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33rd PAGE meeting – 5th June 2025

Optimizing Sunitinib Dosing in Metastatic Renal Cell Carcinoma (mRCC)

Addressing Confounding Bias and Immortal Time Bias in Exposure- and Toxicity-survival Analyses

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Towards Better Dosing of TKIs

Tyrosine kinase inhibitors (TKIs)

- Targeted therapies

Old paradigm

- Maximum tolerated dose (MTD)
- Higher dose = more efficacy
- Designed for chemotherapy

TKIs ≠ Chemo

- Target-specific
- Higher dose ≠ more efficacy
- Chronic use impacts quality of life

New paradigm

- Optimized dose
- Balanced efficacy vs. toxicity

Many older TKIs are still labeled at MTD

In need of dose optimization!

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Sunitinib

- Multi-targeted VEGFR inhibitor
- Most cost-effective first-line therapy for metastatic renal cell carcinoma (mRCC)
- Labeled at MTD - 50 mg daily 4/2 (4 weeks on 2 weeks off)

Dose-limiting toxicities (DLTs):

- Fatigue, diarrhea, hand-foot syndrome, etc.
- Dose reductions (~32%)
- Treatment discontinuation (~8%)

Faivre et al., J Clin Oncol 2006
Motzer et al., JAMA 2006
Motzer et al., J Clin Oncol 2012

VEGFR: vascular endothelial growth factor receptors
MTD: maximum tolerated dose

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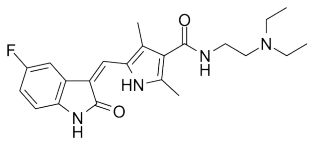
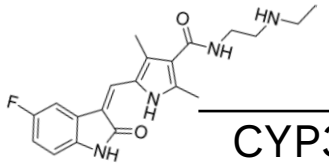
Sunitinib – Large IIV in PK

Sunitinib



CYP3A4

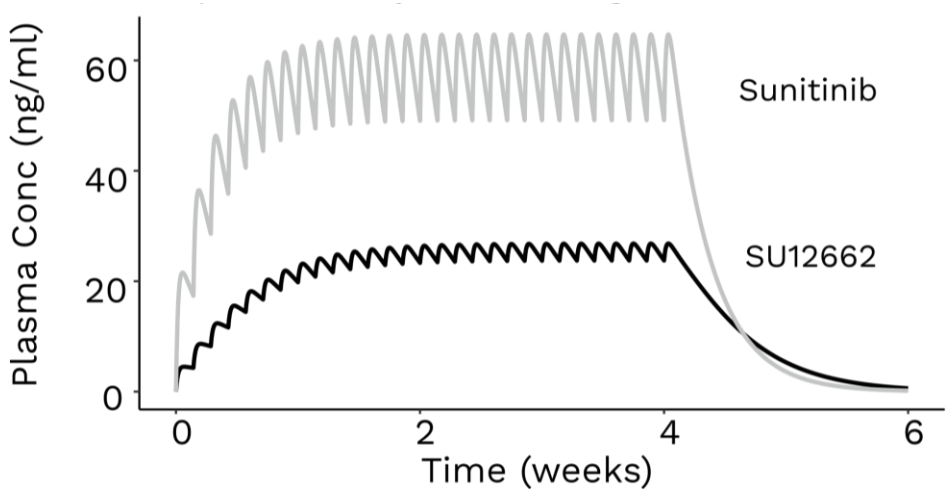
SU12662



CYP3A4

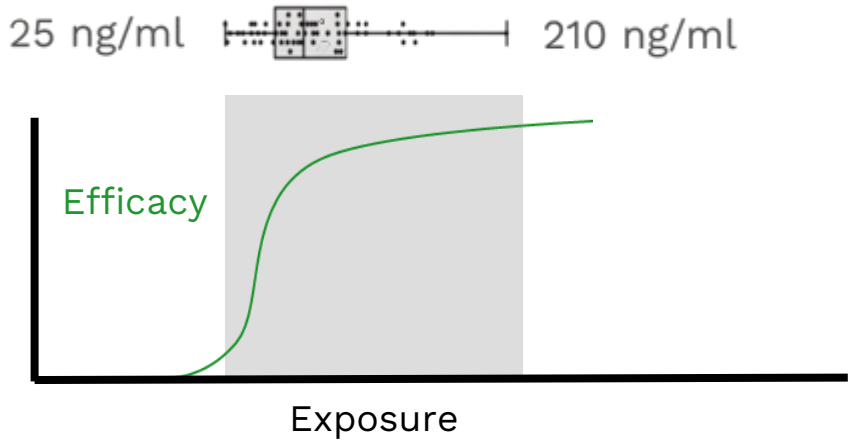
Inactive forms

PK profiles of cycle 1 (50 mg 4/2)



Gandhi et al. Cancer Chemother Pharmacol 2022

Combined $C_{trough,\,ss}$ (sunitinib + SU12662)



IIV: inter-individual variability

$C_{trough,\,ss}$: trough concentration at steady state

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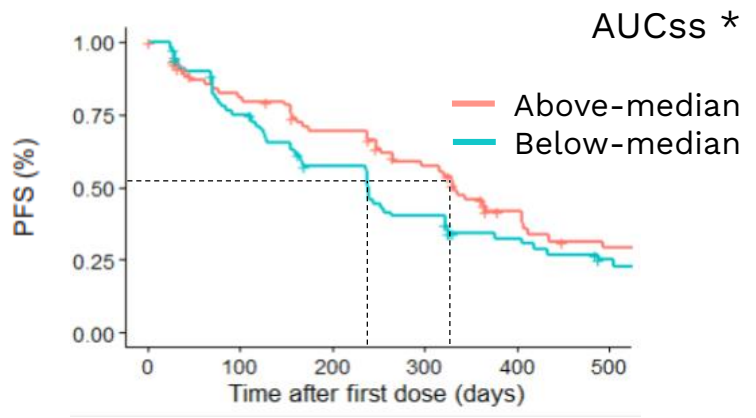
Efforts to Dose Individualize in mRCC

Therapeutic drug monitoring (TDM)

Dose escalation in patients with combined $C_{trough,\,SS}$ < 50 ng/ml if tolerable

Higher Exposure → Longer PFS

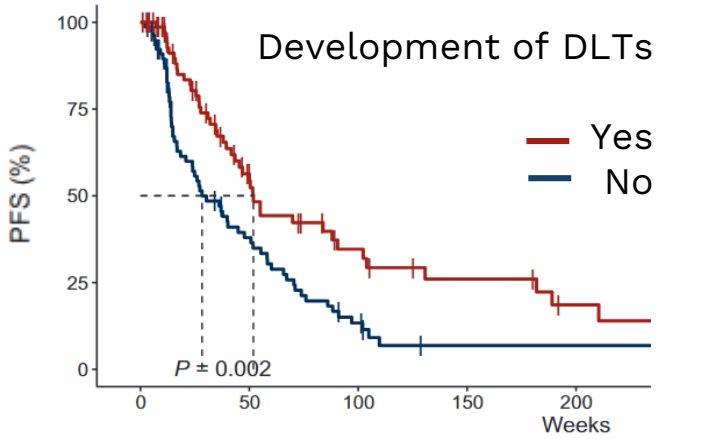


* corr(AUC_{SS}, $C_{trough,\,SS}$) = 0.97

Toxicity-guided dosing

Titrate patients towards the individual MTD

DLTs → Longer PFS



Widmer et al. Eur J Cancer 2014
Westerdijk et al. Br J Clin Pharmacol 2021
Giraud et al. ESMO Open 2024

MTD: maximum tolerated dose
PFS: progression-free survival
DLT: dose-limiting toxicity

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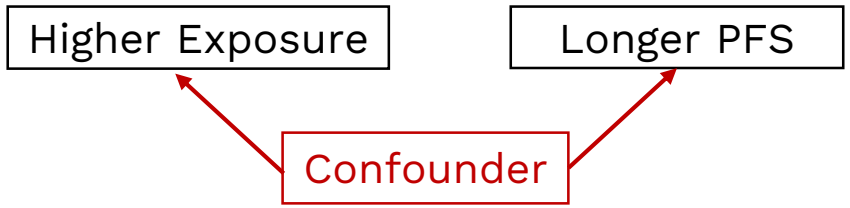
Limitation of Evidence

Therapeutic drug monitoring (TDM)	Toxicity-guided dosing
Dose escalation in patients with combined $C_{trough,\,SS}$ < 50 ng/ml if tolerable	Titrate patients towards the individual MTD



Lack of randomization
Data from a single dose of 50 mg 4/2

Widmer et al. Eur J Cancer 2014
Westerdijk et al. Br J Clin Pharmacol 2021
Giraud et al. ESMO Open 2024

MTD: maximum tolerated dose
PFS: progression-free survival
DLT: dose-limiting toxicity

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Aims of the study

- To identify and address confounders affecting both sunitinib PK and outcomes
- To re-evaluate the impact of DLTs on patient outcomes
- To improve the dosing strategies of sunitinib in patients with mRCC

DLTs: dose-limiting toxicities
mRCC: metastatic renal cell carcinoma

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Revisit Historical Trial Data in mRCC

Study	Phase	Dose	# IDs received sunitinib	# IDs with PK data
1006	II	50 mg 4/2	106	105
014	II		64	60
034	III		375	42

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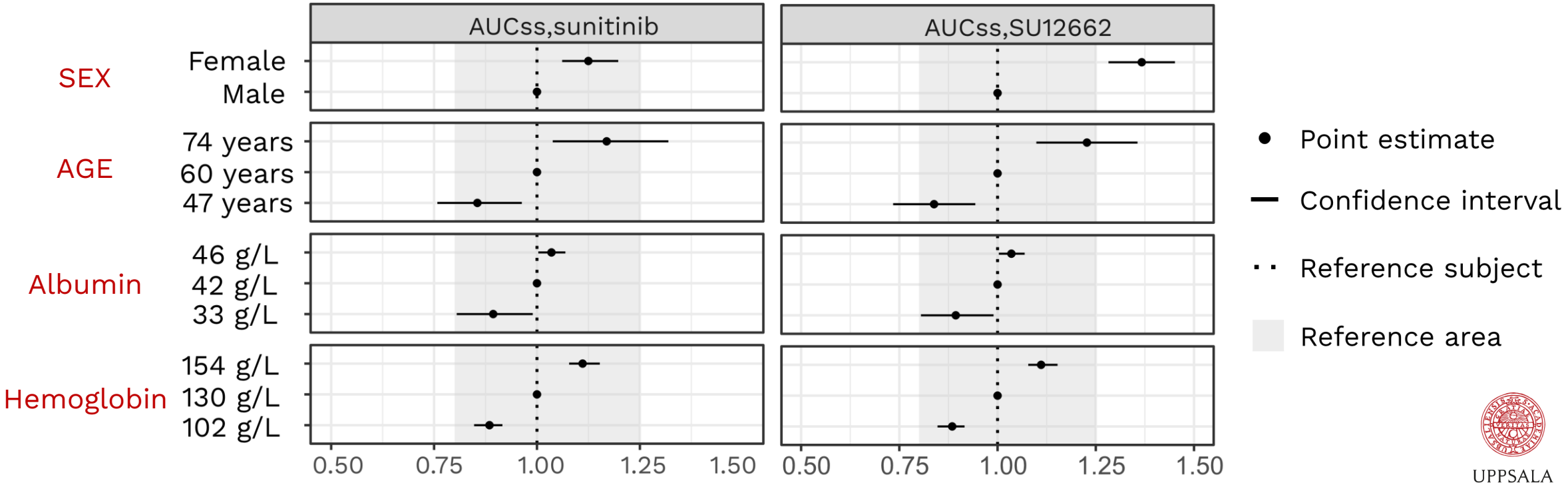
Population PK analysis

Study	Phase	Dose	# IDs received sunitinib	# IDs with PK data
1006	II	50 mg 4/2	106	105
014	II		64	60
034	III		375	42

- Allometric scaling applied based on body weight



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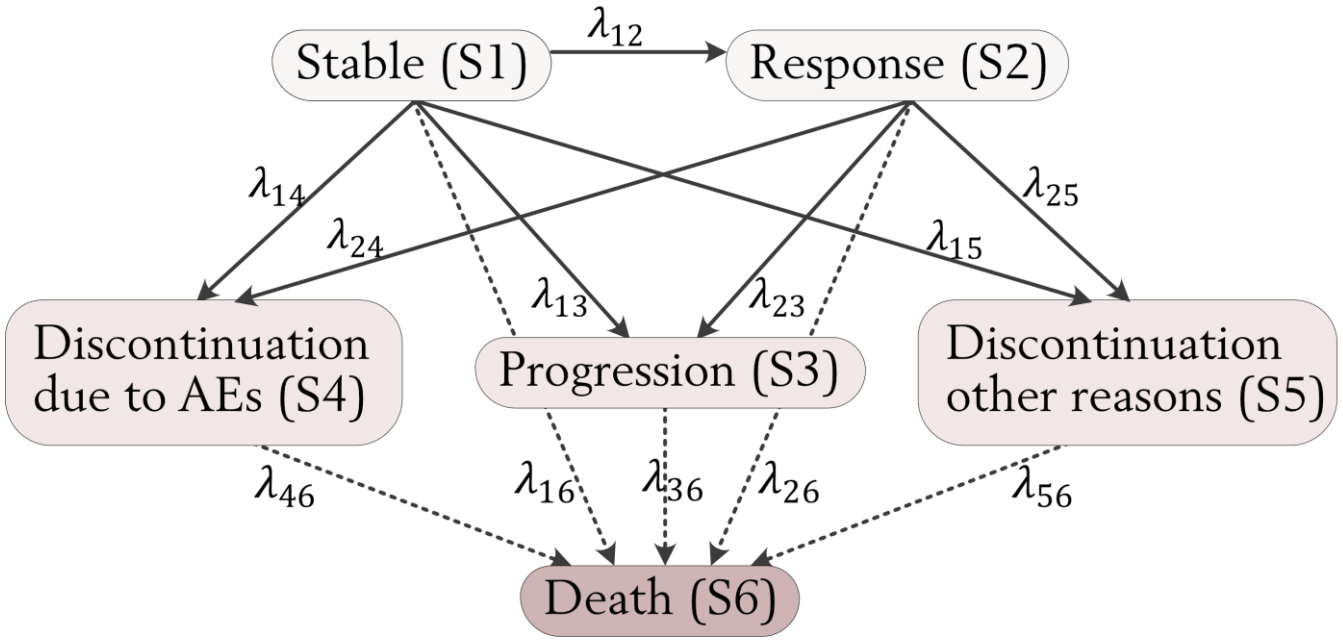
Survival analysis

Study	Phase	Dose	# IDs received sunitinib	# IDs with PK data
1006	II	50 mg 4/2	106	105
014	II		64	60
034	III		375	42

- A six-state multistate survival model



Krishnan et al., CPT:PSP 2021
Krishnan et al., CPT 2023
Liu et al., CPT:PSP 2023

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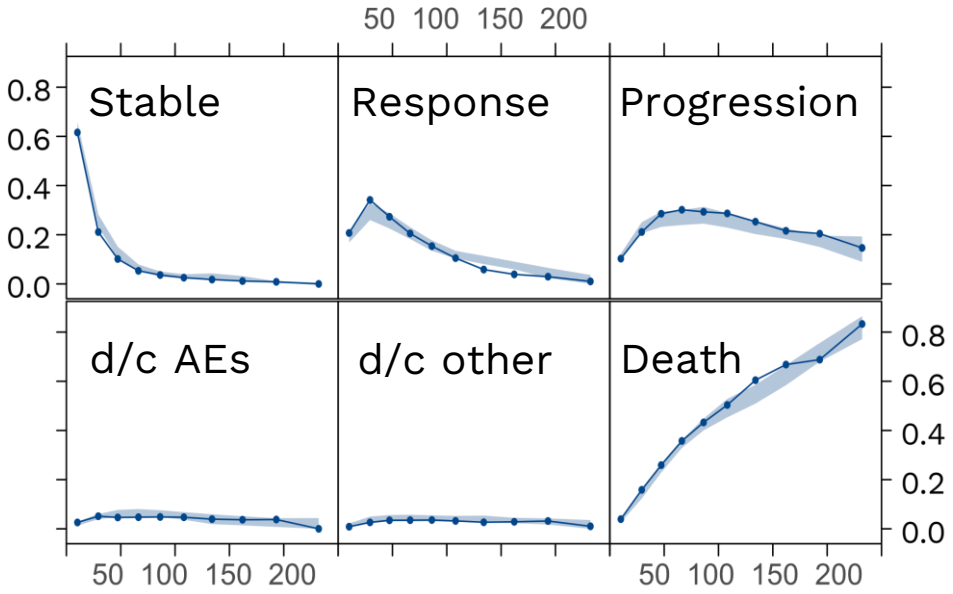
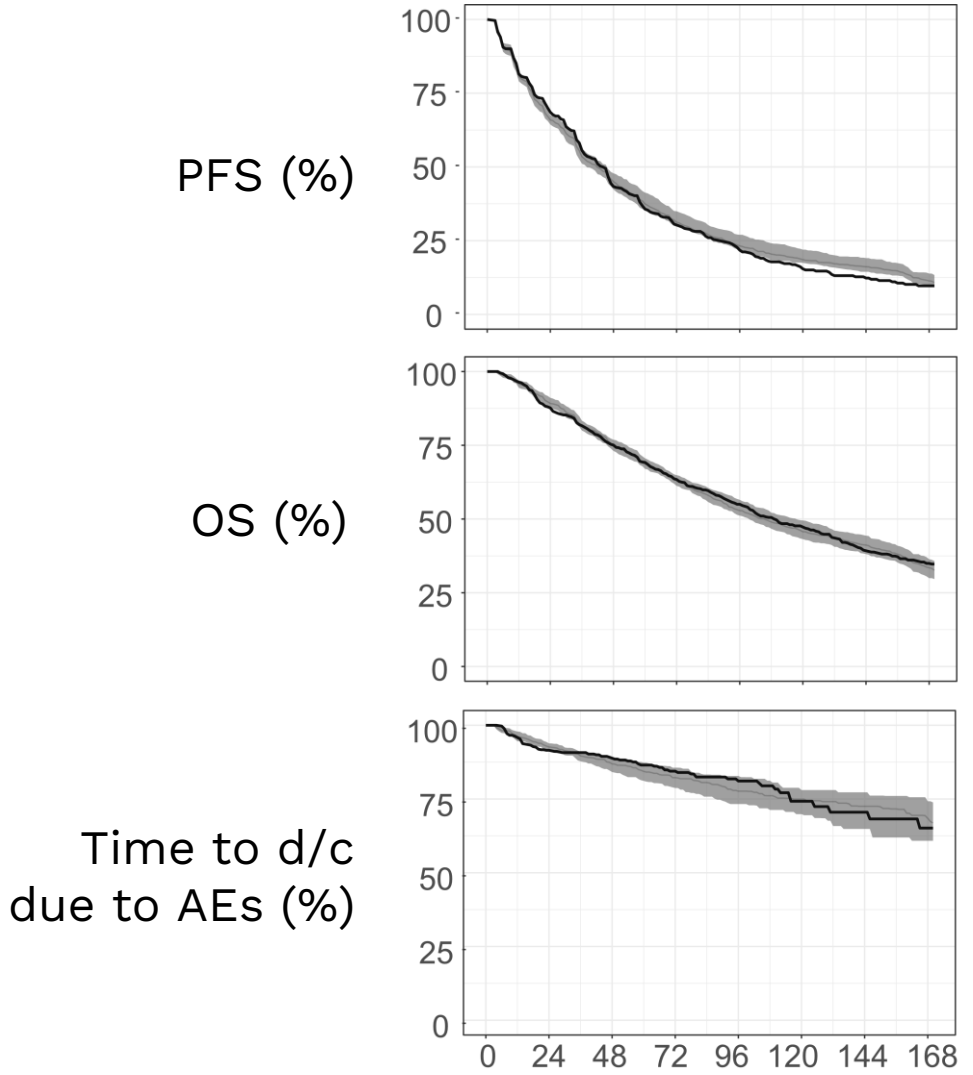
Description of multiple endpoints



Visual predictive checks (VPCs)
Solid lines represent the observed data,
and shaded areas are 95% PIs.



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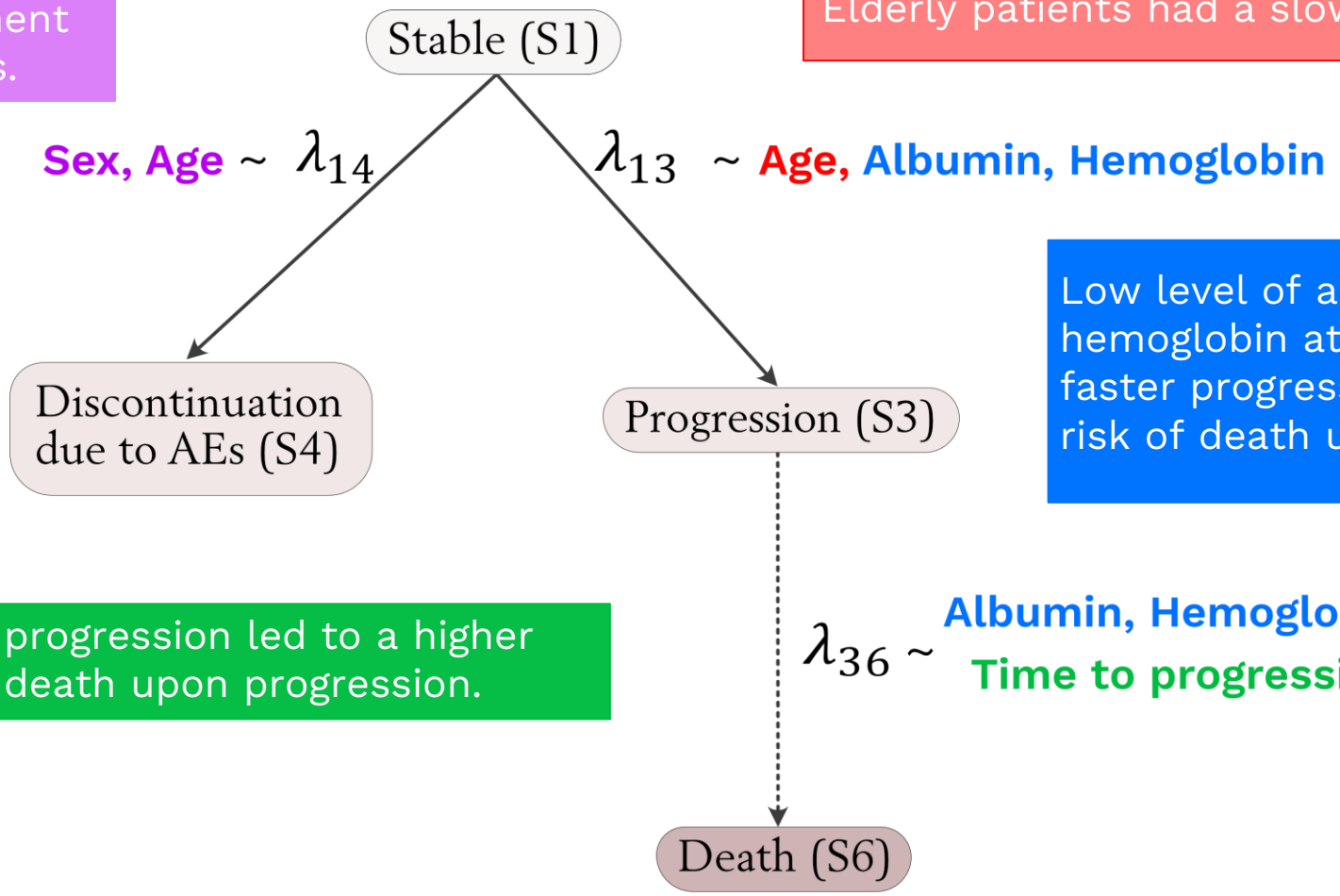
Covariate Effects on Clinical Outcomes

Females and elderly patients had a higher risk of treatment discontinuation due to AEs.

Elderly patients had a slower progression.



Low level of albumin and hemoglobin at baseline-> faster progression and a higher risk of death upon progression.

Faster progression led to a higher risk of death upon progression.

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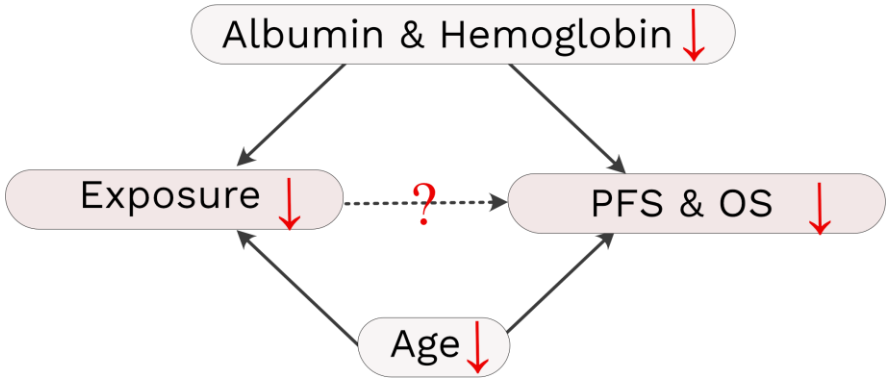
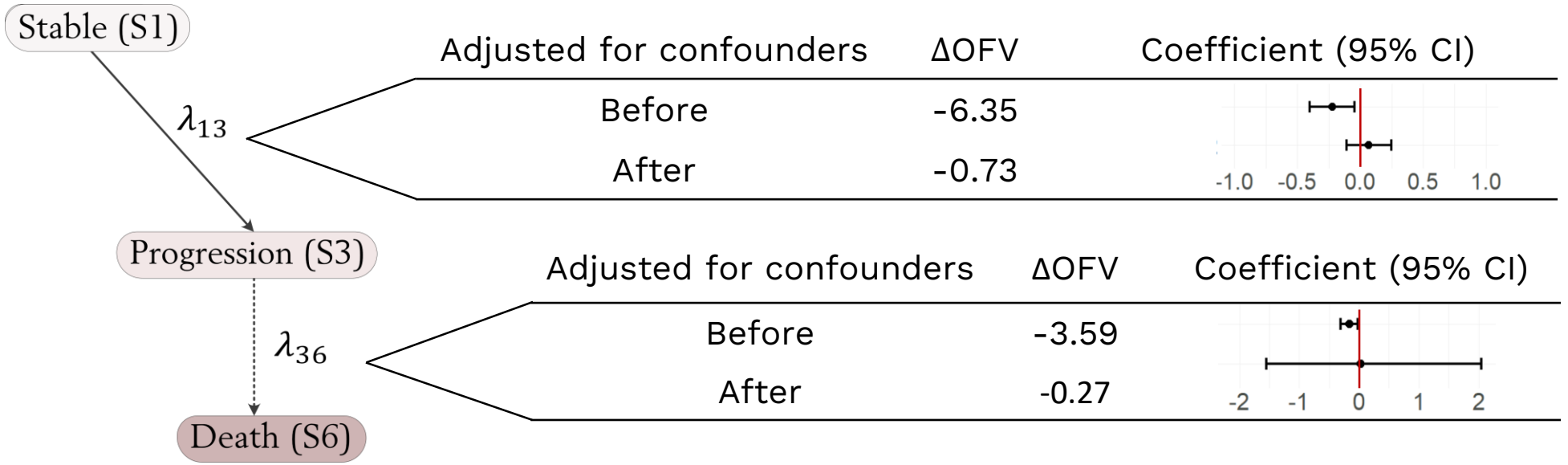
Exposure-Survival Analysis



- AUCss at cycle 1 (sunitinib + SU12662)



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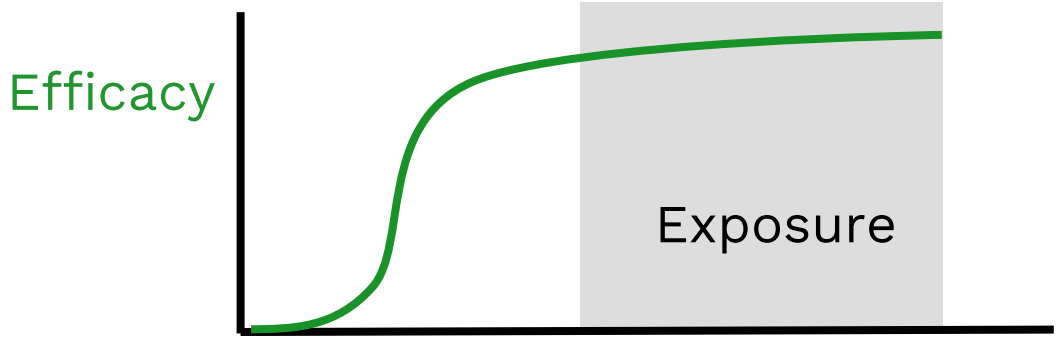
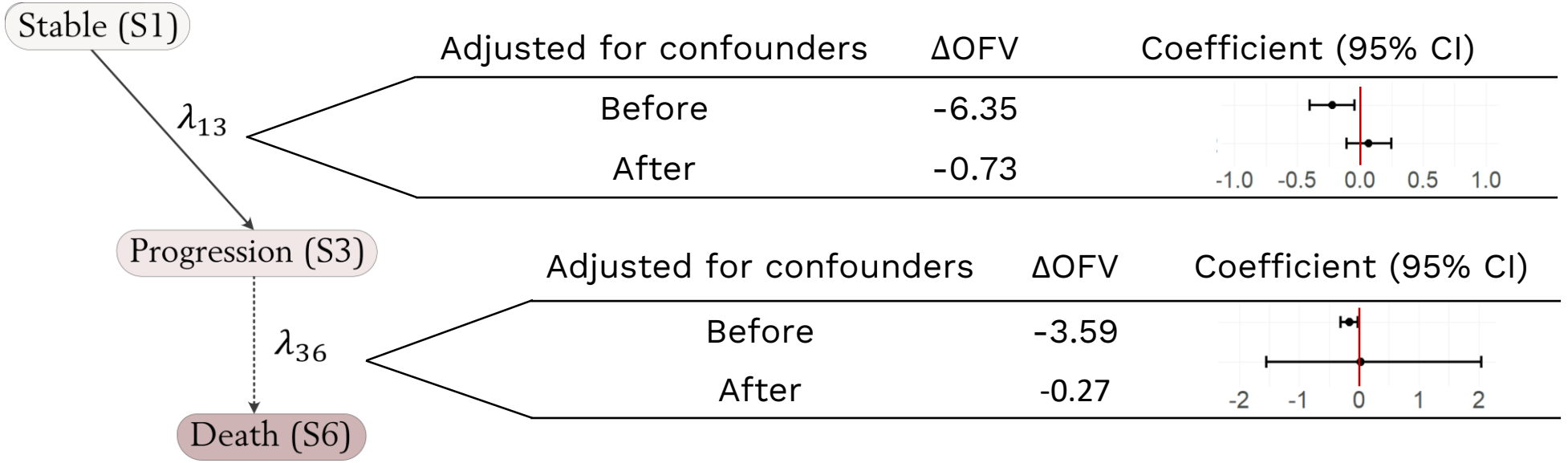
Exposure-Survival Analysis



- AUCss at cycle 1 (sunitinib + SU12662)



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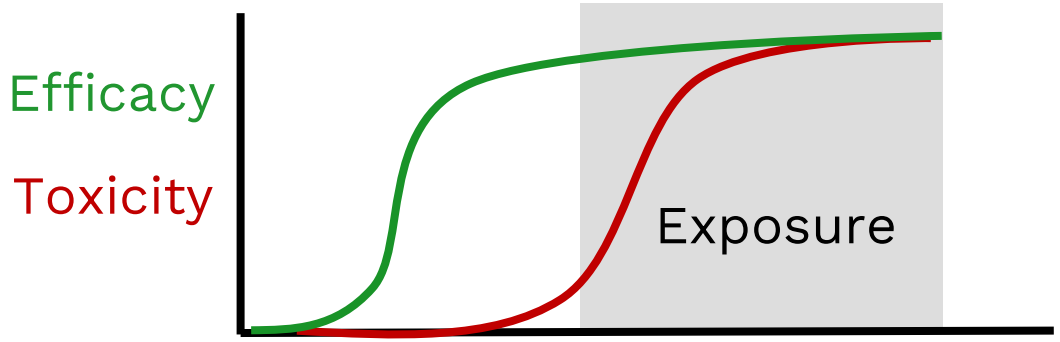
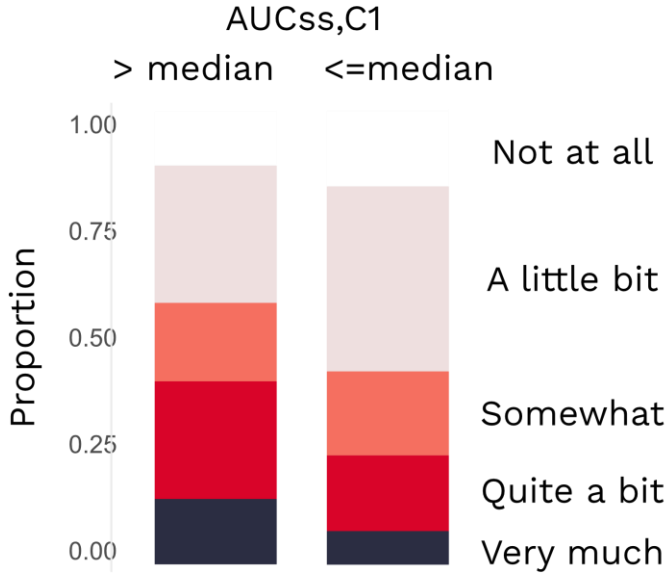
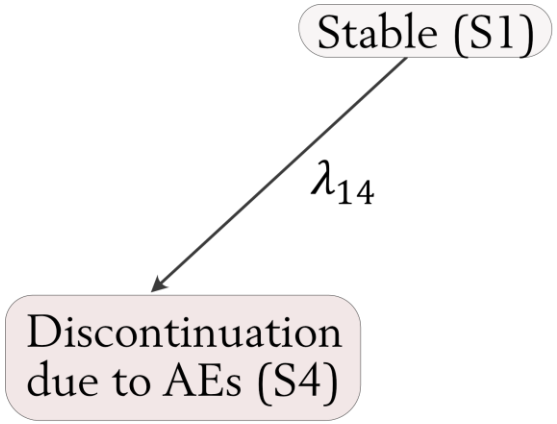
Exposure-Survival Analysis

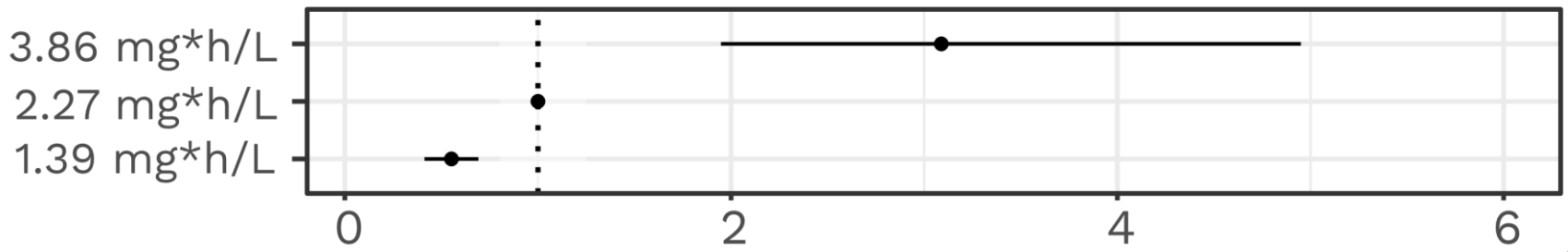


- AUCss at cycle 1 (sunitinib + SU12662)

’I am bothered by side effects’ – cycle 1 day 28







Median and 95% CI considering parameter uncertainty.

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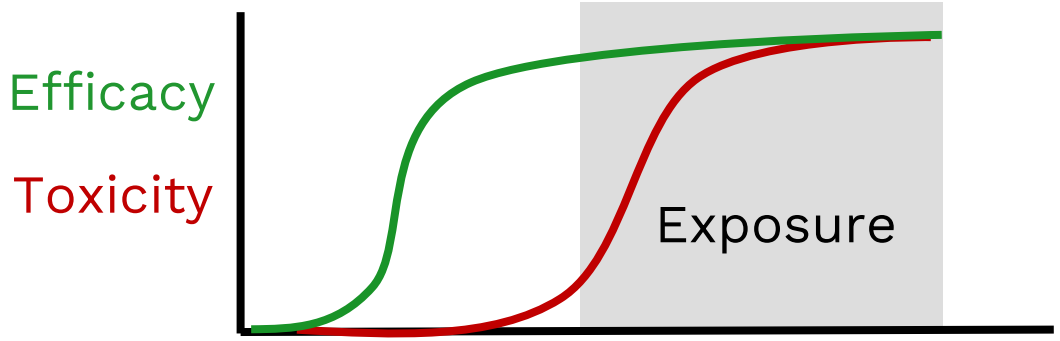
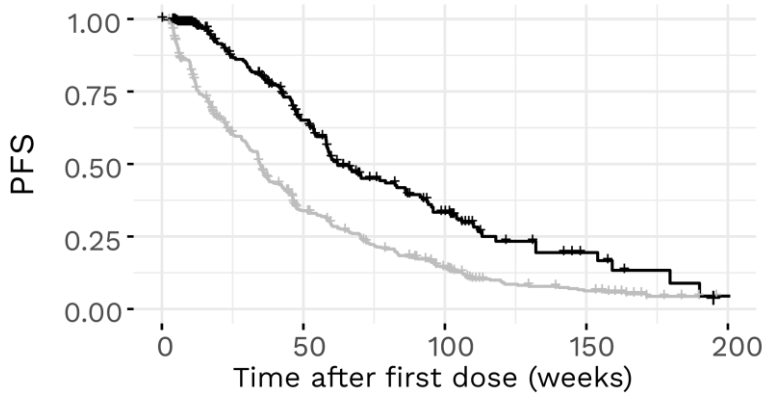
Toxicity-Survival Analysis



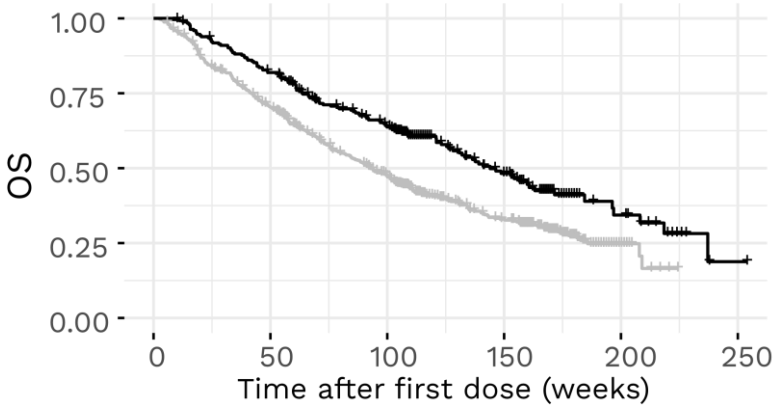
Titrating patients towards individual MTD ≠ improved efficacy

→ Why patients with DLTs seem to have better PFS and OS?



DLTs
(dose reduction
due to AEs)

Yes (n=92)
No (n=453)



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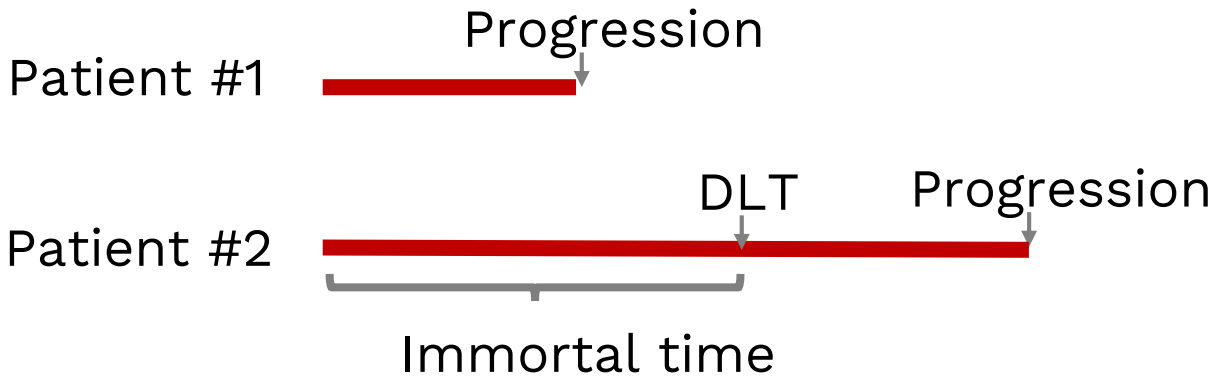
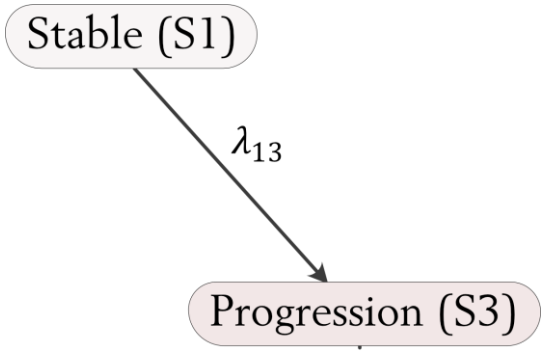
DLTs: dose-limiting toxicities
PFS: progression-free survival
OS: overall survival

Immortal Time Bias





DLTs on λ_{13}	ΔOFV	HR (95% CI)
Known at baseline	-56.7	0.34 (0.23, 0.44)
Time-varying	-0.73	1.18 (0.83, 1.53)

DLT: dose-limiting toxicity
HR: hazard ratio
CI: confidence interval
OFV: objective function value

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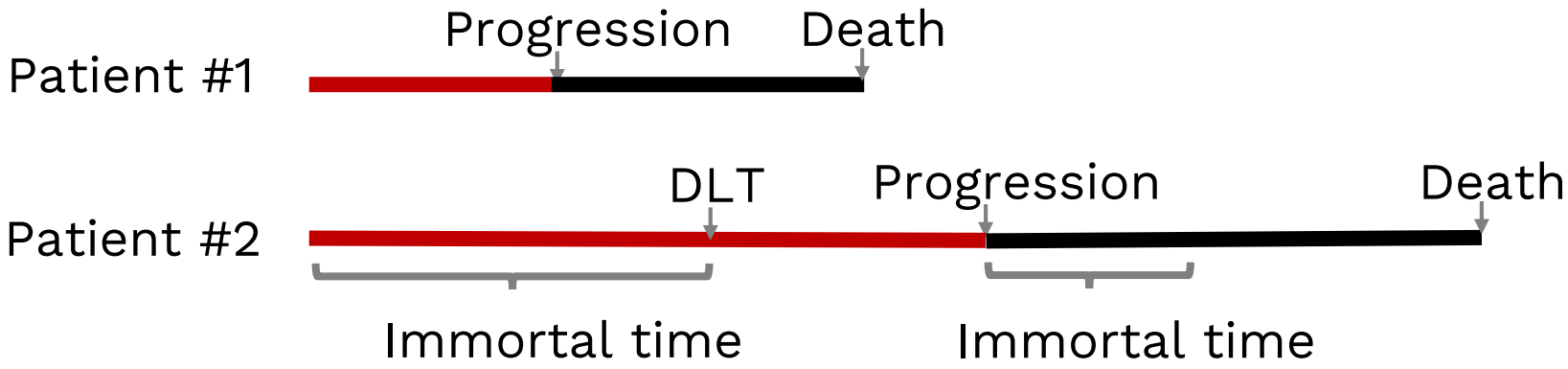
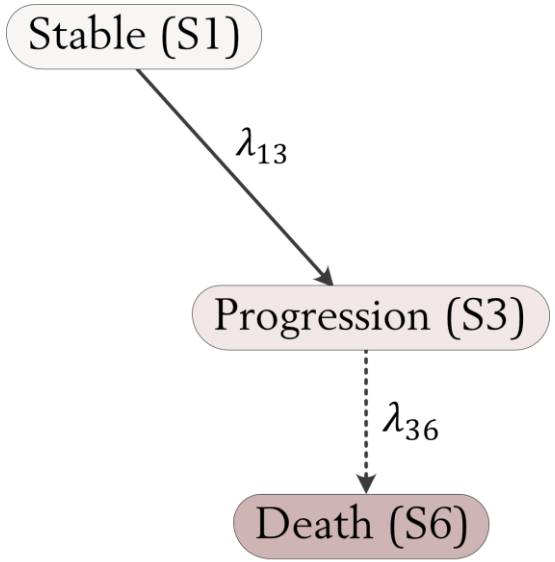
Immortal Time Bias





Include time to Progression on λ_{36}	ΔOFV	HR (95% CI)
Before	-9.72	0.73 (0.59, 0.87)
After	-0.49	0.92 (0.71, 1.13)

DLT: dose-limiting toxicity
HR: hazard ratio
CI: confidence interval
OFV: objective function value

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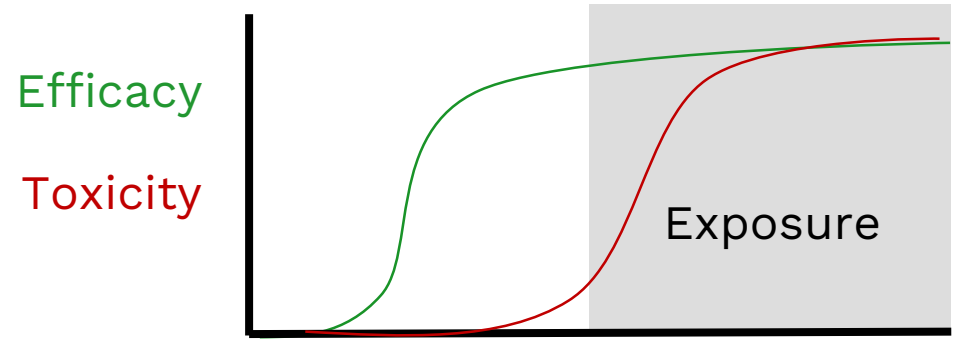
Key findings – sunitinib dosing in mRCC



- Higher exposure ≠ more efficacy
- Higher exposure increased the risk of AE-related discontinuation
- DLTs did not translate to a survival benefit
- Concentration or toxicity-guided dose escalation might be harmful
- Alternative dosing strategies
  - Lower starting dose level (e.g., in older females)
  - Use TDM early to identify high exposure and guide dose reduction

DLTs: dose-limiting toxicities
MTD: maximum tolerated dose
TDM: therapeutic drug monitoring

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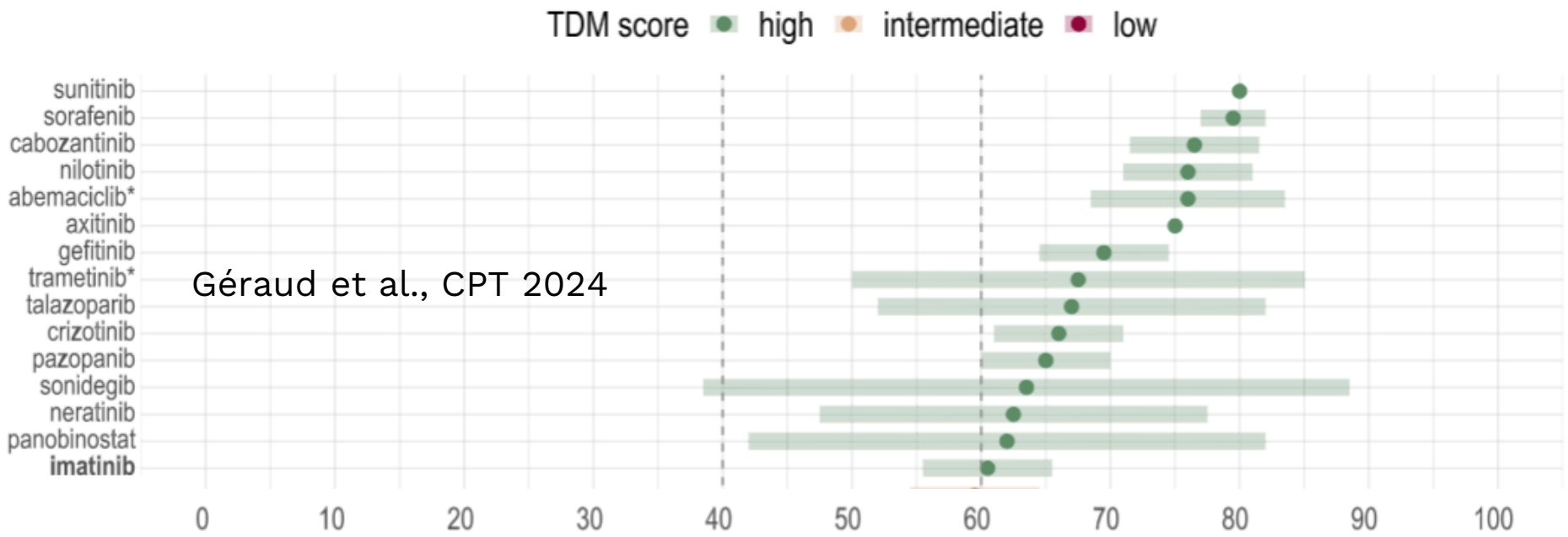
Sunitinib is not alone



Géraud et al., CPT 2024

Good to revisit the TDM recommendations for other oral TKIs

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Acknowledgments

- Patients involved in the clinical studies and their families
- PhD supervisors: Lena E. Friberg, Mats O. Karlsson
- Colleagues from the Uppsala Pharmacometrics and PKPD groups
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