Slide 1

The time course of tumour size changes with gemcitabine

What can we learn about pharmacology?

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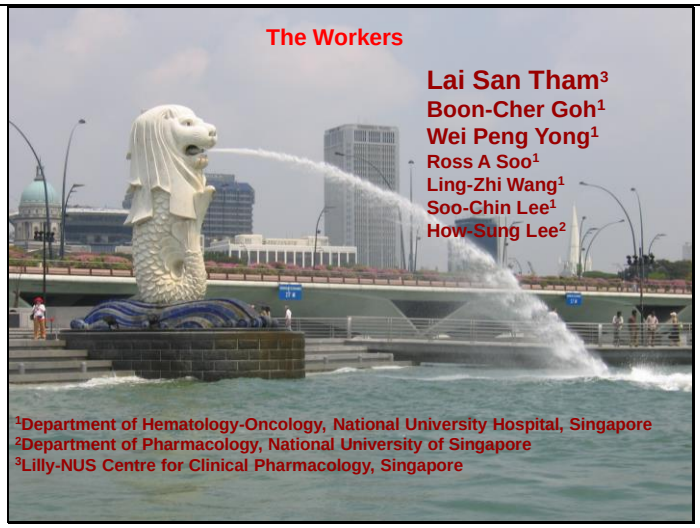

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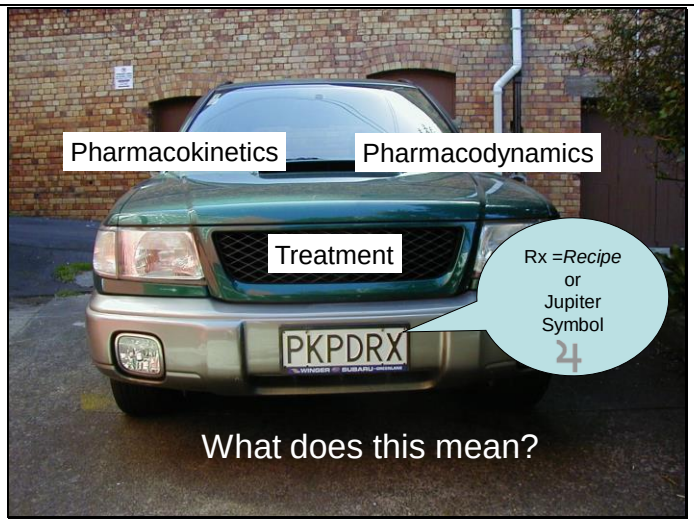
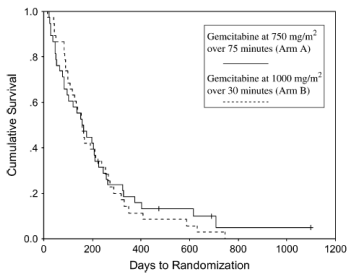
Outline

- What does Pharmacology mean?
- The War on Cancer
- Tumor response Study
  - A pharmacodynamic model for the time course of tumor shrinkage in patients with 'big cell' lung cancer
- Tumour size and Survival
- Drug Development Strategy

Slide 4		PK = Pharmacokinetics: What the body does to the drug PD=Pharmacodynamics: What the drug does to the body Rx=Treatment: What the prescribed and patient need to know.
Slide 5	**The 'new' War on Cancer** **Kennedy, Hutchison call for new war on cancer** Posted by Foon Rhee, deputy national political editor March 26, 2009 1:13 AM Email | Link | Comments (20) Calling for a renewed war on cancer, Senators Edward M. Kennedy of Massachusetts and Kay Bailey Hutchison of Texas introduced legislation today designed to improve research and treatment. In a joint article, the two senators point out that since the United States declared the original war on cancer in 1971, the mortality rate has decreased by only 6 percent, far less than for heart disease and stroke.	http://www.boston.com/news/politics/politicalintelligence/2009/03/kennedy_hutchis.html
Slide 6	**"Why We're Losing the War on Cancer"** **Accelerating Anticancer Agent Development and Validation Workshop** June 20-22, 2007 **Keynote Address: "Learning Too Little, Too Late: Why We Need a New Paradigm for the Cancer Clinical Trial"** Clifton Leaf Former Executive Editor *Fortune* We do clinical trials to LEARN—as quickly as possible—which treatments have the best shot of working.	

Slide 7	**Resisting RECIST** **Appendix V, Table 3.** Definition of best response according to WHO or RECIST criteria* | Best response	WHO change in sum of products	RECIST change in sums longest diameters
CR	Disappearance; confirmed at 4 wks†	Disappearance; confirmed at 4 wks†
PR	50% decrease; confirmed at 4 wks†	30% decrease; confirmed at 4 wks†
SD	Neither PR nor PD criteria met	Neither PR nor PD criteria met
PD	25% increase; no CR, PR, or SD documented before increased disease	20% increase; no CR, PR, or SD documented before increased disease | *WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response, PR = partial response, SD = stable disease, and PD = progressive disease. Throwing away data?	Repeated continuous scale measurement (tumour size) is converted into 4 categories at the end of the trial which reduces information content by categorisation and ignoring time course.
Slide 8	**Singapore Infusion Rate Study** 'Big Cell' Lung Cancer • Open Label, Randomized, phase II trial • Gemcitabine (28 patients in each arm) – days 1 and 8 every 3 weeks x 6 cycles – Arm A: 750 mg/m² over 75 minutes – Arm B: 1000 mg/m² over 30 minutes • Carboplatin – Target AUC of 5mg/mL*min – given on day 1 of each cycle prior to the gemcitabine infusion • No differences in – response rate (primary endpoint) – survival (secondary – not powered)  **Figure 1.** Progression free survival. Soo RA, Wang LZ, Tham LS, Yong WP, Boyer M, Lim HL, et al. A multicentre randomised phase II study of carboplatin in combination with gemcitabine at standard rate or fixed dose rate infusion in patients with advanced stage non-small-cell lung cancer. Ann Oncol. 2006;17(7):1128-33.	Hypothesis is that formation of CTP is saturable and thus high infusion rates may be less effective because of saturation of formation of active substance. This then leads to the objective of this study to test the hypothesis. However, note that this design confounds dose and duration of infusion.
Slide 9	**Tumour Size Measurements** • 261 measurements of tumour size – Largest dimension of the primary tumour measured from CT images using electronic calipers – Used only for RECIST category in primary publication ☹ – 'Discovered' during gemcitabine PK analysis • Measurements at protocol baseline, cycles 2, 4 and 6, and bimonthly – Actual mean follow up 3.5 months	

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Gemcitabine Pharmacology

- Gemcitabine (dFdC)
  - Inactive pro-drug
- dFdCTP (gemcitabine triphosphate)
  - Intracellular, active, tri-phosphate metabolite
- dFdU
  - Major extracellular, inactive metabolite

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Exposure Response

- Which Exposure Measure?
  - Dose
    - Cannot distinguish PK from PD causes of variation
  - AUC
    - Can be used to identify causes of PK variability through model linking Dose to AUC
    - Discards information about time course of concentration
  - C(t)
    - Can distinguish PK from PD variability
    - Can be used to describe and predict schedule dependence

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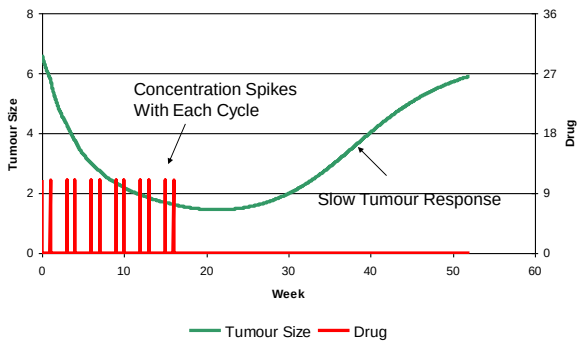
Why Dose by Dose Concentration Time Course, C(t),Won't Work



Slide 13	**How to Describe Drug and Tumour Time Course?** • What Determines the Wash Out of Drug Effect? – "KPD" model for pharmacokinetics without concentration – What "apparent half-life" of drug would explain the effect time course? – Can be based on Dose or AUC – C(t) not required • Why is Tumour Response to Drug Delayed? – Time course of tumour response takes weeks – Time course of drug concentration is complete within a few hours – Binding of drug to DNA probably rapid – Effect of DNA damage on cell proliferation probably slow – Takes time for damaged/dead cells to be removed	Since a delay exists between tumor response and drug administration, the time course of exposure to drug at the tumor effect site was described by an apparent half-life using a "KPD" model. The KPD model assumes drug is administered as a bolus amount (the dose) which is eliminated with an apparent half-life (T1/2,effect) that explains the time course of effect.
Slide 14	**Tumour Size Model** Tumour Growth Rate $\frac{dSize}{dt} = (RateIn \cdot Size) - \frac{1}{T_{turnover}} \cdot Size^2$ Tumour Turnover Kinetics Simple Feedback *Semi-mechanistic* *Natural history of tumour growth has rapid growth with asymptote* *Feedback inhibits growth*	Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, 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):4213-8.
Slide 15	**KPD Drug Effect and Tumour Turnover** • Effect assumed to slow rate of proliferation of new tumour cells Dose $Effect(t) = 1 - \frac{E\max \cdot Ae(t)}{Dose_{50} + Ae(t)}$ Drug Effect Model **Effect Compartment** $\frac{dAe}{dt} = k_1 \cdot (Dose - Ae)$ $k_1 = \frac{\ln(2)}{T_{1/2,effect}}$ **Tumour Compartment** $\frac{dSize}{dt} = Growth \cdot Effect(t) - k_2 \cdot Size^2$ $k_2 = \frac{1}{T_{turnover}}$ KPD Model Tumour Size Model $T_{1/2,effect}$ describes delay in drug effect $T_{turnover}$ describes delay in tumour response	

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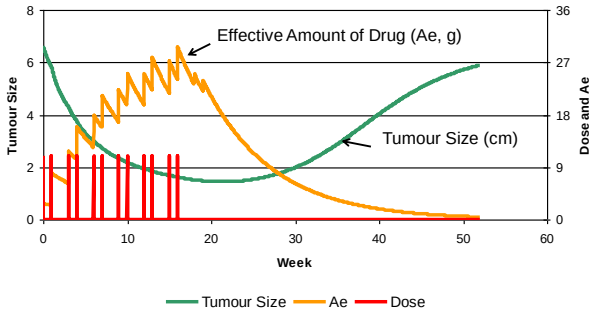
KPD plus Turnover



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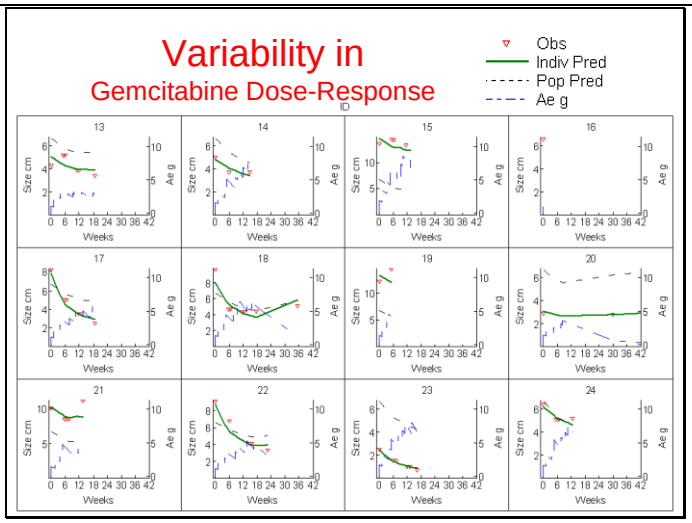
Variability in Gemcitabine Dose-Response



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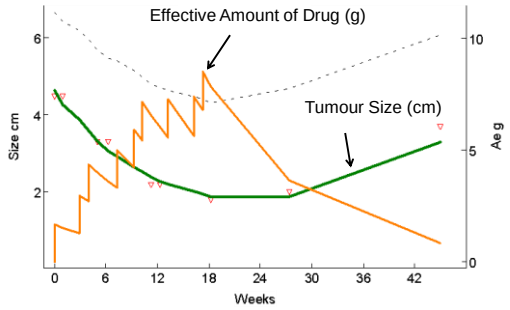
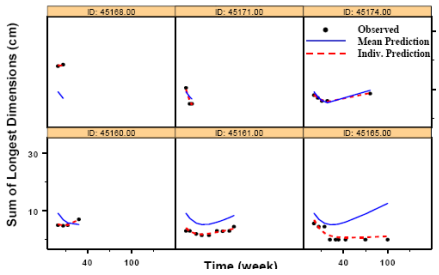
Tumour Size Turnover and Pharmacodynamics

Parameter	Final Estimate	BSV %	95% CI
$Size_0$, tumour size at baseline (cm)	6.7	54.6	(5.7, 7.8)
$T_{turnover}$, Tumour turnover *(week)	1.6	24.7	(0.3, 2.64)
$Dose_{50}$, Gemcitabine at 50% baseline size (gram)	3.2	136	(0.5, 16)
$T_{1/2,effect}$, KPD Effect half-life (week)	2.5	29	(0.61, 12.0)
Residual Error			
Proportional error	12%	-	(9, 16)

* = Scaled to baseline tumour size
BSV=Between Subject Variability (apparent coefficient of variation)
95%CI=Empirical confidence interval from 1000 bootstraps

Slide 19	**Why Stop Treatment?** 	Tumour is still getting smaller when protocol dosing stops.
Slide 20	**Which Exposure Metric?** • No better fit with intracellular gemcitabine metabolite (or dfdU) compared to gemcitibine AUC • No better fit with individual predicted AUC compared with individual dose of gemcitabine • Dose is the simplest exposure metric	
Slide 21	**What Was Learned About Exposure-Response?** • No evidence that differences in exposure time course [C(t)] can influence tumour response • No evidence that intracellular metabolite is better then dose as a predictor of tumour response • Unable to learn about influence of dose and duration of infusion *Didn't learn very much!* *Uninformative design* *"Absence of evidence is not evidence of absence"*	AUC does not reflect exposure time-course

Slide 22	**How Can Tumour Response be Used?** • Can quantitate individual sensitivity (ED50) and time course (drug effect and tumour 'half-lives') • Complements toxicity based models e.g. Friberg myelosuppression model (optimal dosing?) • Link to survival probability (Claret et al 2009, Wang et al 2009)	Claret, L., P. Girard, et al. (2009). "Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics." J Clin Oncol. Wang, Y., C. Sung, et al. (2009). "Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development." Clin Pharmacol Ther **86(2): 167-74.**
Slide 23	**FDA Model Linking Tumour Size with Survival** Elucidation of Relationship Between Tumor Size and Survival in Non-Small-Cell Lung Cancer Patients Can Aid Early Decision Making in Clinical Drug Development [1]Division of Pharmacometrics, Office of Clinical Pharmacology, US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Division of Clinical Pharmacology 5, Office of Clinical Pharmacology, US Food and Drug Administration, Silver Spring, Maryland, USA; [3]Division of Oncology, Office of New Drugs, US Food and Drug Administration, Silver Spring, Maryland, USA. Correspondence: Y Wang (yaning.wang@fda.hhs.gov) Wang Y, Sung C, Dartois C, Ramchandani R, Booth BP, Rock E, Gobburu J Clin Pharmacol Ther. 2009;86(2):167-74.	
Slide 24	**Wang (FDA) Tumour Size Model** "A model with mixed exponential-decay (shrinkage) and linear-growth (progression) components described the time course of tumor change $$\mathrm{TS}_i(t) = \mathrm{BASE}_i \cdot e^{-\mathrm{SR}_i \cdot t} + \mathrm{PR}_i \cdot t$$ where $\mathrm{TS}_{i(t)}$ *is the tumor size at time t for the ith individual,* BASE_i *is* the baseline tumor size, SR_i *is the exponential tumor shrinkage rate* constant, and PR_i *is the linear tumor progression rate."* *Empirical model* *No dose or exposure information used* Wang Y, Sung C, Dartois C, Ramchandani R, Booth BP, Rock E, et al. Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin Pharmacol Ther. 2009;86(2):167-74.	Wang Y, Sung C, Dartois C, Ramchandani R, Booth BP, Rock E, et al. Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin Pharmacol Ther. 2009;86(2):167-74.

Slide 25	**Claret Tumour Size Model** The model is described by the differential equation below: $\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D(t) \cdot \text{Exposure}(t) \cdot y(t) \quad y(0) = y_0 \qquad (1)$ with $K_D(t) = K_{D,0} \cdot e^{-\lambda t} \qquad (2)$ in which y(t) is the tumor size at time t, y_0 is the baseline tumor size, K_L is the tumor growth rate, $K_D(t)$ is the drug-constant cell kill rate that decreases exponentially with time (according to λ) from an initial value of $K_{D,0}$ to account for the progressive development of resistance, Exposure(t) is the drug exposure at time t. Because no pharmacokinetic data were available, the daily dose was used as a metric for exposure to drive drug effect. *DailyDose(t)*exp(-λ*t) 'resistance' function cannot be distinguished from a KPD model with drug elimination* Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, et al. Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics. J Clin Oncol. 2009.	Claret L, Girard P, Zuideveld KP, Jorga K, Fagerberg J, Bruno R. A longitudinal model for tumor size measurements in clinical oncology studies. Abstracts of the Annual Meeting of the Population Approach Group in Europe ISSN 1871-6032 2006;15:abstract 1004. Claret L, Girard P, Hoff PM, Van Cutsem E, Zuideveld KP, Jorga K, et al. Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics. J Clin Oncol. 2009.
Slide 26	**Tumour Size and Survival** Wang/Claret • **ECOG (0/1), baseline tumor size (centered at 8.5 cm) as covariates** • **Tumor size predictors (early biomarker)** – **Individual predicted tumor size percent reduction at 4, 6 or 8 weeks relative to baseline (TPR_{wkx})** *Linear Shrinkage Rate over 8 weeks* • **Model development** – **Parametric survival model (log-normal)** $\log(T) = \alpha_0 + \alpha_1 \times \text{ECOG} + \alpha_2 \times (\text{Baseline} - 8.5) + \alpha_3 \times \text{PTR}_{wk8} + \varepsilon_{TD}$ FDA Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology Meeting, March 18–19, 2008. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4351b1-01-FDA.pdf Wang Y, Sung C, Dartois C, Ramchandani R, Booth BP, Rock E, et al. Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. Clin Pharmacol Ther. 2009;86(2):167-74.	
Slide 27	**Tumour Size Predictions** **Model Fits for Individuals**  FDA Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology Meeting, March 18–19, 2008. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4351b1-01-FDA.pdf	

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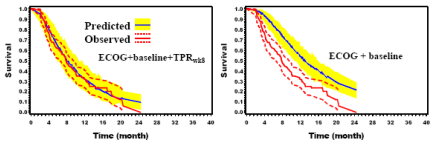
Tumour Size Improves Prediction of Survival

Contribution of TPR_{wk8}
A1 Model Predicts C1



FDA Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology Meeting, March 18–19, 2008. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4351b1-01-FDA.pdf

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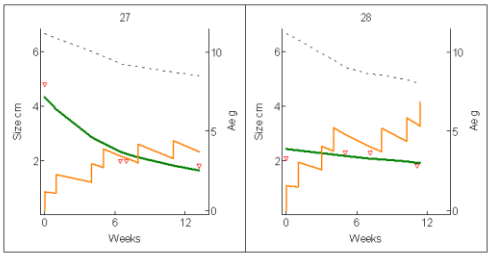
Which Patient Will Survive Longer?

T death=94 weeks ID T death=64 weeks



Wang et al. use a single 8 week estimate of tumor progression rate.
These patients have the same 8 week tumour size but different response time course

Perhaps survival models should include full time course of tumour size?

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Can Anti-Cancer Drugs Be Developed More Efficiently?

Traditional Oncology

- Open Phase 2 trials
  - Biased outcome
- Dose
  - Pick the biggest dose
- Outcome
  - Categorical (RECIST)
- Dosing Regimen
  - '3 week cycle x 6'
  - BSA dosing (discredited theory)

Clinical Pharmacology

- Blinded Phase 2 trials
  - Unbiased
- Dose
  - Designed to learn Dose Response
- Outcome
  - Continuous biomarker (Tumour size)
- Dosing Regimen
  - Drug and patient individualized
  - Guided by PKPD (Evans et al. 1998)

Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl J Med. 1998;338(8):499-505.

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