Statistical Methods in Early Drug Development of Targeted Therapies

A Day in the Life of an Industry Statistician

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Presenter's Conflict of Interest

- Gary Clark is a full-time employee of Array BioPharma Inc
- Gary Clark has stock options in Array BioPharma Inc
- However, the presentation today reflects the personal opinions of Gary Clark and not necessarily those of Array BioPharma Inc

GTSSB

(greatest thing since sliced bread)

A new targeted therapy designed to be effective in patients with abnormalities in a specific biological pathway

A short story about the development of a new drug

Suppose Drug Discovery delivers GTSSB to Clinical Development and asks the Biostatisticians to design the first clinical trials

What types of clinical trials should we design?

What questions should <u>we</u> ask before answering their question?

Primary Questions for an Anticancer Agent

Early dose-finding/dose-ranging questions

- What is the optimal dose and schedule for this agent?
- What is the toxicity profile for this agent?

Preliminary activity/efficacy questions

- Does this agent have activity/efficacy for patients with cancer?
  - If so, in which tumor types?
  - For all patients, or only in selected subsets?
  - How should activity or efficacy be defined?

Later stage efficacy questions

- How does efficacy compare with standard therapies?

Questions for Drug Discovery

- What is the drug supposed to do?
  - eg, Inhibit a single molecular pathway? Inhibit multiple pathways? Interfere with an important process required by a cancer cell to survive or metastasize?
- How is it supposed to work?
  - eg, Small molecule? Antibody? Vaccine? Cytotoxic? Cytostatic? Single agent? In combination?
- What preclinical data are available?
  - eg, Pharmacokinetics? Pharmacodynamics? Toxicity profile? Potential biomarker(s)?
- What do we know about this class of agents?
- Is there a target product profile?

What does Drug Discovery provide to Clinical Development?

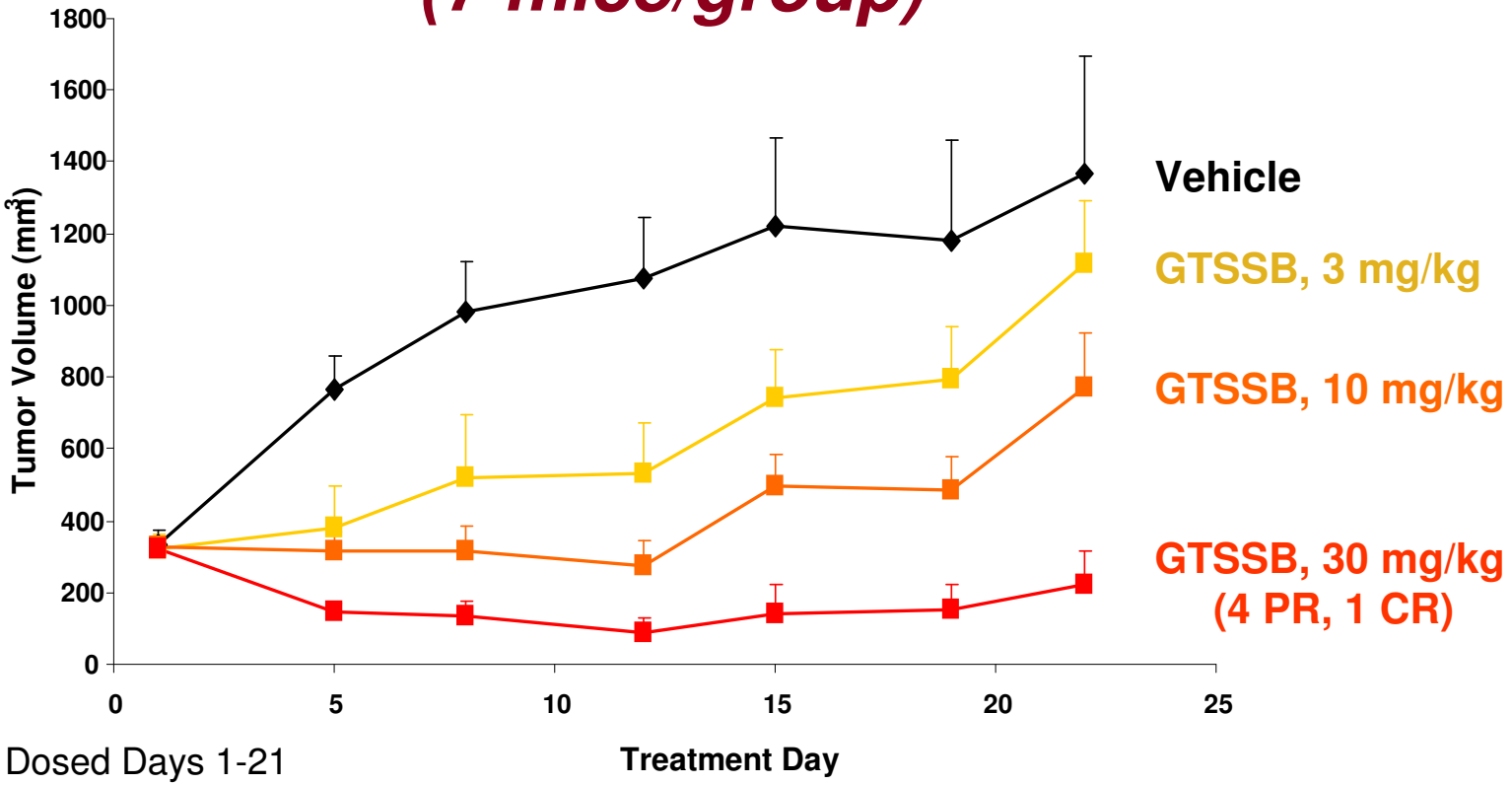
Examples of Toxicokinetic Parameters Following Oral Administration of a Single Dose of GTSSB to Rats

	30 mg/kg		100 mg/kg		300 mg/kg	
PK Parameter	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
C_{max} (µg/mL)	13.8	10.0	26.6	12.7	35.5	24.2
T_{max} (hr)	1.0	2.0	2.0	2.0	4.0	4.0
$t_{1/2}$ (hr)	5.66	8.09	8.69	6.68	10.9	6.67
AUC_t (hr·µg/mL)	165	73.0	277	131	447	256
AUC_{inf} (hr·µg/mL)	176	81.0	325	142	576	282

C_{max} = observed maximum plasma concentration
T_{max} = time to maximum concentration
$t_{1/2}$ = terminal elimination half-life
AUC_t = area under the plasma concentration curve from 0 to t
AUC_{inf} = area under the plasma concentration curve extrapolated to infinity

GTSSB (PO, QD): Activity *in vivo*

(7 mice/group)



Dosed Days 1-21

GTSSB shows significant dose-related inhibition of Colo-205 human colorectal cancer tumor growth in nude mice

Are we ready to design dose-finding studies in cancer patients?

Choosing a Schedule

- What is the expected $t_{1/2}$?
- Do we expect efficacy and/or toxicity to be related to:
  - C_{max} ?
  - AUC ?
  - C_{min} ?
  - Time above a threshold ?
- Are there known/presumed biological effects?

Choosing a Starting Dose

- In GLP (Good Laboratory Practice) toxicity studies
  - Up to 100 mg/kg/day was tolerated in rats
  - Up to 3 mg/kg/day was tolerated in monkeys
- Human equivalent doses
  - 600 mg/m^2/day based on rats
  - 36 mg/m^2/day based on monkeys
- Apply safety factor of 10 to monkey NOAEL (No Observed Adverse Effect Level)
  - 3.6 mg/m^2
  - 5.8 mg/day (for BSA of 1.62)
- Starting dose of 5 mg QD (for ease of packaging and dose escalation)

Single-agent or Combination Studies?

- Generally need to establish safety and tolerability as a single agent in cancer patients
  - Upper management likes to see single-agent efficacy, but that may not be necessary *(eg, bevacizumab)*
- Can then usually proceed to dose-finding combination studies
  - Be prepared for drug-drug interactions
- Starting doses and schedules can be tricky
  - Standard dose of standard therapy but lower dose of new agent?
  - Lower doses of both agents?
  - Simultaneous administration of both agents?
  - Pharmacological separation? Does order matter?

Choosing a Dose Escalation Scheme

- Standard 3+3
- Modified 3+3 with a swing patient (4+2)
- Rolling 6
- Accelerated titration
- PK-guided dose escalation
- Modified continual reassessment (CRM)
- Escalation with overdose control (EWOC)
- Other model-based adaptive designs (usually Bayesian)

Planning Ahead

- GTSSB was designed to be a new targeted therapy that will be effective in patients with abnormalities in a specific biological pathway
- Biomarker X “might” be a good patient selection marker
- Suppose dose-finding studies will be conducted and we will have a recommended Phase II dose and schedule

What types of clinical trials should we design and how might this change the design of the current study?

Patient Selection

- Should we include unselected patients in initial studies?
- Should we focus on specific tumor types in which the prevalence of the target is high?
- Should we select specific patients based on biomarker results?
  - Is a companion diagnostic test available?
  - What is required to “validate” the test?
  - When do we need a “validated” test?

Patient selection early in drug development runs the risk of selecting the wrong biomarker and/or the wrong assay

2004

Erbitux™ (cetuximab) Package Insert

- Erbitux administered as a single agent is indicated for the treatment of **EGFR-expressing**, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

2005

VOLUME 23 · NUMBER 9 · MARCH 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors That Do Not Express the Epidermal Growth Factor Receptor by Immunohistochemistry

Ki Young Chung, Jinru Shia, Nancy E. Kemeny, Manish Shah, Gary K. Schwartz, Archie Tse, Audrey Hamilton, Dorothy Pan, Deborah Schrag, Lawrence Schwartz, David S. Klimstra, Daniel Fridman, David P. Kelsen, and Leonard B. Saltz

2009

ASCO Advises Oncologists: Test for KRAS Mutations

The American Society for Clinical Oncology (ASCO) has published a provisional clinical opinion (PCO) advising doctors to test patients with colorectal cancer for KRAS mutations before treating them with medicines that include Erbitux® (cetuximab) or Vectibix™ (panitumumab)

http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.21.9170

Advice Regarding Patient Selection

- Do not use selection/enrichment strategies too early unless:
  - You are absolutely certain of target functionality
  - You have a validated assay that can reliably assess the status of the biomarker
- Collect tissue samples to obtain preliminary information about biomarkers in early development studies to generate hypotheses for future definitive studies
- Conduct randomized clinical trials with appropriate control arms in early development

Drug Development Strategy

Suppose Target Product Profile (TPP) includes an indication for patients with pancreatic cancer who are positive for biomarker X

- One possible Phase I development strategy:
  - Phase I dose-escalation study in all comers (select sites that have access to patients with GI cancers)
    - Complete PK sampling
    - Tissue optional
  - Phase I expansion cohort of patients with pancreatic cancer treated at recommended Phase II dose (add more sites that treat pancreatic cancer)
    - Sparse PK sampling
    - Tissue mandatory to look for more biomarkers

    AND / OR
  - Phase I expansion cohort of patients with pancreatic cancer who are positive for biomarker X treated at recommended Phase II dose

Drug Development Strategy

- Subsequent Phase 1b and Phase II development strategies:
  - Phase Ib study in combination with gemcitabine
    - Maybe all comers
    - Maybe all patients with pancreatic cancer
    - Maybe patients with pancreatic cancer who are positive for biomarker X
    - Complete PK sampling to look for DDI
    - Tissue optional, perhaps mandatory near MTD if no selection
  - Phase II/III study in combination with gemcitabine in patients with pancreatic cancer
  - Maybe select if biomarker X looks promising
  - Tissue mandatory if no selection

Status of GTSSB

- GTSSB is now being evaluated in several Phase III clinical trials
- Some studies use one or more selection biomarkers
- Some studies use histological subtypes that are known to have a high prevalence of these selection biomarkers

Take-home Messages

- At each step in the development process, carefully assess the preliminary information that is available
  - Is the right question being asked?
  - Is the preliminary information sufficient for addressing the question being asked?
  - Should additional preliminary study(s) be conducted before launching a definitive study to answer the question?
  - Will the results of the study I am designing be helpful in designing the next set of clinical trials?
- Discuss single-agent and combination strategies early in development, taking into account potential indications for the agent

Take-home Messages

- Drug development is a team sport and Biostatisticians should be active participants on the team
  - Requires strong foundation in statistics, augmented by knowledge of molecular biology, translational research, clinical research, regulatory requirements, etc., and familiarity with terminology from all disciplines
- Early drug development of targeted therapies requires an understanding of biological pathways, biomarkers, preclinical experimental designs, PK, PD, etc. in order to design efficient clinical trials
- These concepts are independent of the setting (eg, academia, big pharma, small biotech)