Enhancing Benefit-Risk Assessment: Integrating Survival Data and Longitudinal Patient-reported Outcome Data

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Typical trade-offs in oncology B/R assessment

- Benefit-risk (B/R) assessments in oncology typically weigh (progression-free) survival improvements against detriments in toxicity
  - Example: Is 11 months of PFS with 40% toxicity preferred to 9 months PFS with 10% toxicity?

- While these trade-offs are foundational, they don't capture patient experiences and burden over time

- Can assessing 'time spent in state' help overcome these limitations?
  - Example: Is 9 months of PFS with toxicity followed by 2 months with no toxicity preferred to 9 months PFS with no toxicity?

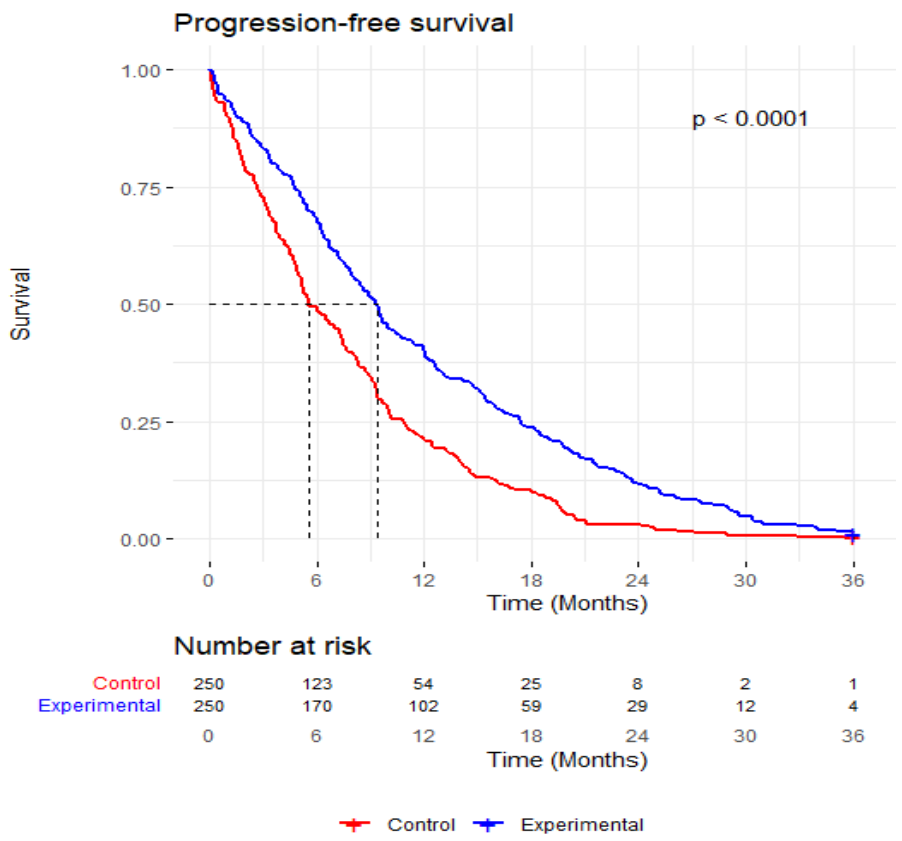
Hypothetical case study

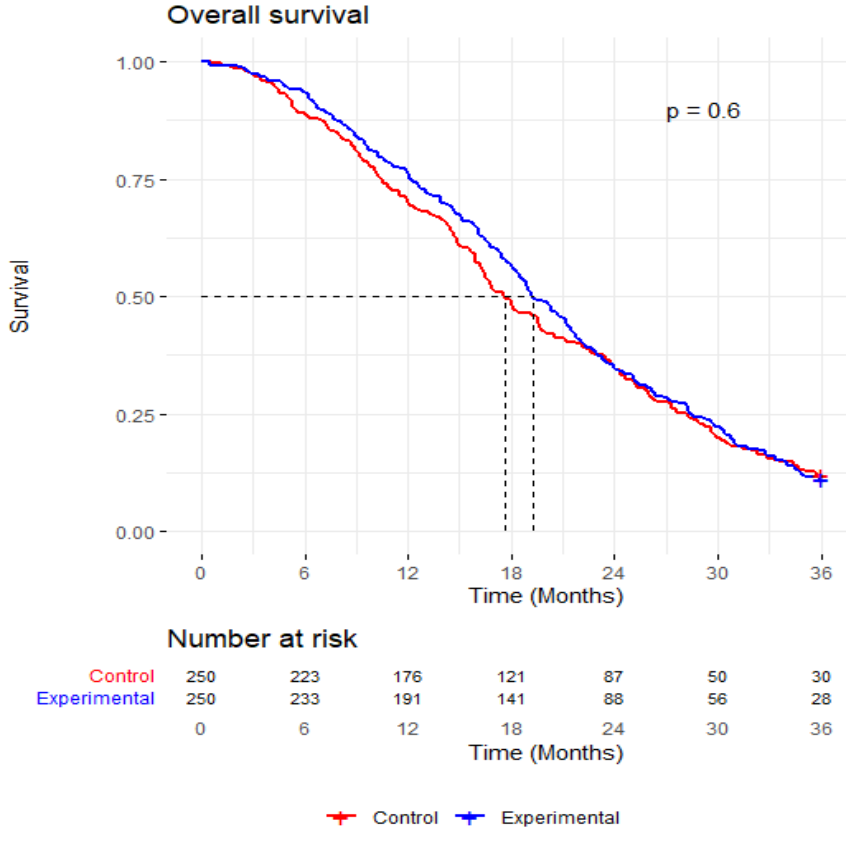
- Simulation of a hypothetical phase 3 trial (N=500) targeting patients with newly diagnosed glioblastoma

- Outcomes: **Time to onset of patient-reported symptomatic adverse events that significantly impair their daily activities ("significant toxicity"),** duration of significant toxicity, time to disease progression, and time to death

- Use **traditional survival and cumulative incidence** analysis and compare to **multi-state modeling** for modeling transitions between different health states over time

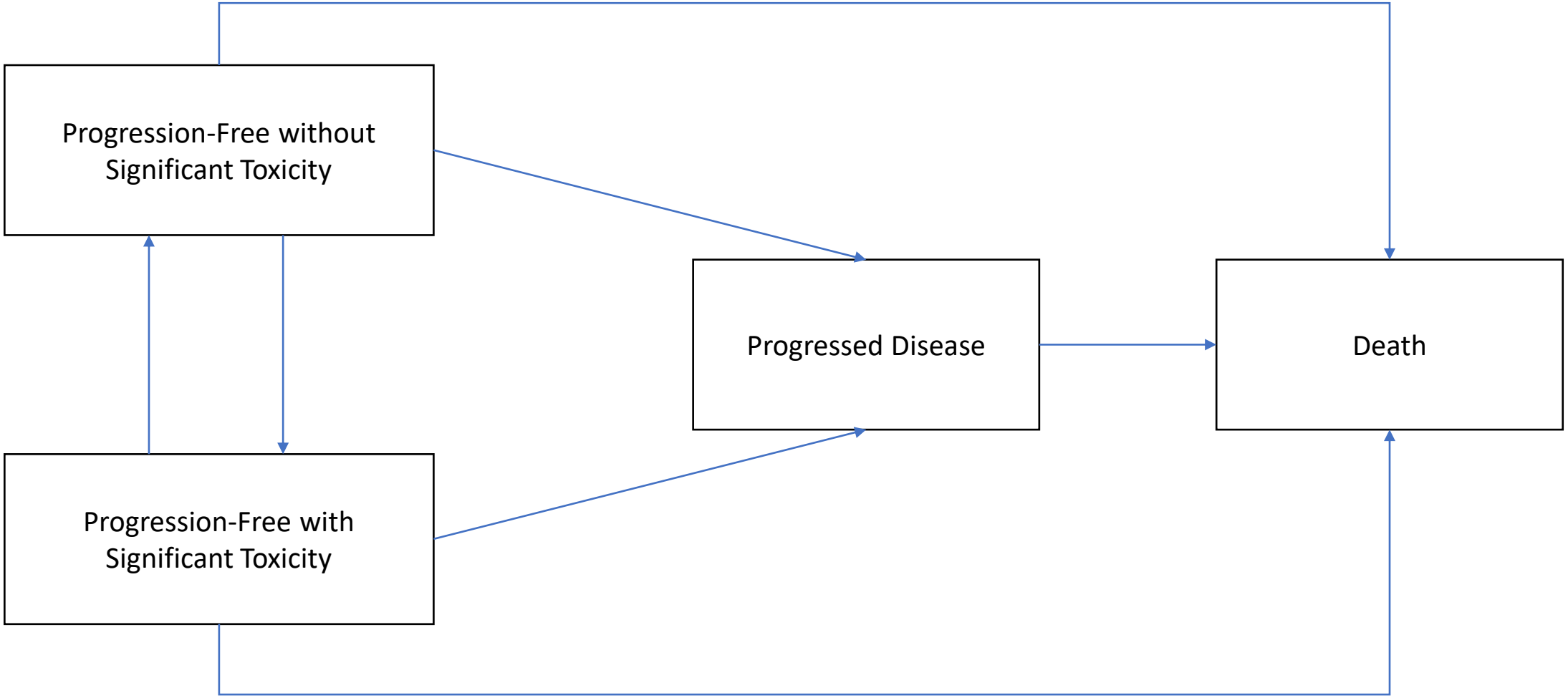
Traditional analysis



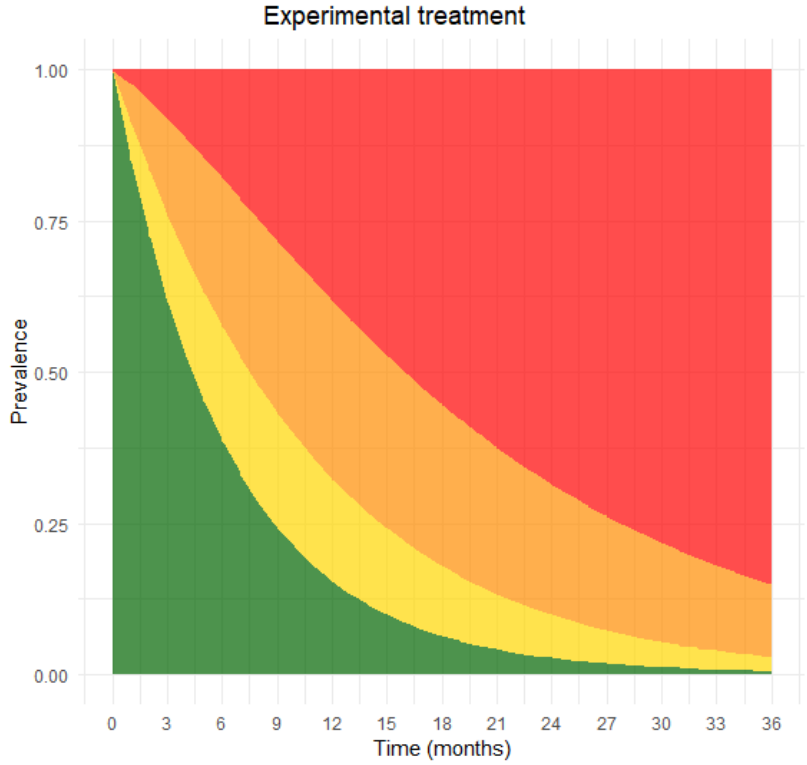


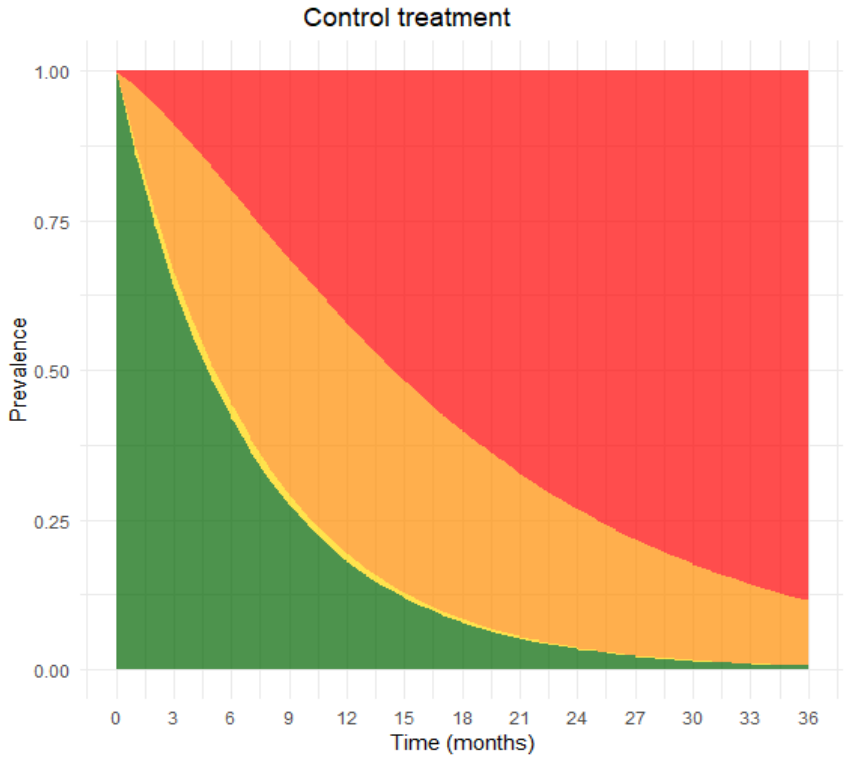
Effect	Description	Unit	Experimental	Control
PFS	Median time from randomization to disease progression or death	Months	9.4	5.6
OS	Median time from randomization to death	Months	19.2	17.6
Toxicity	Proportion of patients experiencing significant toxicity	%	48.4	15.2

Multi-state model



Analysis based on time spent in state





Description	Unit	Experimental	Control
Time spent *progression-free without significant toxicity* (green area)	Months	6.4	7.0
Time spent *progression-free with significant toxicity* (yellow area)	Months	3.8	0.3
Time spent in the *progressed disease* state (orange area)	Months	7.7	9.4
Time spent in the *death* state from baseline to month 36 (red area)	Months	18.1	19.3

Conclusions

- Exploring new approaches to complement traditional benefit-risk assessment
  - Multi-state modeling allows integrating diverse data types to define health states, like HRQoL or toxicity
  - Can be combined with health-state utilities to perform quality-adjusted survival calculations

- Next steps:
  - Is it useful? Is comparing time spent in different health states informative in addition to comparing time versus cumulative incidence of toxicity?

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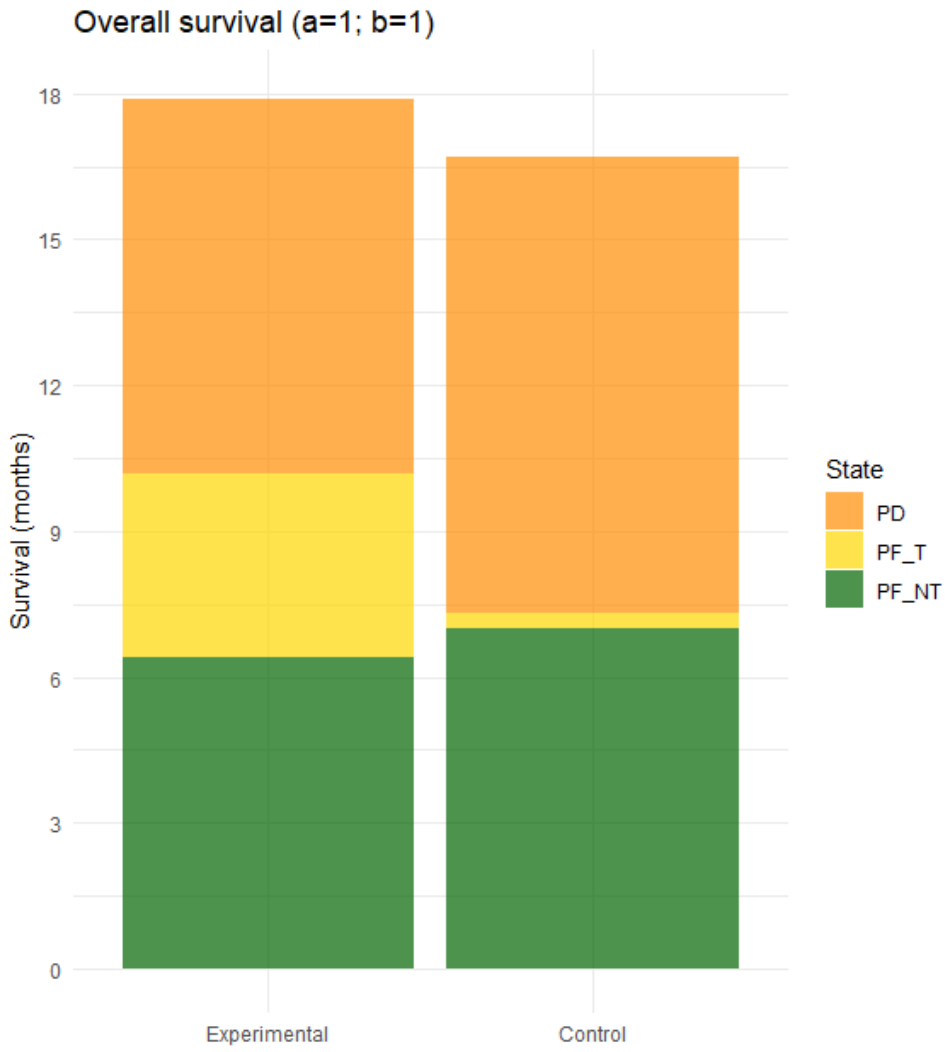
Hypothetical quantitative B/R assessment

State	Utility
Progression-free without significant toxicity (PF_NT)	1
Progression-free with significant toxicity (PF_T)	a
Progressed disease (PD)	b
Death	0



Hypothetical quantitative B/R assessment