Toxicity Testing for Oncology Drugs
Theresa Reynolds, Krishna Allamneni

Presentation objectives

1. Convey:
   a) Special considerations for the development of oncology drugs and
   b) How they impact the toxicology program
2. Describe the value of a PD marker in oncology and cite examples
3. Describe the key similarities & differences in toxicity evaluation for small and large molecules
4. Present current regulatory guidance and impact on drug development for oncology
Despite new therapies, little change in overall cancer incidence

Age-adjusted cancer incidence rate in the U.S. from 1975-2005

Despite new therapies, little change in overall cancer incidence

Estimated number of cancer survivors in the United States from 1971 to 2005

a) Why do oncology drugs have special considerations for drug development?

b) What are they, & how do they impact the toxicology program?
Special considerations for oncology drugs - why?

- High unmet medical need
- Life-threatening & refractory nature of the disease
- Failure of standard of care; Limited therapeutic options
- Patients eligible for phase 1 & 2 trials have not responded to established therapy

Regulatory guidance for oncology drug development

Recent publication of special regulatory guidance reflects the significance of this patient population

These will be discussed in detail later in the presentation
Special considerations for oncology drugs

• Phase 1 in patients
• Treatment extension for patients that benefit
• Small therapeutic index
• Timing of toxicity studies

Special considerations for oncology drugs

• Phase 1 conducted in patients
  – Have not responded to standard of care (SOC)
  – Disease progression despite SOC
  – Early enrollment of patients → possibility of benefit
• Phase 1a typically single-dose escalation to maximum tolerable dose (MTD)
• Phase 1b typically multiple-doses for up to 3 months to assess benefit

Special considerations for oncology drugs

Treatment can be extended early in drug development for patients that benefit
  – Criteria can be set as early as phase 1 to show evidence of benefit to allow treatment beyond timeframe supported by toxicology studies
Special considerations for oncology drugs

Small therapeutic index
- Desired pharmacologic activity is often interference with life-sustaining pathways
- Accepted that toxicities may occur, risk of potential toxicity weighed against poor disease prognosis

Timing & duration of toxicity studies
- Reproductive toxicity studies can be conducted concurrent with phase 3, or not conducted (cytotoxics)
- Duration of chronic toxicity studies
  - 6 months for biotherapeutics & small molecule cytotoxics
- Carcinogenicity studies not required for registration

Impact on the toxicology program
Objectives of toxicity testing

- Identification of initial safe starting dose and dose escalation schemes for clinical trials
- Identification of potential target organs of toxicity and reversibility of effect
- Identification of safety parameters for clinical monitoring

Impact on toxicology program

- Phase 1 conducted in patients
  - Disease state can make patients more sensitive to toxicities
  - Impact of toxicology data on clinical risk
    - Identify findings
    - Confer with project clinical scientist
    - Impact of findings on phase 1 monitoring
    - Inclusion/exclusion criteria

Toxicology data identify hazards to be monitored and considered in risk/benefit decision making

Impact on toxicology program

Treatment can be extended early in drug development for patients that benefit
- Longer phase 1-enabling toxicology studies may be needed to support early clinical trials that intend to show benefit

**Duration of clinical testing must be supported by**

- Toxicology studies of equivalent duration
  - 12 weeks

Clinical assumptions, e.g.: projected therapeutic dose (10 mg/kg), route & frequency of administration (e.g. IV, weekly), treatment duration (e.g. 12 weeks)
Early extension of treatment for patients who benefit

Favorable risk/benefit profile can enable continued treatment beyond the duration supported by toxicology.

Protocol-specified benefit criteria met?

Yes

No

Stop treatment

Extension phase

Impact on toxicology program

Small therapeutic index

- Because toxicities are expected to manifest, characterization of the toxicity profile is balanced with animal welfare.
- Mortality is not a desired endpoint; Doses tested in toxicology studies should:
  - Define the severely toxic dose in 10% of rodents (STD10) and
  - The highest non-severely toxic dose (HNSTD) in non-rodents.

*JJ De George, CH Ahn, PA Andrews, ME Brower, Cancer Chemotherapy and Pharmacology, 1997

Value of a PD marker in oncology
Activity, efficacy & toxicity, value of a PD marker

- Shows drug is active
- Can dose to effect in toxicology studies and clinical trials
- Can separate toxicity from activity
- PD is a marker of activity not efficacy
  - Must be borne out by clinical efficacy data

Value of a PD marker example 1: Rituxan®

Rituxan® (monoclonal antibody to B-cell CD20 receptor)
PD marker: depletion of B-cells in blood;
Monitorable in toxicology studies & patients
  - Demonstrates relevance of toxicology studies
  - Allows separation of active vs. toxic doses
  - Supports activity-based first in human (FIH) dose
  - Reduces dose-escalations to attainment of active dose
Clinically validated via reduction in tumor volume

Value of a PD marker example 2: Avastin®

Avastin® (monoclonal antibody to VEGF)
Inhibits growth of new blood vessels
No PD marker
  - Active dose extrapolated from animal tumor models
  - No prospective way to separate active dose from toxic dose
  - First in human (FIH) dose a fraction of safe dose determined toxicology studies

VEGF: vascular endothelial growth factor
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3. Key similarities & differences in nonclinical safety evaluation for small and large molecules

- Biologics have complex structural and biological activity compared to small molecules
- Drug development plans for small molecules are different from large molecules

Graphic Courtesy Rolf G. Werner (Boehringer Ingelheim) Apr 2008 Presentation

Key similarities & differences in toxicity evaluation for small and large molecules

- Off-target toxicities
- Species selection based on metabolism
- Pharmacologically driven species selection

How do small molecules differ from biologics?

<table>
<thead>
<tr>
<th></th>
<th>Small molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>Low, e.g. &lt;500 daltons</td>
<td>High e.g. 10-1000 kilodaltons</td>
</tr>
<tr>
<td>Dose route</td>
<td>Oral</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Species specificity</td>
<td>Species-independent</td>
<td>Species-specific</td>
</tr>
<tr>
<td>- On-target toxicities</td>
<td></td>
<td>- On-target toxicity</td>
</tr>
<tr>
<td>- Species selection based on metabolism</td>
<td></td>
<td>- Pharmacologically driven species selection</td>
</tr>
<tr>
<td>Typical toxicities</td>
<td>Mechanism/structure-based</td>
<td>Exaggerated pharmacology</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Yes</td>
<td>Internalized and degraded</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Not relevant</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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Drug development plans for small and large molecules are different

<table>
<thead>
<tr>
<th>Development plans</th>
<th>Small molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory environment</td>
<td>Conventional</td>
<td>Nonconventional</td>
</tr>
<tr>
<td>Relevant species</td>
<td>Toxicology program in 2 species</td>
<td>One relevant species</td>
</tr>
<tr>
<td>Basis for clinical starting dose</td>
<td>Less conservative</td>
<td>MTD, NOEL, HNSTD</td>
</tr>
<tr>
<td></td>
<td>More conservative</td>
<td>MABEL, NOEL, NOAEL</td>
</tr>
</tbody>
</table>

MTD: maximum tolerated dose, NOEL: no observed effect level, NOAEL: no observed adverse effect level, MABEL: minimal anticipated biological effect level, HNSTD: highest non-severely toxic dose

Preclinical drivers for small molecules

- Early stage discovery toxicology
  - In silico, in vitro receptor binding, hERG, cell based/in vivo screens to enable lead selection
- Predictivity of models
  - In vitro/in vivo correlations
  - Cross-species comparisons
- Cross functional interactions
  - Lead and backup (safety, activity, PK)
- Established impurity qualification
- Appropriate formulations

Lead optimization scheme

<table>
<thead>
<tr>
<th>Activity, Pharm. Sci, DMPK</th>
<th>Tox testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency selectivity</td>
<td>In silico genotoxicity: Ames; in vitro hERG</td>
</tr>
<tr>
<td>Tier 1 (similar/chemical stability)</td>
<td>Tier 2 (stability)</td>
</tr>
<tr>
<td>Cell assay for efficacy</td>
<td>hERG IC50</td>
</tr>
<tr>
<td>5-in-1 IV PO non PK</td>
<td>In vitro hepatocytes; target receptors (iterative)</td>
</tr>
<tr>
<td>PK (rodent) CYP IC50</td>
<td>NTP IC50, in vivo toxicity, PK non-rodent</td>
</tr>
<tr>
<td>Metabolite activity in vitro</td>
<td>Exploratory rodent single and repeat dose</td>
</tr>
<tr>
<td>Exploratory PK non-rodent</td>
<td>Genotoxic panel</td>
</tr>
<tr>
<td>Candidate selection</td>
<td>Acute toxicity/TG</td>
</tr>
</tbody>
</table>
Challenges specific to small molecules

- Therapeutic index
- Higher attrition rates
  - Low translatable nonclinical risks to clinic
  - Substantial off-target activity
  - Complex ADME issues
- Identify “predictable” liabilities earlier
  - Therapeutic index
  - Nature of toxicities (predictable, reversible, monitorable)
  - Biomarkers
  - Mode of toxicity
  - Human relevance

Cytotoxic vs. non-cytotoxic oncology drugs

- Classical anti-neoplastic agents (cytotoxic)
  - Relatively non-specific MOA
  - Narrow therapeutic index
  - Regulatory path relatively straightforward
    - Genotoxicity, carcinogenicity, and reproductive toxicity not required for registration
- Non-cytotoxics (cytostatics, immune modulators)
  - Relatively specific MOA
  - Specific targeted inhibition
  - Relatively non-toxic
  - Wider therapeutic margin
  - Regulatory path novel

More on targeted inhibitors

- Target specific signalling alterations, e.g. kinases
  - Only in presence of activating mutations in cancer cells
- Generally less toxic than cytotoxics
- Complex pathway interactions
  - E.g. feedback, crosstalk
- Emerging field
  - Long term toxicities unknown
  - Starting clinical dose considerations
  - Translation of preclinical safety to clinic?
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Toxicology plan for small molecules

- Target evaluation
- Lead ID
- Lead optimization
- Candidate selection
- Phase I
- Phase II
- Phase III
- Post approval

- IND Filing
- NDA Filing

- Mechanistic toxicity
- In silico pharmacokinetics, cardiovascular

- In vivo SP

- Genotoxicity
- Cardiotoxicity
- Off-target receptor binding

- Impurity qualification
- Indication/MOA-specific

Oncology drug failures

Identifying predictable preclinical safety liabilities earlier can lead to design selection of better drug candidates


4.

Current regulatory guidance and impact on drug development for oncology
Regulatory guidance for oncology drug development

Recent publication of special regulatory guidance reflects the significance of this patient population.

Specific regulatory guidance for oncology drugs

- ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- EMEA (1998); Note for Guidance on the Pre-Clinical Evaluation of Anticancer Medicinal Products. The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, January 1998; (CPMP/SWP/997/96)
- MHLW is developing nonclinical guidance to address various mechanisms of anti-cancer therapy excluding biologics

IND-enabling toxicology program for oncology drugs

<table>
<thead>
<tr>
<th>Toxicokinetics</th>
<th>Small molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encouraged</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dose-ranging</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Repeat dose study*</td>
<td>2 species</td>
<td>One species</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>Core battery only in case of concern</td>
<td>No standalone studies required</td>
</tr>
<tr>
<td>Genotoxicity*</td>
<td>Maybe</td>
<td>No</td>
</tr>
<tr>
<td>Tissue cross-reactivity</td>
<td>No</td>
<td>Yes (monoclonals)</td>
</tr>
<tr>
<td>Starting dose basis</td>
<td>Rodent STD</td>
<td>Rodent non-rodent</td>
</tr>
</tbody>
</table>

* Duration to match clinical regimen
* Only if testing normal volunteers or disease-free patients
* Programs should be developed case-by-case based on scientific rationale; the table above is simplified for comparison purposes only.
Selecting phase I starting dose:

example

- Drug A resulted in 10% (2/20) mortalities in rats at 30 mg/kg in the 28 day study
  - Rat STD_{50} = 30 mg/kg
  - Human equivalent dose is 30 x 6 = 180 mg/m^2
- Dogs tolerated 1/10th (10-fold safety margin) of this dose = 18 mg/m^2
- Phase 1 starting dose = 18 mg/m^2
  - mg/m^2 to mg/kg in humans, use 37 as the conversion factor
  - 18 mg/m^2 or 18/37 = 0.5 mg/kg
  - ~30 mg (60 kg patient)


**NDA-enabling toxicology program for oncology drugs**

<table>
<thead>
<tr>
<th>Small molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species</td>
<td>Rodent and non-rodent</td>
</tr>
<tr>
<td>Sub-chronic toxicity</td>
<td>13 wks for non-cytotoxic</td>
</tr>
<tr>
<td>Chronic toxicity</td>
<td>No longer than 6 months</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>Yes^a</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>Maybe^b</td>
</tr>
<tr>
<td>Safety pharmacology</td>
<td>None</td>
</tr>
<tr>
<td>Reproductive toxicity^c</td>
<td>Yes</td>
</tr>
</tbody>
</table>

^a IC stage C, or Segment II reproductive toxicology studies evaluated the period from implantation to birth (gestation period of approximately) may be unnecessary depending on intended patient population (late stage patients); ^b Organ injury toxicology studies required concurrent with Phase 3. ^c Embryofetal toxicity studies need concurrent with Phase 3. Fertility studies and peri-postnatal studies needed prior to registration.

<table>
<thead>
<tr>
<th>Target evaluation</th>
<th>Lead ID</th>
<th>Lead optimization</th>
<th>Candidate selection</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Post approval</th>
</tr>
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<tbody>
<tr>
<td>NDA filing</td>
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**Non-clinical testing for drug combinations**

- May not be necessary for testing in advanced cancer patients
- May exclude if:
  - No PK, PD, or metabolic interactions anticipated
  - Drugs are not packaged as a combination
  - All components well characterized individually

EMEA: guideline on the non-clinical development of fixed combinations of medicinal products (Oct 2005)

FDA: nonclinical safety evaluation of drug or biologic combinations (March 2006)
Regulatory guidance impurities

- Impurity thresholds not appropriate for oncology drugs intended to treat advanced stage patients
- Relevant for cytostatics, or drugs likely to be administered to early stage cancer patients with longer life expectancy
- Guidance documents
  - ICH Q3A(R) impurities in new drug substances, 2002
  - ICH Q3B(R) impurities in new drug products, 2003
  - ICH Q3C impurities: guideline for residual solvents, 1997
  - EMEA, guideline on the limits of genotoxic impurities, 2006
  - EMEA, questions and answers on the CHMP guideline on the limits of genotoxic impurities, 2008
  - Establishment of allowable concentrations of genotoxic impurities in drug substance and product, 2005, PhRMA position paper.
  - FDA 2008: Genotoxic and carcinogenic impurities in drug substances and products: recommended approaches and acceptable limits

ICH S9

The following is an overview of current expectations and shouldn't be used for designing a drug development program; original source documents and guidance should be consulted

- The current guidance addresses three key topics
  - Starting dose
  - Duration of chronic studies
  - Reproductive toxicity studies
- Clear guidance for “late stage or advanced cancer”
  - Importance of scientific rationale


ICH S9 major topics (1 of 3)

start dose

- Approaches to setting the first in human start dose
  - Pharmacologically active dose but reasonably safe
  - Based on all available PK/PD, toxicity data
  - Allometric scaling by body surface area for small molecules; Body weight basis for biologics
  - Biologics with agonistic properties, consider minimally anticipated biologic effect level (MABEL)
ICH S9 major topics (2 of 3) duration of chronic toxicity studies

- Current approach – 6 month duration
- ICH S9 proposed 3 month Tox studies to be submitted prior to phase 3
- Adequate for biologics?

ICH S9 major topics (3 of 3) reproductive toxicology

- Conducted concurrent with phase 3 and submitted for registration, or not conducted (cytotoxics) altogether
  - Mechanism of action of the drug on fertility and fetal development
- Provision to include fertility endpoints in general tox studies

Thank you for your attention

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