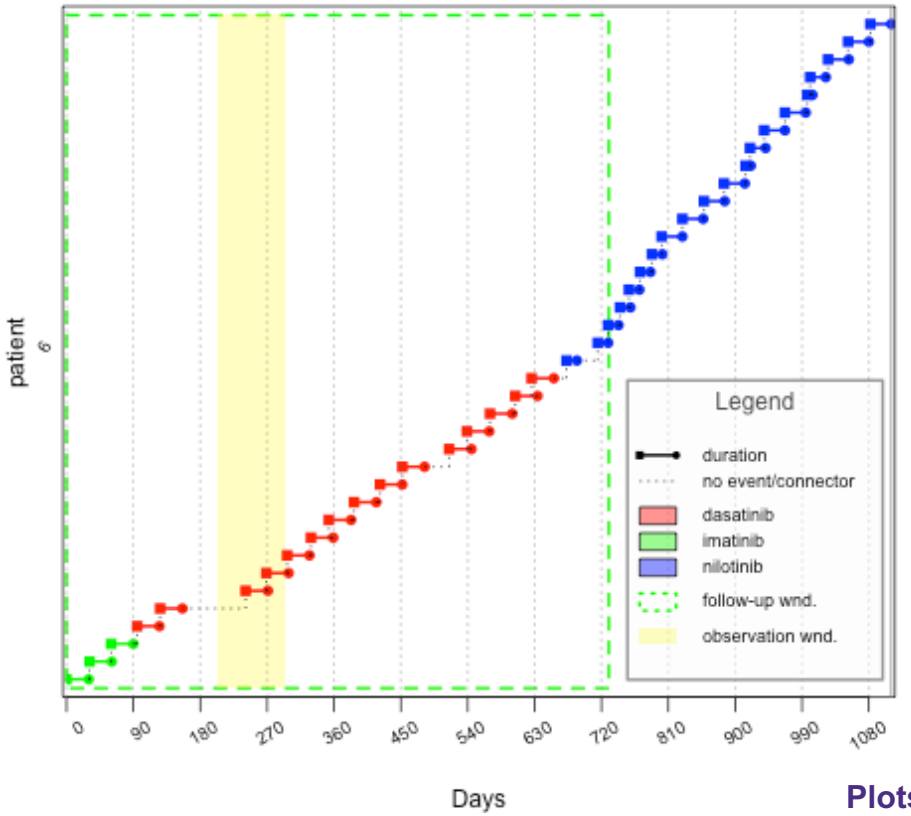
Adherence trajectory

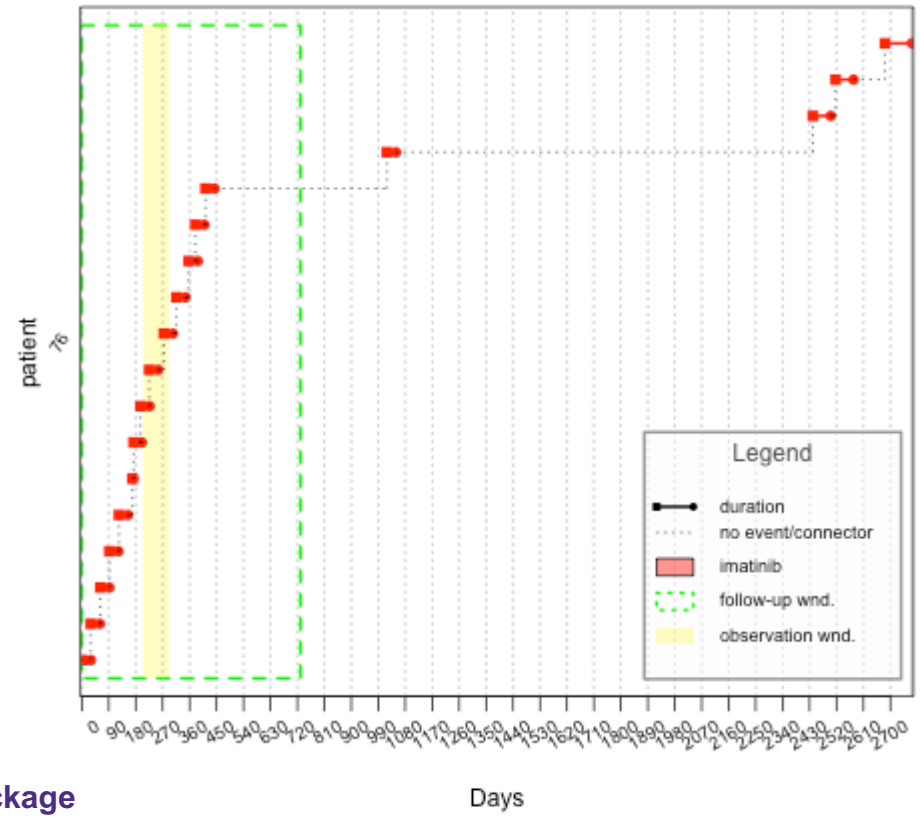


Days since treatment initiation

Adherence trajectory

- Longitudinal treatment data of patients

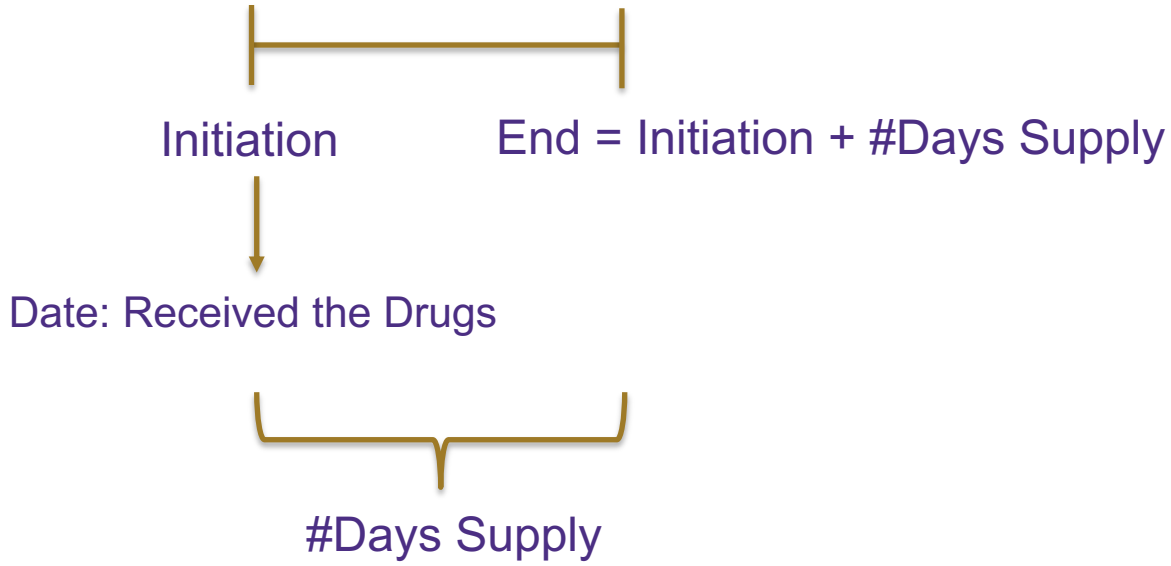




Plots using AdhereR package

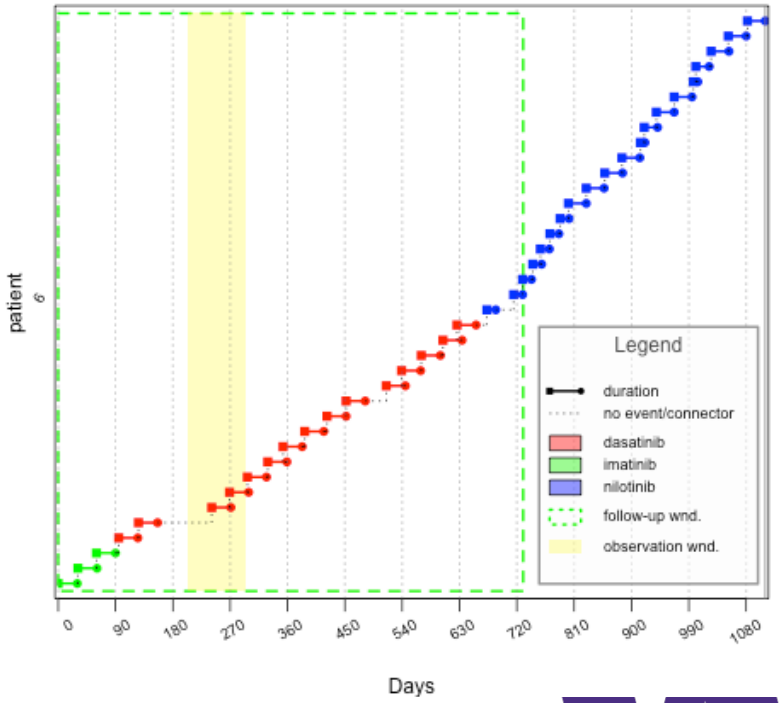
Treatment data

> We have treatment events of patients



Variables:

- Drug Generic name
- Drug Strength prescribed
- Days supplied to patient
- Amount supplied
- Units
- Directions provided to patient



Adherence metric calculation

- We calculate the *CMA* (continuous multiple-interval measures of medication availability/gaps):
  - A metric that captures medical adherence (from 0 to 1, where 1 is perfect adherence)
  - There are 9 classes of CMA that can produce very different estimates of adherence and each of them is defined by 4 parameters (OW, values capped at 100%, medication oversupply and carry over, medication available before a first event is considered)
  - Implemented in ***AdhereR***
- CMA9: We consider carry over from before the OW and within OW

$$\frac{\#OW\ days, each\ weighted\ by\ its\ ratio\ days\ supply}{OW\ start\ to\ OW\ end}$$

Relapse free survival -> cumulative incidence