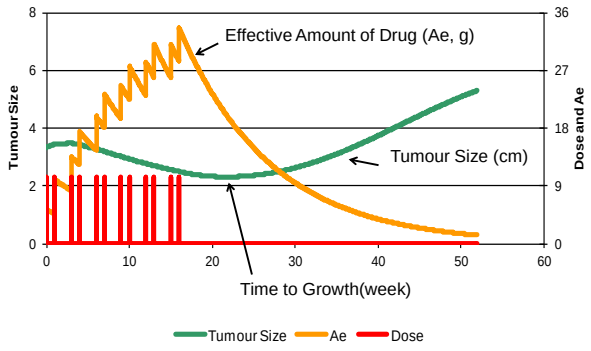
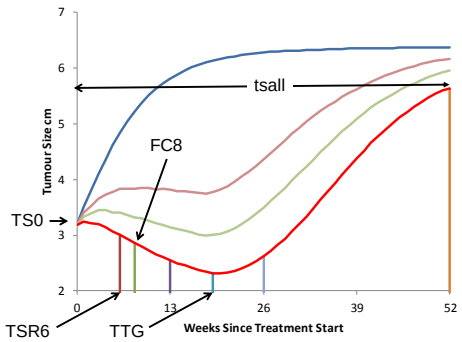
Slide 1	# Power and Type 1 Error of Tumour Size Metrics Used to Predict Survival Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland	http://www.page-meeting.org/default.asp?abstract=3142
Slide 2	# Evaluation of Tumour Size Metrics • Objectives – Identify tumour size metrics for predicting survival – Explore the effect of tumour measurement censoring on metrics predicting survival Acknowledgements to France Mentre and Benjamin Ribba for discussions on shrinkage and Type 1 error 	
Slide 3	# Model for Tumour Size  Tham, L.S., et al., *A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients.* Clin Cancer Res, 2008. 14(13): p. 4213-8	

Slide 4	**How Might Tumour Size Be Linked to Survival?** • Bigger tumour size is a bigger load on body • Survival expected to be longer with smaller tumour size (e.g. due to treatment effect) • Risk of death is related to time course of tumour growth 	
Slide 5	**Tumour Time Course and Size Metrics**  Curves for control treatment (blue), 0.5 (brown), 1 (green) and 2 (red) g/m^2 gemcitabine based on median of 5,000 individual curves for each treatment	
Slide 6	**Simulation Experiment** • 6 x 3 weekly 2 dose cycles with 0, 0.5, 1, 2 g/m^2 dose (typical gemcitabine dose up to 3 g/m^2) – Weight and height simulated to calculate BSA and FFM • 100 subjects randomized to each of 4 treatments • Stochastic simulation of tumour size and survival – Tham tumour size model – Tumour baseline size 50% of asymptotic maximum – 20% random dropout over 1 year • Tumour size metrics used to model survival hazard with simulated survival event data 	Simulation of weight and height $THETA 70 ; TBWKG_STD KG 1.76 ; HTM_STD M $OMEGA BLOCK(2) 0.01 ; PPV_TBWKG 0.004 0.005 FIX ; PPV_HTM

Slide 7	**Major Scenarios** • Type 1 Error – Simulated tumour size and treatment effect on tumour but no effect on hazard of survival • Power – Tumour growth only (no simulated treatment effect) – Tumour size with treatment effect – Treatment effect • No treatment 30% 1 y survival • 5, 10, 15, 20% increase in 1 y survival • Each scenario tested with all tumour metrics and selected hazard model combinations (Weibull, Gompertz, S0) • 1000 simulated trials per tumour metric 	http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional/page11 "The absolute benefit in 1-year survival was 5%, which corresponds to an increase in 1-year survival from 30% with a single-agent regimen to 35% with a doublet regimen [e.g. platinum + gemcitabine]"
Slide 8	**Tumor Metric Calculation** • Predicted from Tham parametric model using either: – 'TRUE': Individual simulation parameters or – EBE: Empirical Bayes estimated parameters with tumour measurements every 6 weeks • Tumour size determined at weekly intervals for fixed time metrics (e.g. TTG, TSR6) 	
Slide 9	**Models, Software, Statistics** $h(t) = \lambda_0 \cdot \exp(\beta_W \cdot \ln(t)$; Weibull $+ \beta_G \cdot t$; Gompertz $+ \beta_0 \cdot TS0$ $+ \beta_M \cdot TumourMetric)$ Likelihood of event interval (1 week) or right censored NONMEM 7.3.0, First-Order, ADVAN6, SIG=3,TOL=3 gfortran compiler Hypothesis test: Likelihood ratio Chi-Square	

Slide 10

Type 1 Error

EBE <3.7% >6.4%

EBE Type 1 error

EBE diff <5% >5%

EBE Bias

TRUE <3.7% >6.4%

95% prediction interval n=1000

Mean Survival y	tspre	css	ntrt	tsall	s0fc8	Wttg	tsr6
5	4.9%	4.2%	4.5%	3.5%	5.3%	9.7%	34.2%
2	5.2%	5.3%	5.3%	2.8%	5.9%	19.3%	59.3%
1	5.2%	4.1%	4.0%	2.4%	12.1%	33.9%	89.6%
0.5	4.8%	3.3%	3.0%	3.1%	27.5%	60.5%	99.7%
0.2	3.8%	3.5%	3.1%	2.7%	62.9%	92.3%	100.0%
0.1	3.1%	1.9%	1.8%	2.5%	75.6%	98.4%	100.0%
0.05	2.0%	1.1%	1.2%	2.7%	53.7%	99.8%	100.0%
5	-0.4%	-1.2%	0.0%	-0.2%	-0.7%	4.2%	32.5%
2	-1.1%	-0.2%	0.0%	-0.5%	-0.8%	15.6%	57.7%
1	-0.2%	-0.5%	0.0%	0.0%	6.7%	28.6%	87.8%
0.5	-0.3%	-0.2%	0.0%	0.2%	22.1%	52.0%	98.0%
0.2	0.3%	0.4%	0.0%	-0.3%	58.6%	70.6%	98.7%
0.1	0.1%	-0.4%	0.0%	0.3%	72.5%	41.4%	99.2%
0.05	0.5%	-0.2%	0.0%	0.7%	52.6%	2.4%	99.7%
5	5.3%	5.4%	4.5%	3.7%	6.0%	5.5%	1.7%
2	6.3%	5.5%	5.3%	3.3%	6.7%	3.7%	1.6%
1	5.4%	4.6%	4.0%	2.4%	5.4%	5.3%	1.8%
0.5	5.1%	3.5%	3.0%	2.9%	5.4%	8.5%	1.7%
0.2	3.5%	3.1%	3.1%	3.0%	4.3%	21.7%	1.3%
0.1	3.0%	2.3%	1.8%	2.2%	3.1%	57.0%	0.8%
0.05	1.5%	1.3%	1.2%	2.0%	1.1%	97.4%	0.3%

Slide 11

Power Tumour + Treatment

Control group survival 30% 1 year

EBE >tsall

EBE Excess Power

EBE diff <5% >5%

EBE Bias

TRUE <3.7% >6.4%

95% prediction interval n=1000

Treatment Survival % 1 year	tsall	tspre	s0fc8	css	ntrt	Wttg	tsr6
35	37.6%	29.3%	19.9%	6.6%	5.8%	58.5%	82.8%
40	78.2%	66.9%	45.2%	10.8%	9.3%	66.1%	70.2%
45	98.2%	96.1%	85.7%	20.5%	16.6%	74.9%	60.3%
50	100.0%	99.7%	98.4%	26.9%	23.6%	79.6%	53.2%
35	-1.3%	0.2%	-3.4%	0.8%	0.0%	48.0%	76.8%
40	-1.0%	1.4%	-11.3%	0.6%	0.0%	51.0%	52.6%
45	-0.4%	1.0%	-6.7%	2.0%	0.0%	55.7%	19.5%
50	0.0%	0.0%	-0.9%	3.1%	0.0%	54.5%	-11.8%
35	38.9%	29.1%	23.3%	5.8%	5.8%	10.5%	6.0%
40	79.2%	65.5%	56.5%	10.2%	9.3%	15.1%	17.6%
45	98.6%	95.1%	92.4%	18.5%	16.6%	19.2%	40.8%
50	100.0%	99.7%	99.3%	23.8%	23.6%	25.1%	65.0%

LRT Nul $h(t) = \lambda_0$

LRT Metric $h(t) = \lambda_0 \cdot \exp(\beta_M \cdot TumourMetric)$

Slide 12

Power Treatment Effect

Control group survival 30% 1 year

EBE >tsall

EBE Excess Power

EBE diff <5% >5%

EBE Bias

TRUE <3.7% >6.4%

95% prediction interval n=1000

Treatment Survival % 1 year	tsall	tspre	s0fc8	css	ntrt	Wttg	tsr6
35	7.0%	2.0%	3.8%	3.6%	3.0%	38.8%	72.7%
40	24.2%	6.7%	1.6%	2.0%	1.9%	28.1%	46.7%
45	55.9%	15.3%	1.7%	0.5%	0.4%	12.6%	20.1%
50	76.1%	24.9%	3.3%	0.3%	0.1%	4.7%	8.5%
35	-0.7%	0.0%	0.1%	0.6%	0.0%	34.7%	70.9%
40	-1.6%	0.1%	-6.5%	0.2%	0.1%	25.4%	43.4%
45	-6.0%	-0.6%	-18.8%	0.1%	0.0%	11.1%	17.2%
50	-6.7%	-3.2%	-36.1%	0.2%	0.0%	4.0%	5.8%
35	7.7%	2.0%	3.7%	3.0%	3.0%	4.1%	1.8%
40	25.8%	6.6%	8.1%	1.8%	1.8%	2.7%	3.3%
45	61.9%	15.9%	20.5%	0.4%	0.4%	1.5%	2.9%
50	82.8%	28.1%	39.4%	0.1%	0.1%	0.7%	2.7%

LRT Nul $h(t) = \lambda_0 \cdot \exp(\beta_M \cdot tsall(PD = 0))$

LRT Metric $h(t) = \lambda_0 \cdot \exp(\beta_M \cdot TumourMetric)$

Slide 13

Which Tumour Metric?

- Type 1 Error < 5%
  - tsall, tspre, Css, ntrt (,s0fc8)
- Power to detect (Tumour + Treatment) Effect > 80%
  - tsall, tspre, s0fc8
- Power to detect Treatment Effect > 75%
  - tsall

Full time course of model prediction of tumour size has valid statistical properties and is the most powerful to detect effective treatment

No more complex to compute than other size based EBE metrics

Results are consistent with those of Hansson et al. who showed that the time course of a biomarker was a better predictor of survival hazard than discrete (landmark) time point metrics.

Hansson EK, Amantea MA, Westwood P, Milligan PA, Houk BE, French J, et al. PKPD Modeling of VEGF, sVEGFR-2, sVEGFR-3, and sKIT as Predictors of Tumor Dynamics and Overall Survival Following Sunitinib Treatment in GIST. CPT: pharmacometrics & systems pharmacology. 2013;2:e84.