Evaluation of Therapeutic Drug Monitoring of endoxifen

Clinical trial simulations: observational and randomized trials

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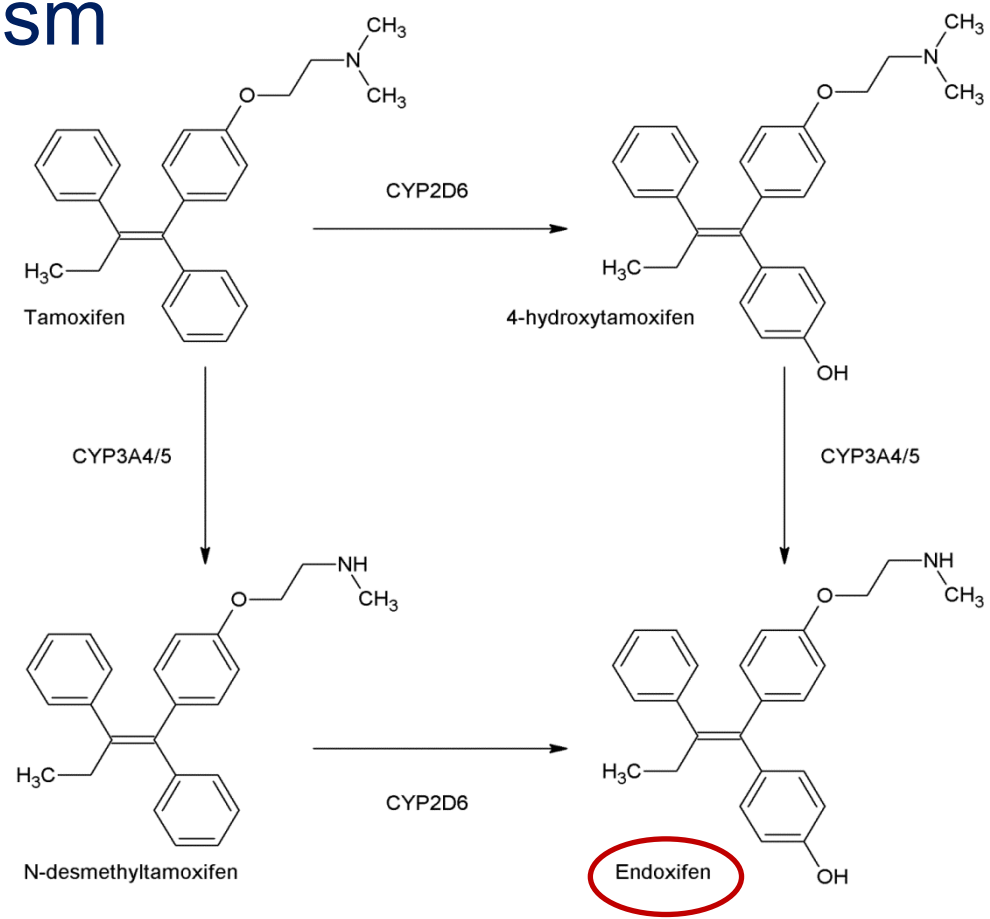
Tamoxifen

- Estrogen receptor positive breast cancer
  - 5 year adjuvant treatment decreases mortality and recurrence rates
  - ~25% of patient experience recurrence within 10 to 15 years

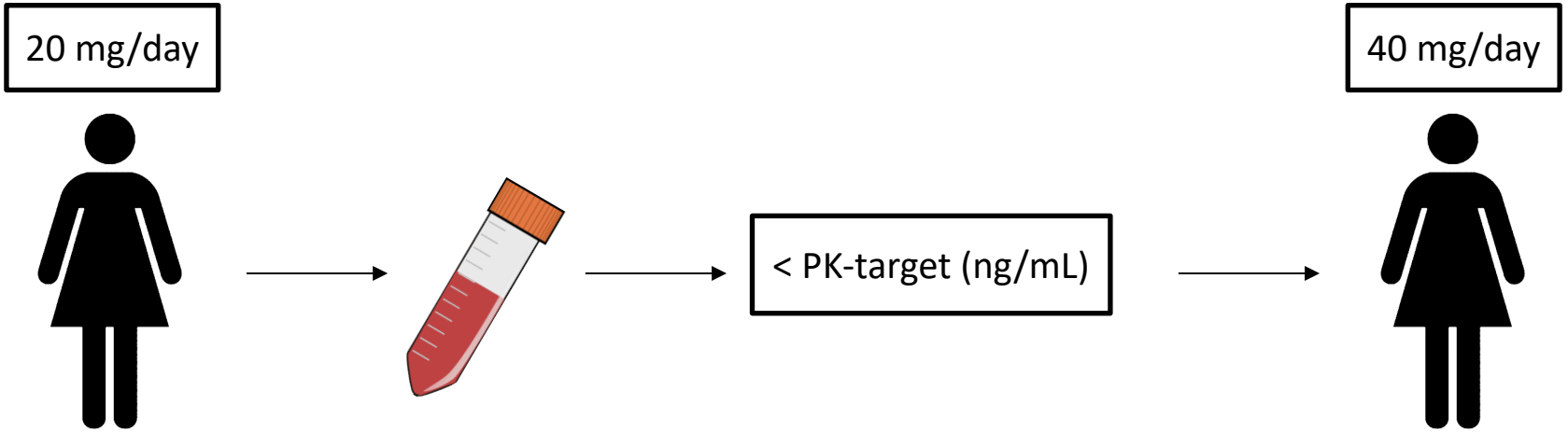
- Patient specific factors explaining variability in response?

Davies, C., Godwin, J. & Gray, R. *Lancet* 771–784 (2011)

Metabolism


CH3
N
CH3
O
H3C
Tamoxifen
CYP2D6
4-hydroxytamoxifen
OH
CYP3A4/5
CYP3A4/5
NH
CH3
N-desmethyltamoxifen
CYP2D6
Endoxifen

Therapeutic Drug Monitoring?



Current evidence for exposure-response?

Endoxifen concentrations associated with recurrence-free survival

	n	menopausal status	PK target	HR (95% CI)
Madlensky et al. (2011)	1370	Pre and post	>5.97 ng/mL	0.70 [0.52-0.94]
CYPTAM-study (2019)	667	Pre and post	Continuous variabele[A]	0.99 [0.95-1.04]

[A] Not able to reproduce previously established PK-target.

Madlensky, L. *et al. Clin. Pharmacol. Ther.* **89**, 718–25 (2011)

Sanchez-Spitman, A. *et al. J. Clin. Oncol.* **37(8)**, 636–646 (2019)

Challenges

- Tamoxifen prevents **late** recurrence
- Approximately 25% of patients experience recurrence

Aims

Determine the feasibility of trials validating TDM of endoxifen.

Part 1: Observational design (no dose adjustments, exposure-response)

Part 2: Randomized controlled trial (TDM vs. no TDM)

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Clinical trial simulations to provide information on:

- Number of patients
- Follow up time
- Power!

Part 1: Observational design

Methods - data

1. Parametric time-to-event model

- Data from Madlensky et al.: n=1370
  - Recurrence and censor times
  - Endoxifen concentrations
  - Covariates: tumor grade, stage and menopausal status.

Madlensky, L. *et al. Clin. Pharmacol. Ther.* **89**, 718–25 (2011)

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2. Distribution of endoxifen concentration in a clinical cohort

- Data from the Netherlands Cancer Institute: n=658
  - Tamoxifen 20 mg/day, endoxifen concentrations → 33% < 5.97 ng/mL

Madlensky, L. *et al. Clin. Pharmacol. Ther.* **89**, 718–25 (2011)

Simulation

- Patient characteristics similar to Madlensky et al.
- Varying n, studies were simulated 1000x
- Cox proportional hazard model comparing low vs. high endoxifen concentrations
- % of trials $p < 0.05$ = power

- **Sensitivity analysis**
  - Effect size
  - Follow up
  - (PK-target)

Madlensky, L. *et al. Clin. Pharmacol. Ther.* **89**, 718–25 (2011)

Results

Weibull

Parameter	Estimate	RSE (%)	Covariate effect
Hazard coefficient λ (/year)	0.0345	21	-
Shape (α)	1.68	6	-
Stage IIB & IIIA	1.01	16	2.75
Stage III C	2.06	12	7.85
Grade 2	0.438	46	1.55
Grade 3	0.718	30	2.05
Postmenopausal status	-0.810	32	0.44
Endoxifen >5.97 ng/mL	-0.348	51	0.71

Covariate effect: exp(estimate)

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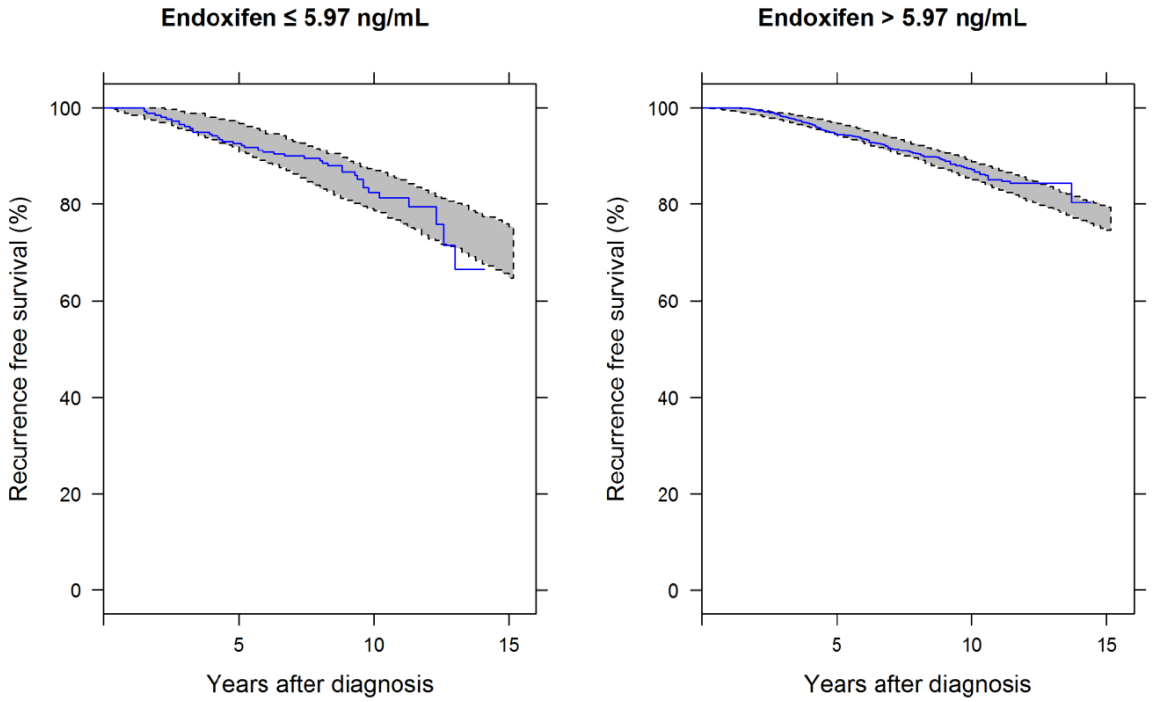
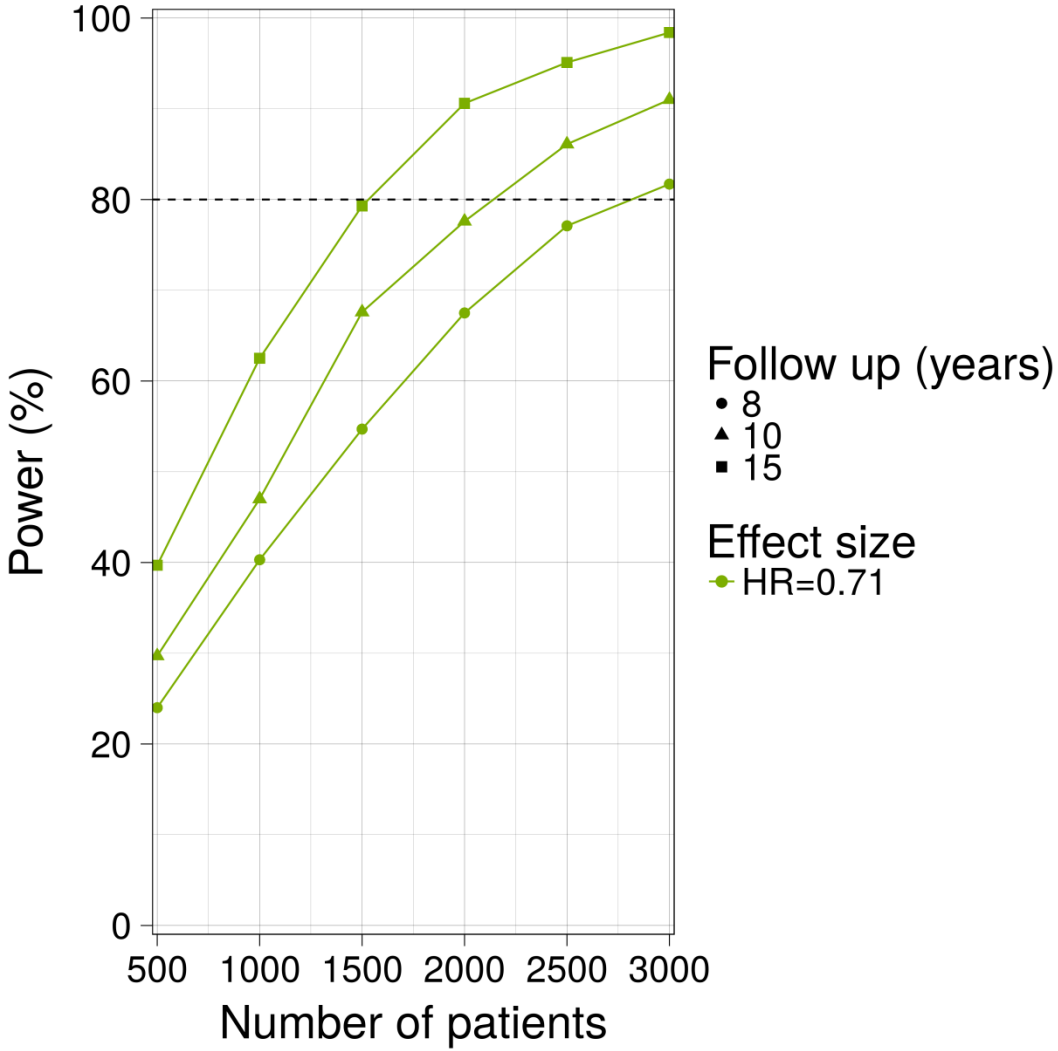

Endoxifen ≤ 5.97 ng/mL
Endoxifen > 5.97 ng/mL
Recurrence free survival (%)
100
80
60
40
20
0
5
10
15
Years after diagnosis

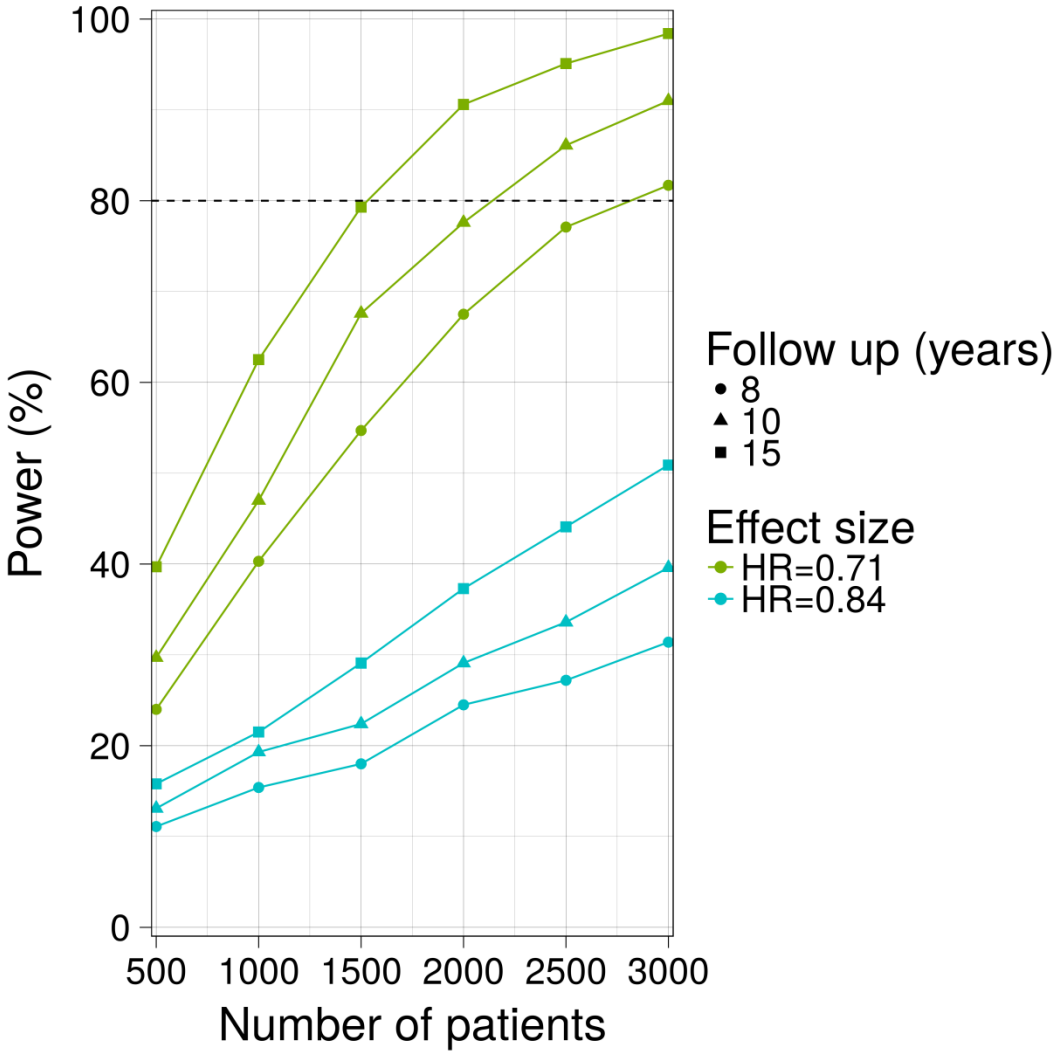
Results

Exposure-response



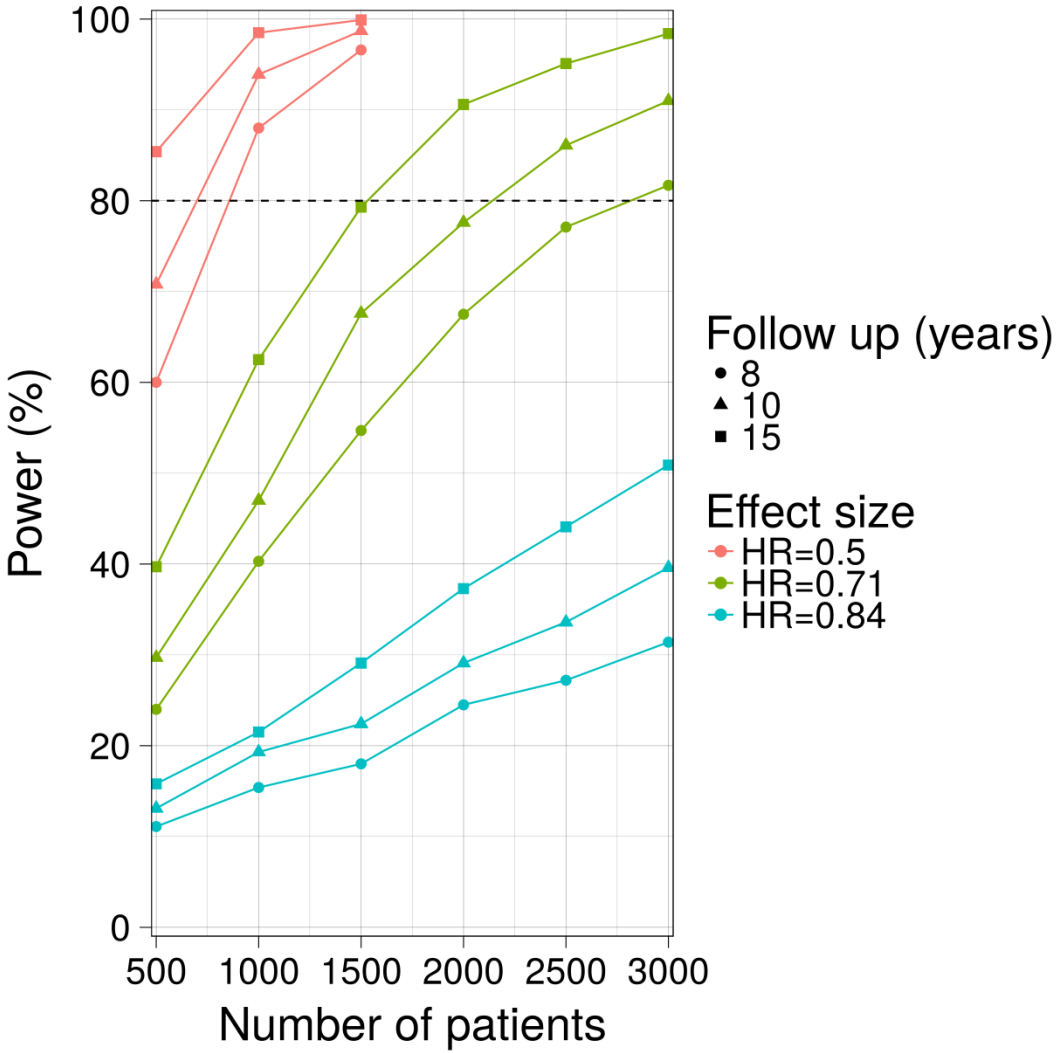
Results

Exposure-response



Results

Exposure-response

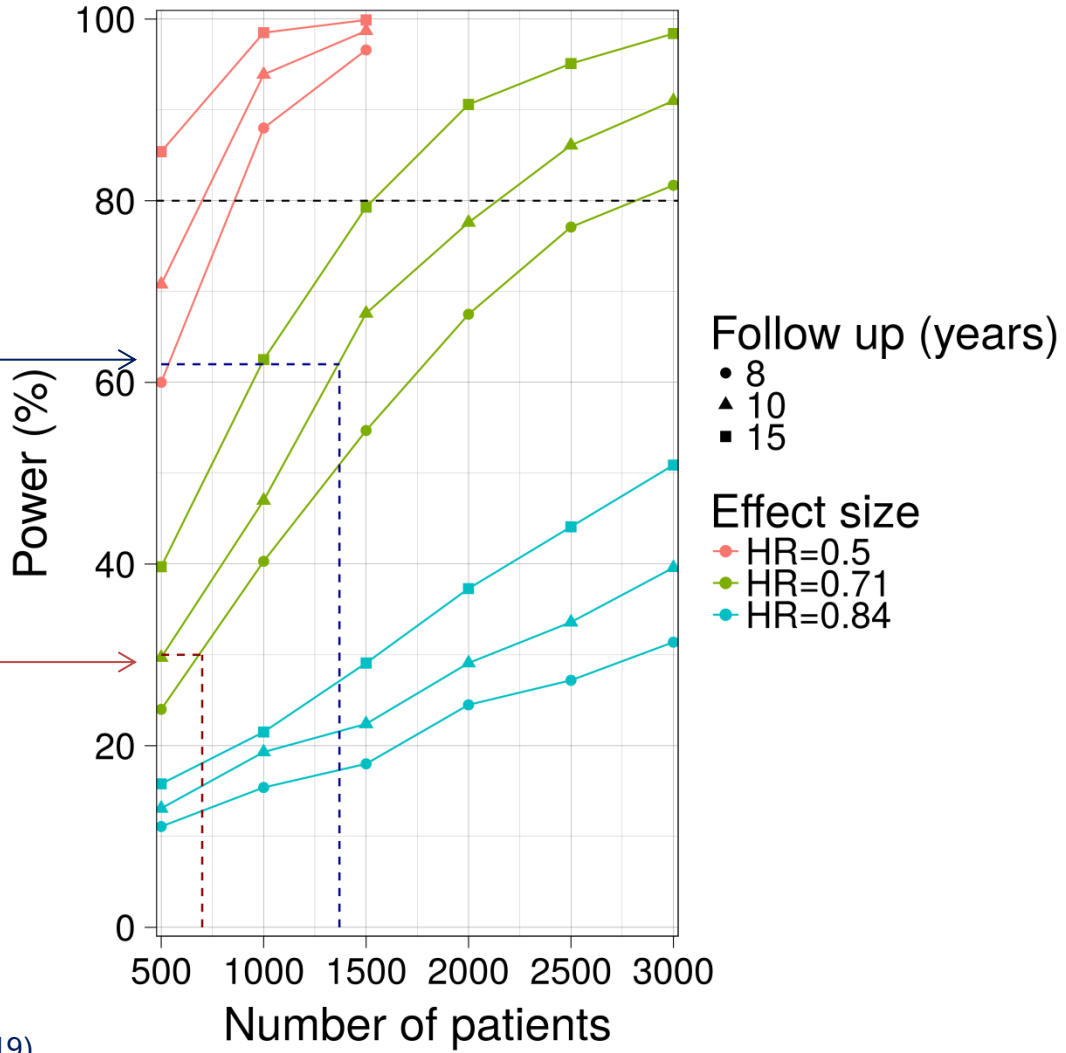


Results

Exposure-response

Madlensky

CYPTAM



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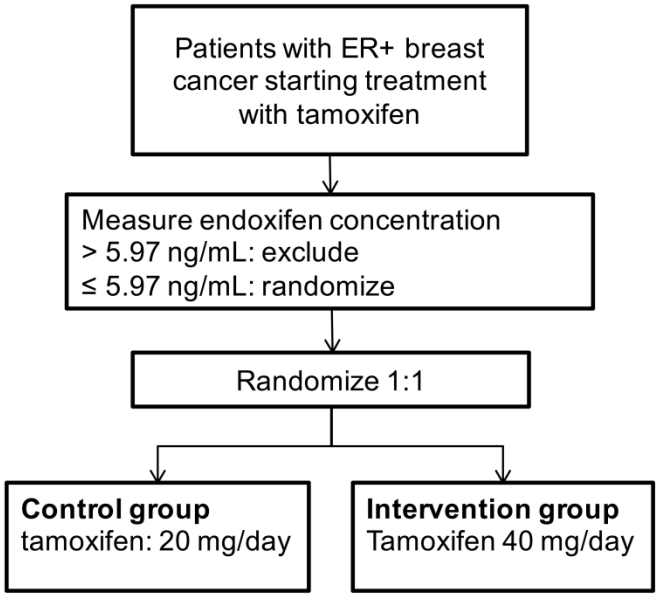
Part 2: Randomized controlled trial

RCT design


Patients with ER+ breast cancer starting treatment with tamoxifen
Measure endoxifen concentration
> 5.97 ng/mL: exclude
≤ 5.97 ng/mL: randomize
Randomize 1:1
Control group
tamoxifen: 20 mg/day
Intervention group
Tamoxifen 40 mg/day

Same model, different distribution

1. Parametric time-to-event model

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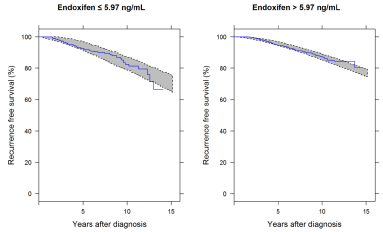
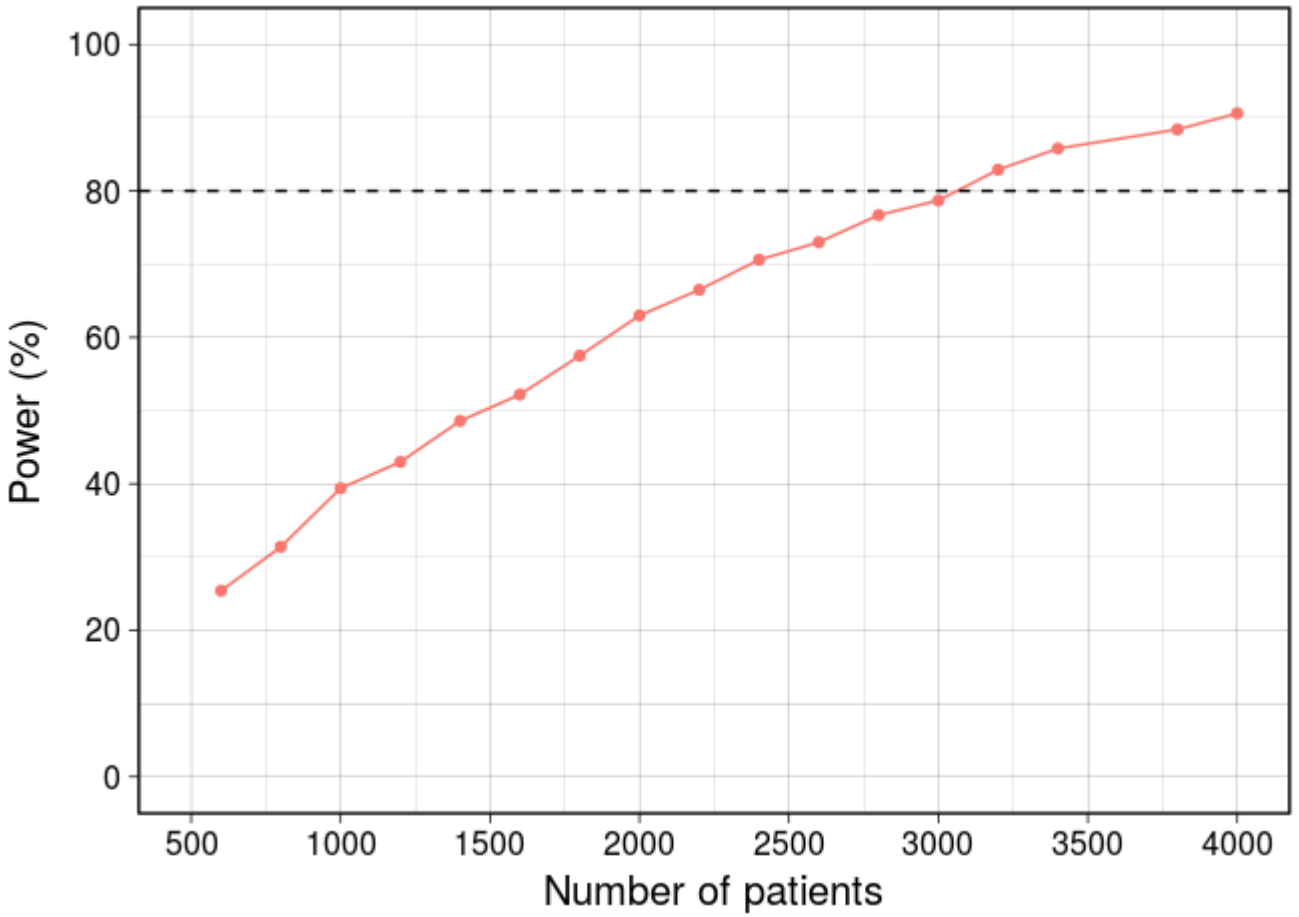


2. Distribution of endoxifen concentration in a population with and without TDM

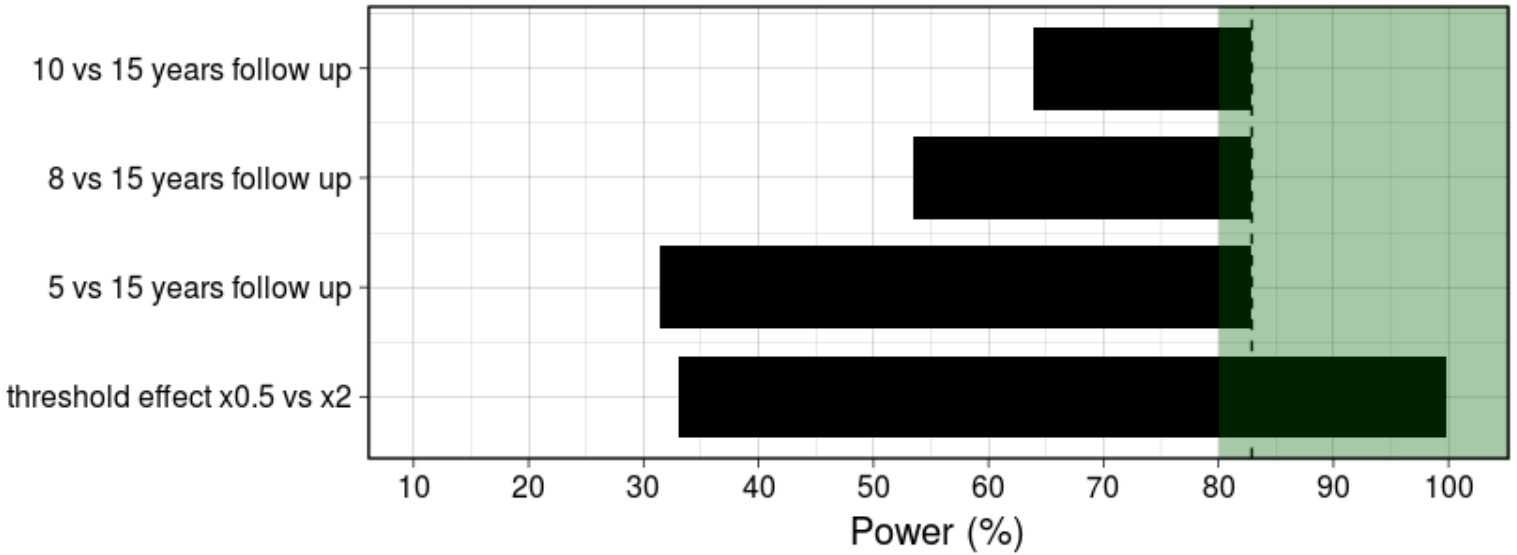
- Data from NKI: n=658
  - Tamoxifen 20 mg/day
  - Endoxifen concentrations → 33% < 5.97 ng/mL
  - **~ 75% of patients reach target concentration after dose increment to 40 mg/day**

Results
RCT


100
80
60
40
20
0
Power (%)
500
1000
1500
2000
2500
3000
3500
4000
Number of patients

Results
RCT

Sensitivity



Summary

1. Observational design
   - Exposure-response: PK target of 5.97 ng/mL, HR 0.71
   - **1500 patients, 15 years follow up**

2. Randomized controlled trial
   - Randomize <5.97 ng/mL
   - **Randomize 3200 patients (= including 9600 patients), 15 year follow up**

Discussion/conclusion

- Observational trial including 1500 patients and 15 years follow up is feasible.

- Should we apply TDM based on current observational trial?

  CYPTAM: 50% decreased risk, power of ~80% → no TDM

  CYPTAM: 30% decreased risk, power of ~30% → undetermined

  Madlensky: 30% decreased risk, power of ~60% → yes?

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Easy to implement

- Endoxifen concentration can be determined after 2 to 3 months
- Low inter-occasional variability(~9%)

Acknowledgements

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Questions?