# Preclinical Requirements for Therapeutic Studies in Humans with Advanced Cancer

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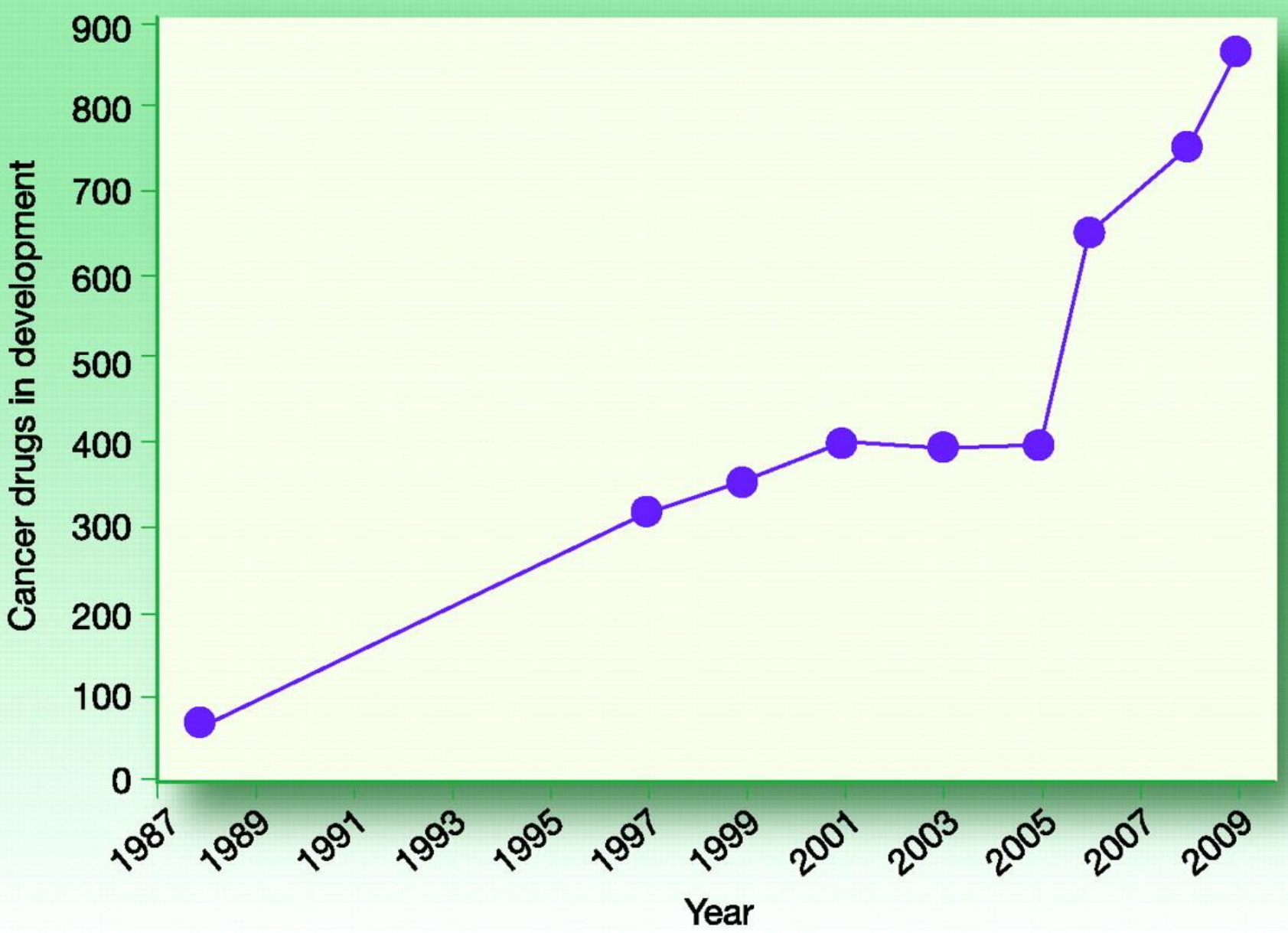
# Disclosures

* I have no financial conflicts of interest relevant to this presentation
* In the last 5 years, I have received honoraria from
  * Pfizer
  * Novartis (research funding as well)
  * Boehringer-Ingleheim
  * Lilly
  * Roche

# Objectives

1. To briefly review the drug development process to ensure everyone is familiar with the terms
2. To review the preclinical components that are required to be included in an IND submission
   * Pharmacology:  mechanism of action, PD
   * Pharmacokinetics
   * Efficacy studies
   * Safety pharmacology
     * Animal toxicology
     * Determination of the safe starting dose for phase I


Cancer drugs in development
900
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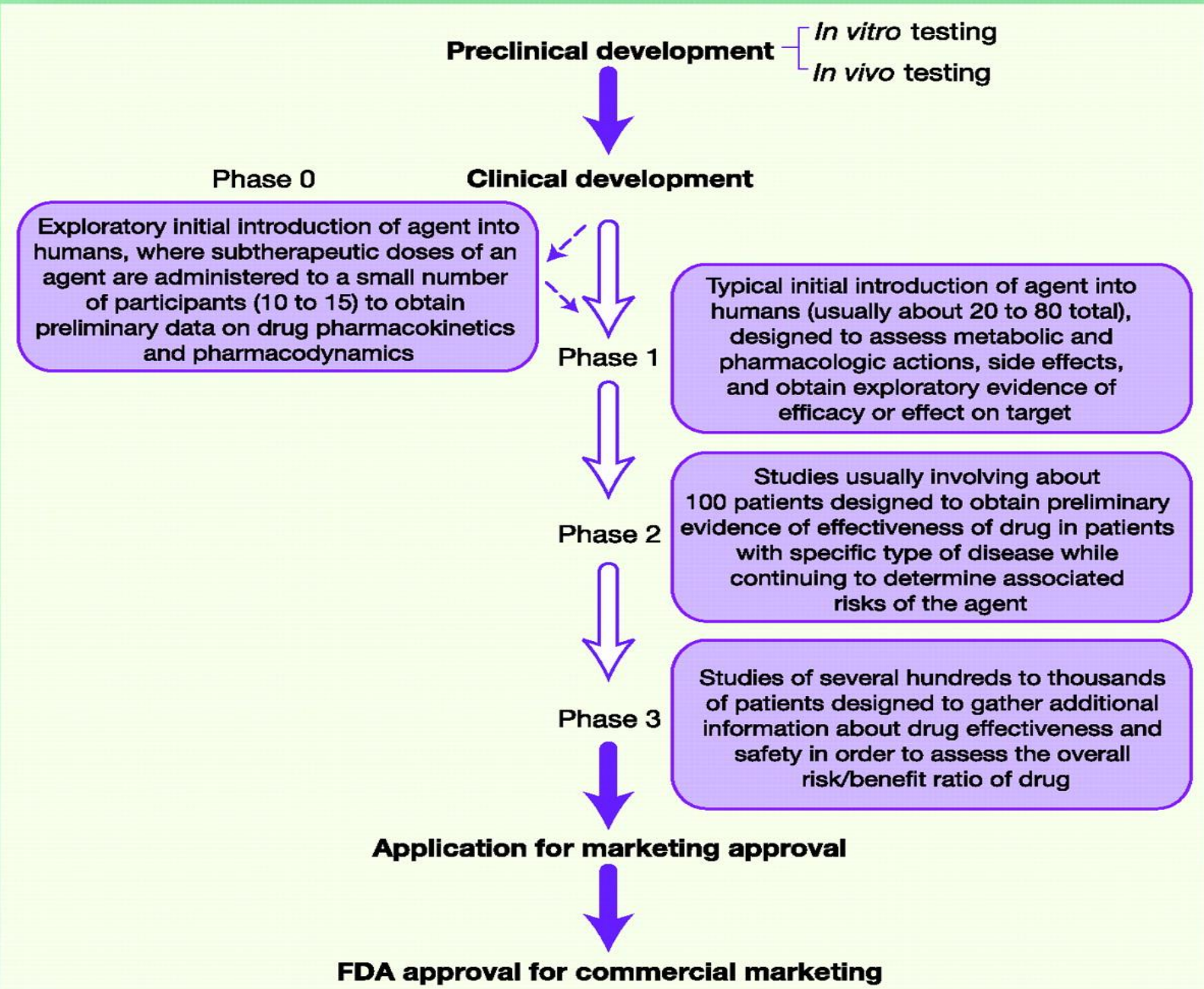

Preclinical development
In vitro testing
In vivo testing
Phase 0
Clinical development
Exploratory initial introduction of agent into humans, where subtherapeutic doses of an agent are administered to a small number of participants (10 to 15) to obtain preliminary data on drug pharmacokinetics and pharmacodynamics
Phase 1
Typical initial introduction of agent into humans (usually about 20 to 80 total), designed to assess metabolic and pharmacologic actions, side effects, and obtain exploratory evidence of efficacy or effect on target
Phase 2
Studies usually involving about 100 patients designed to obtain preliminary evidence of effectiveness of drug in patients with specific type of disease while continuing to determine associated risks of the agent
Phase 3
Studies of several hundreds to thousands of patients designed to gather additional information about drug effectiveness and safety in order to assess the overall risk/benefit ratio of drug
Application for marketing approval
FDA approval for commercial marketing

# Goals of nonclinical studies

* Identify pharmacologic properties of the agent
* Understand the toxicologic profile of the agent
  * Target organs
  * Reversibility
  * Exposure / toxicity relationships
* Determine a safe starting dose for the first-in-human studies

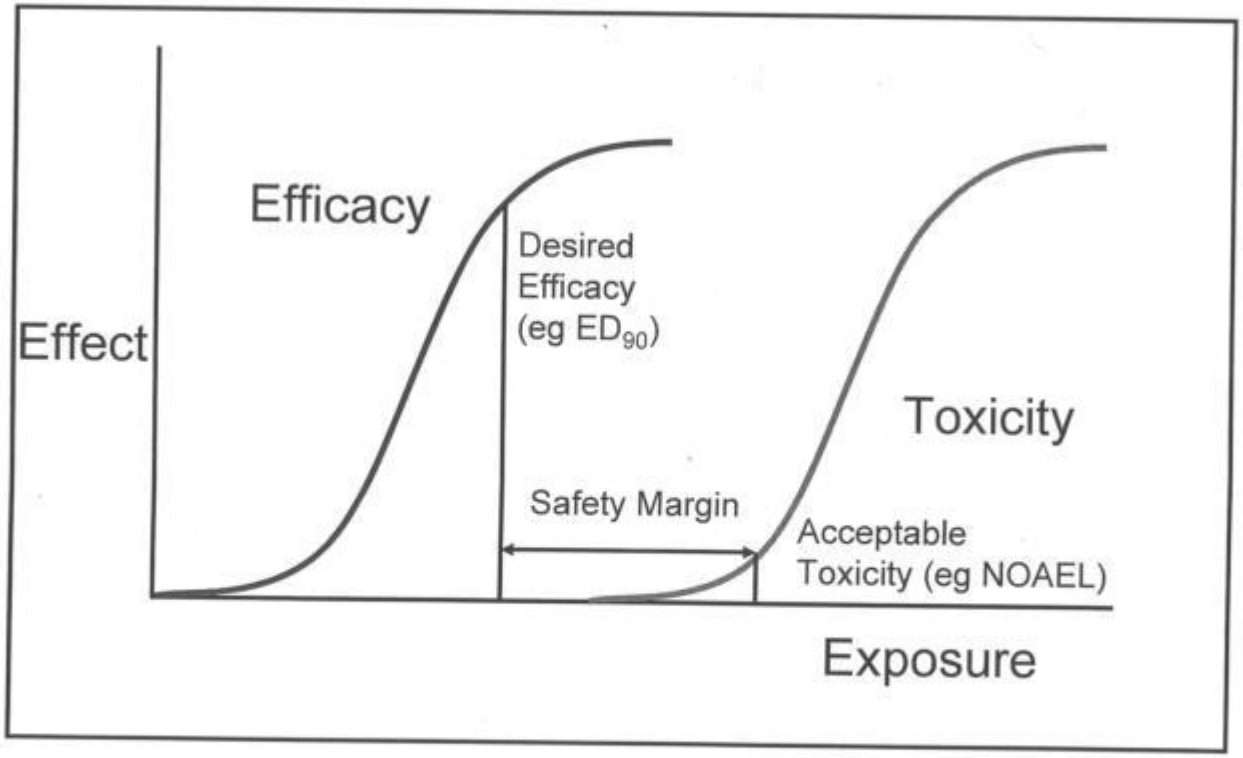
ICH Guidelines S9

# ICH Guidelines

* S9: nonclinical evaluation for anticancer pharmaceuticals
  * Patients with advanced cancer and no remaining treatment options have a life-threatening condition that is often rapidly fatal
  * Doses used to treat malignancy are often near or at dose levels at which adverse effects will be observed
  * Acceptable levels of toxicity are higher

* Recognition that there needs to be flexibility in the type and timing of preclinical studies required for anticancer pharmaceuticals compared to other pharmaceuticals

# Safety margins




**For benign indications, 100-fold margin may be appropriate**

**For terminal conditions, much lower margin may be acceptable**

# The agent: CMC

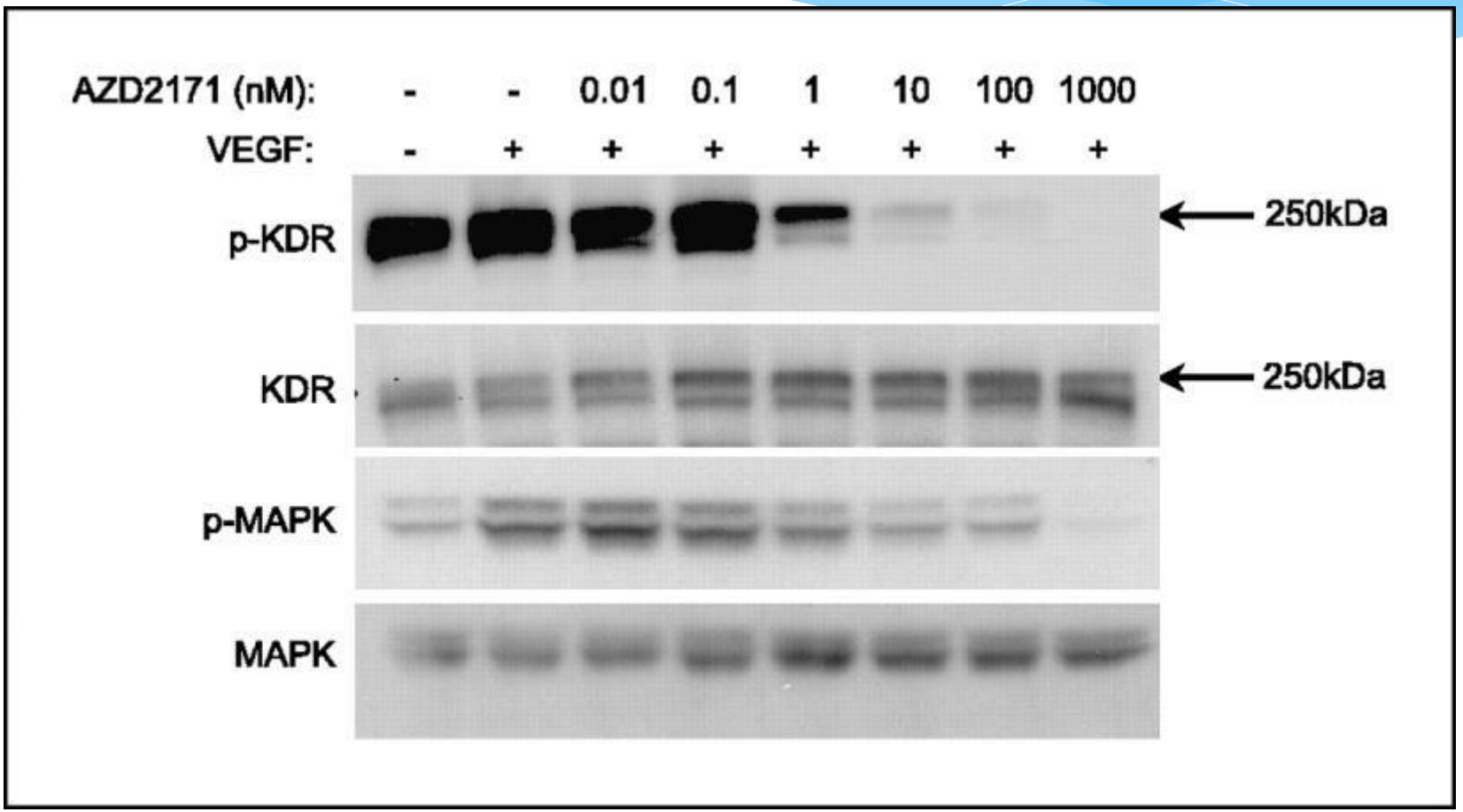
* Chemistry: chemical class and standardized name

* Manufacturing and control
  * GMP (Good Manufacturing Processes)
    * Minimum standards
  * Production
    * Sufficient quantities
    * Practical dosage forms

# Activity / Target

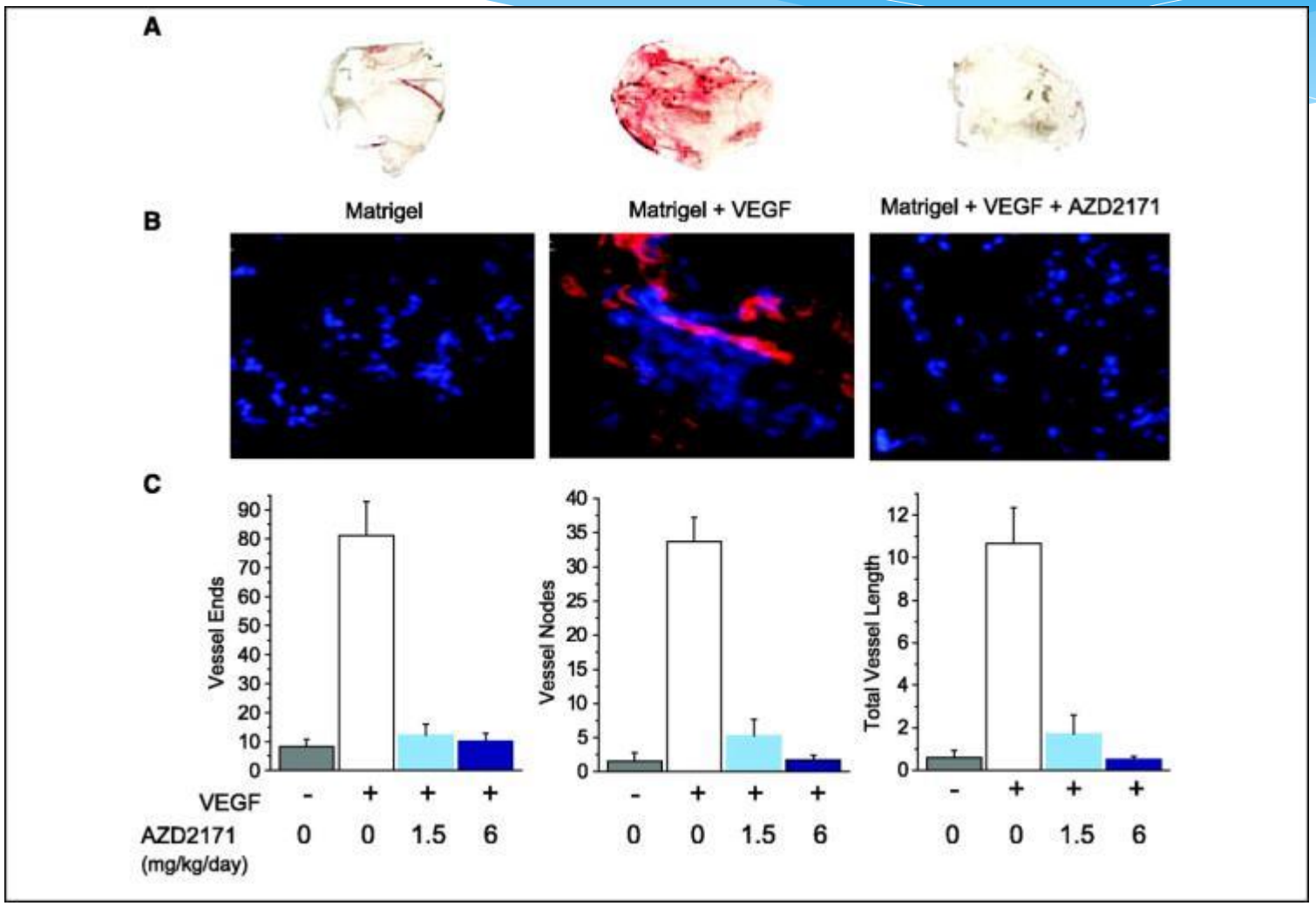
* Expected that there is significant understanding of the mechanism of action of the agent
* These studies are most often performed in *in vitro* models
* Also expected that the agent will show antitumour activity in xenografts at doses that are tolerated
* These early studies should also inform schedule-dependency of the agent
* Inform biomarker development

# AZD2171 inhibits VEGF-stimulated KDR phosphorylation in human endothelial cells.




Wedge S R et al. Cancer Res 2005;65:4389-4400

# AZD2171 inhibits VEGF-induced angiogenesis in vivo.

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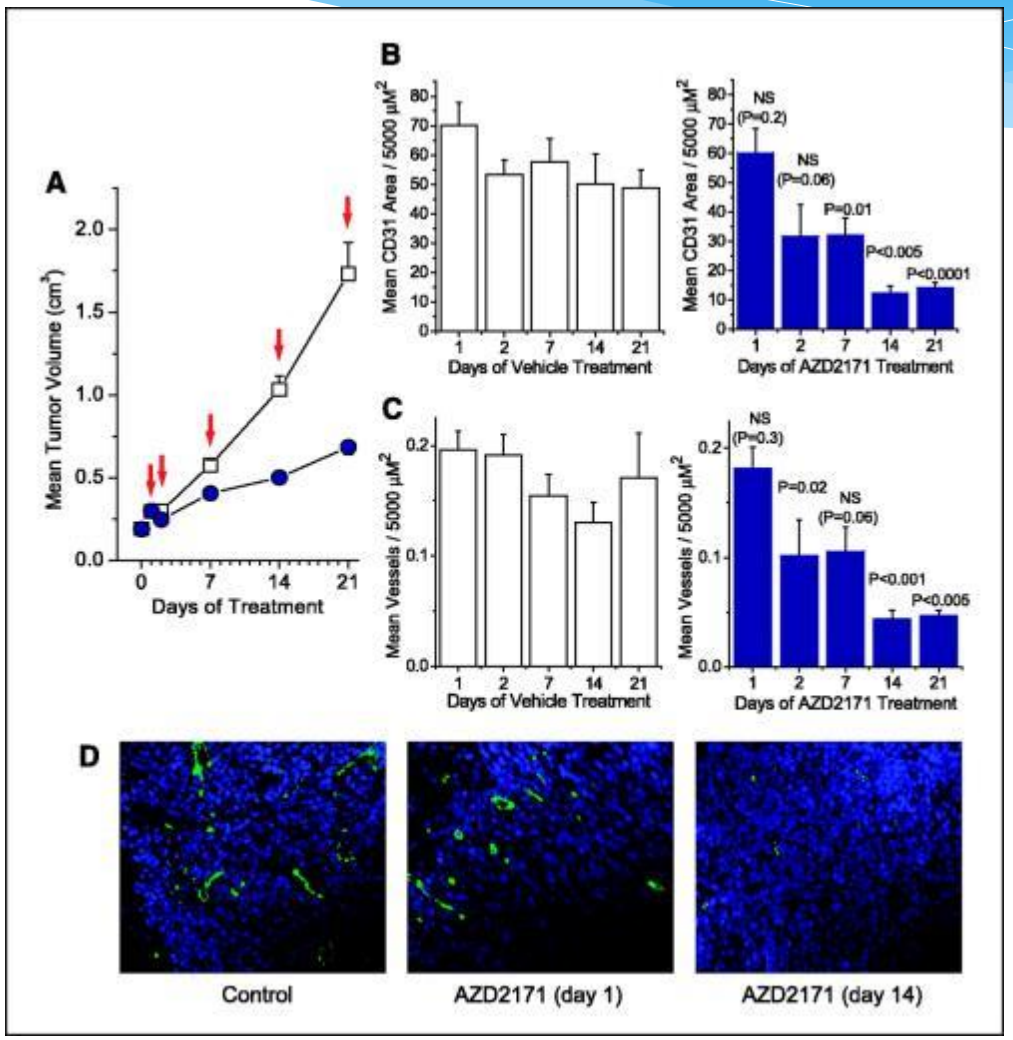
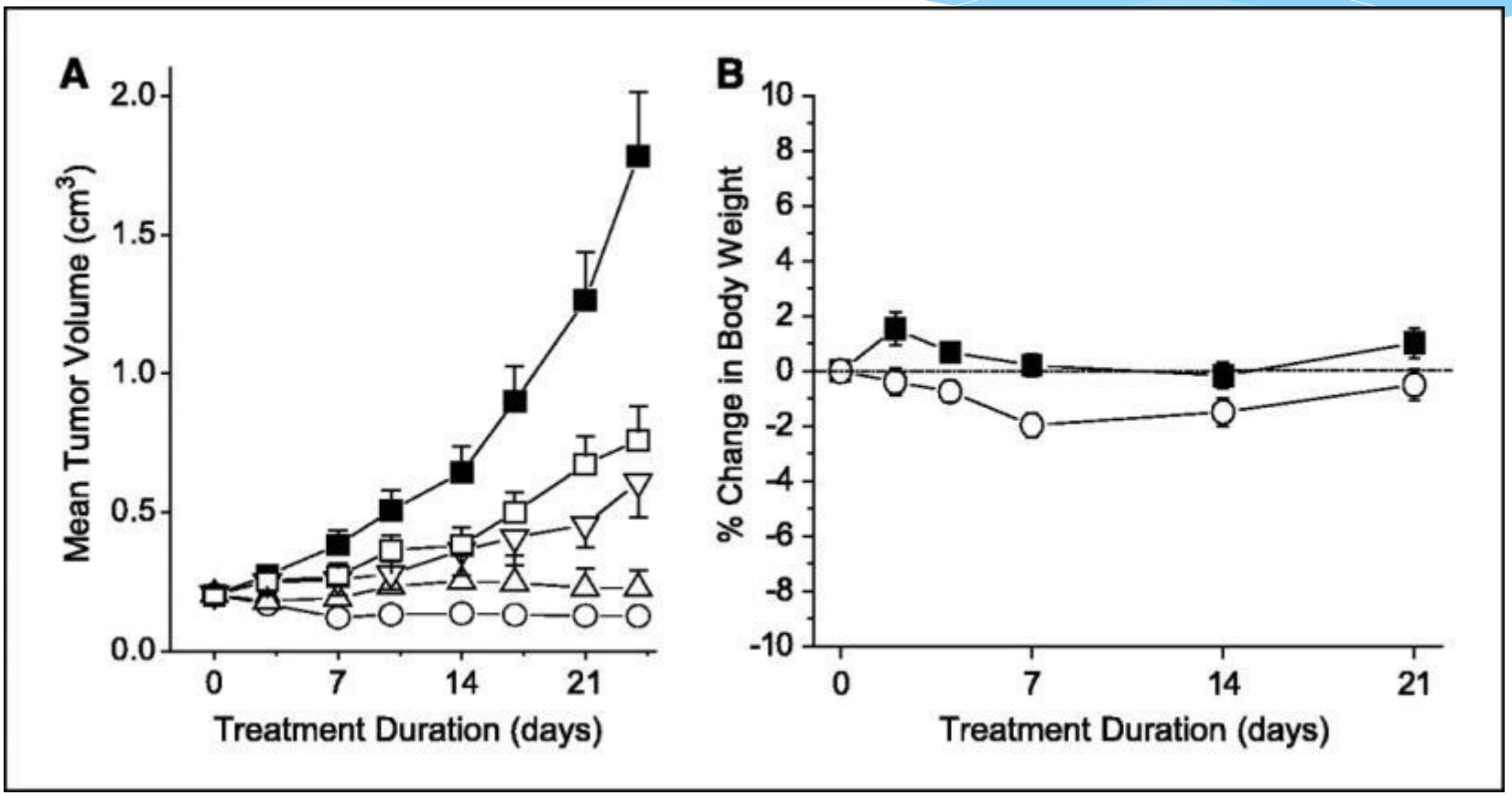
# AZD2171 causes vascular regression in Calu-6 lung tumor xenografts.




**Wedge S R et al. Cancer Res 2005;65:4389-4400**

# AZD2171 inhibits human tumor xenograft growth at doses that are well tolerated.




Wedge S R et al. Cancer Res 2005;65:4389-4400

# The agent: ADME

* Absorption
  * Route of administration
  * Bioavailability
* Distribution
  * Where does it go?
  * Blood-brain barrier?
  * Third-spacing or tissue reservoirs?
  * Plasma protein binding?

# The agent: ADME

* Metabolism:
  * CYP enzymes
  * Metabolites
* Excretion:
  * Routes of elimination
  * Organ(s) of excretion

# Preclinical Pharmacokinetics

* Raw data obtained:
  * Single-dose, multiple dose effects
  * Half-life (plasma, tissue)
  * Exposure (AUC)
  * $C_{max}$
* PK – toxicity relationships
* PK – efficacy relationships

# Preclinical PK: usefulness

* Inform decisions regarding
  * Route of administration
  * Intended ultimate dosing
    * Dose escalation schema based on PK-toxicity relationship
  * Schedule of administration
  * Concomitant medications avoided / allowed

# Preclinical Toxicology / Safety

* Initially can do limited safety pharmacology
  * This assesses vital organ function (CVS, Resp, CNS)
  * EKG / telemetry (QTc prolongation); hERG activity
  * This may halt development prior to significant investment
  * Not mandatory for agents intended for advanced cancer

# Preclinical Toxicology / Safety

* Comprehensive PharmTox objectives
  1. Estimate safe starting dose for clinical studies
  2. Assess toxic effects on target organs (clinical and histopathological) to guide patient monitoring
  3. Assess reversibility of drug effects
  4. Study various dosing schedules

# PharmTox

* In general 2 mammalian species, rodent + non-rodent
  * Typically rat and dog
* GLP certified labs
  * Quality control, confidence in results
* Single-dose and multiple-dose studies
  * Several dose levels
  * Uses the proposed clinical formulation
  * Proposed route of administration
  * Determine life-threatening and non-life-threatening doses

# Single-Dose studies

* 2 species
* Range of doses, including up to MTD
* Determine NOAEL and $STD_{10}$
* PK / toxicokinetics

# Repeat Dosing Studies

* 2 species
* Clinical formulation
* Range of doses up to MTD
* Schedule(s) like those planned for clinical study

# Repeat Dosing Studies

| Clinical Schedule | Examples of non-clinical treatment |
|---|---|
| Once q3-4 weeks | Single dose |
| Daily x 5 q3w | Daily x 5 |
| Daily x 5 q2w | Daily x 5 alt. weeks x 2 dosing cycles |
| Weekly 3 / 4 | Once / week x 3 |
| 2-3 x per week | 2-3 x per week x 4 weeks |
| Daily | 4 weeks |
| Weekly | Weekly x 4 – 5 weeks |

ICH S9 guideline

# Repeat dose studies parameters assessed

| | Rat | Dog |
|---|---|---|
| Clinical observations; food/water consumption | Daily; starting pre-study | Daily; starting pre-study |
| Body weights | Daily; starting pre-study | > Twice weekly from pre-study |
| Ophthalmoscopy | Pre-study, week 4 and end of recovery (week 8) | Pre-study, week 4 and end of recovery (week 8) |
| ECG/BP | N/A | Pre-study, week 4 and end of recovery (week 8) |
| Clinical pathology | Weeks 2 and/or 4 and end of recovery (week 8) | Pre-study, weeks 2 and/or 4 and end of recovery (week 8) |
| Toxicokinetics | Day 1 and 28 (steady state) | Day 1 and 28 (steady state) |
| Necropsy, OW, BM, Histopathology | Main test (week 5) and recovery kill (week 9) | Main test (week 5) and recovery kill (week 9) |

# Repeat Dosing Studies

* Pathological examination done off-therapy important to show the reversibility of the findings
* Which are target organs for toxicity that will require monitoring during phase I?
* Of most concern are:
  1. Toxicities that are irreversible, esp if crucial organ (eyes, liver, heart etc)
  2. Dose-independent toxicities
  3. Toxicities that are not amenable to monitoring (for example, CNS toxicities)

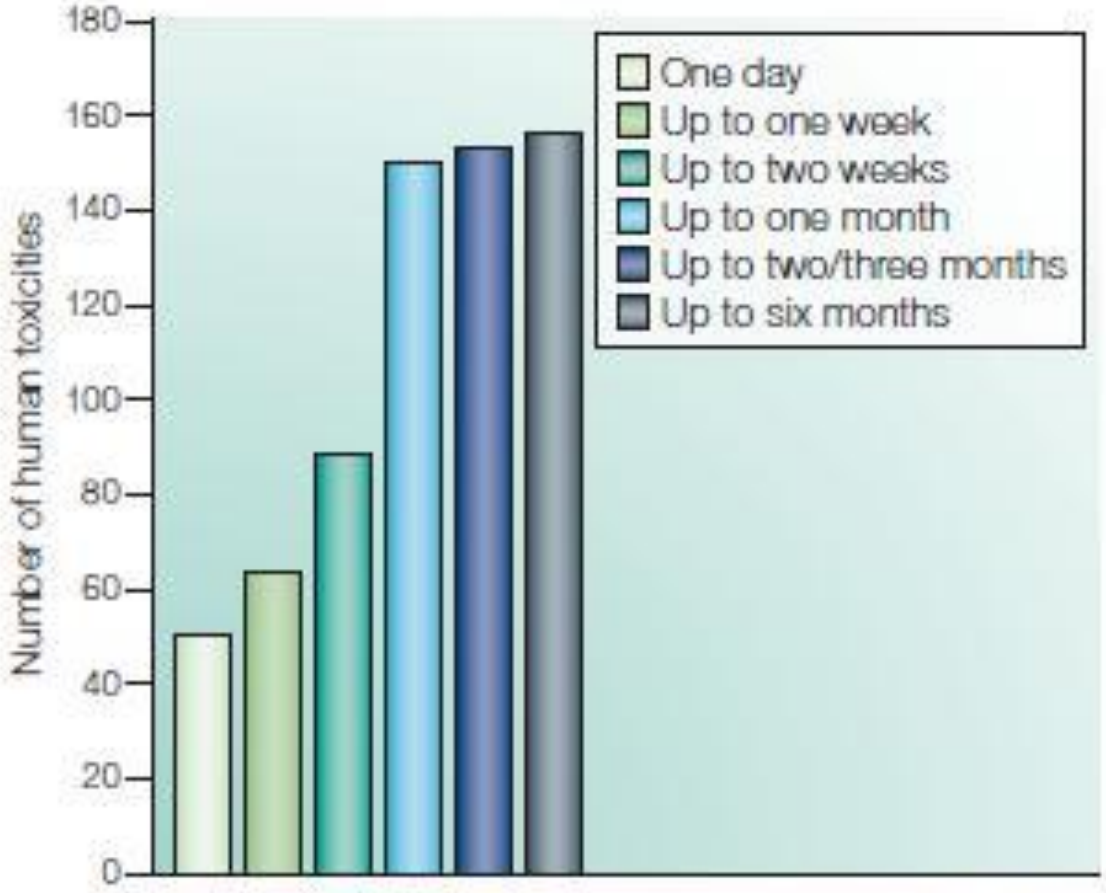


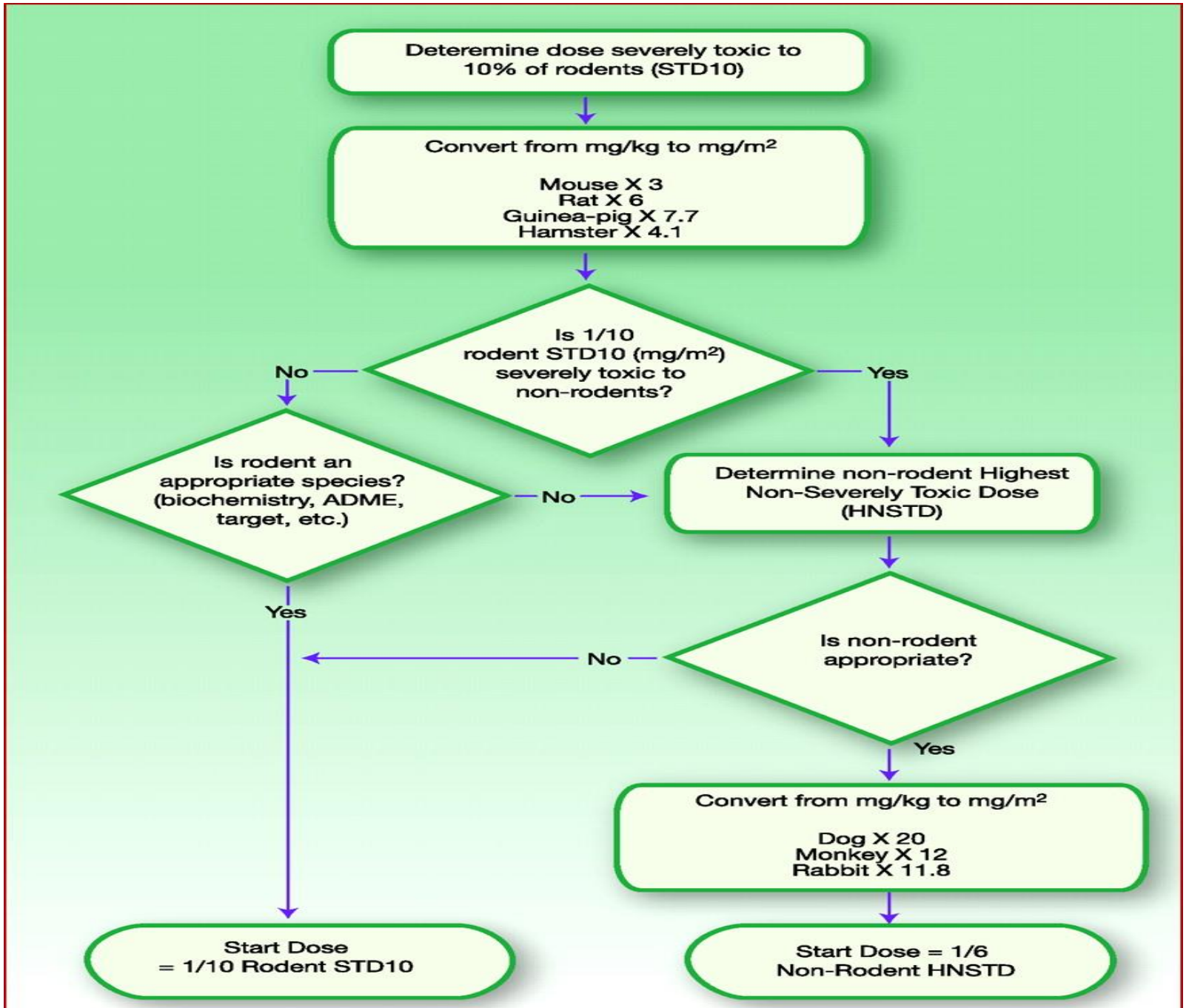

Figure 5 | **Time to first detection of animal toxicity.** The number of toxicities that can be detected in animal systems reaches a plateau at the one-month stage of the study. By this time, 94% of toxicities were detected, but prior to this time some toxicities were not apparent. On the first day, 25% of these observations were from safety pharmacology rather than from toxicology studies. Modified, with permission, from REF. 12 © (2002) Elsevier Science.

# Safe Starting Dose

* Determine $STD_{10}$ in rodent in mg / kg
* Convert to mg / $m^2$ using known conversion factor
* Safe starting dose in humans is one tenth of $STD_{10}$

* In non-rodents, determine the HNSTD in mg / kg
* Convert to mg / $m^2$ using known conversion factor

* Generally, starting dose is the lowest of the two
  * Sometimes unusual situations (eg dogs and platinum)





Senderowicz A M Clin Cancer Res 2010;16:1719-1725

# Safe Starting Dose

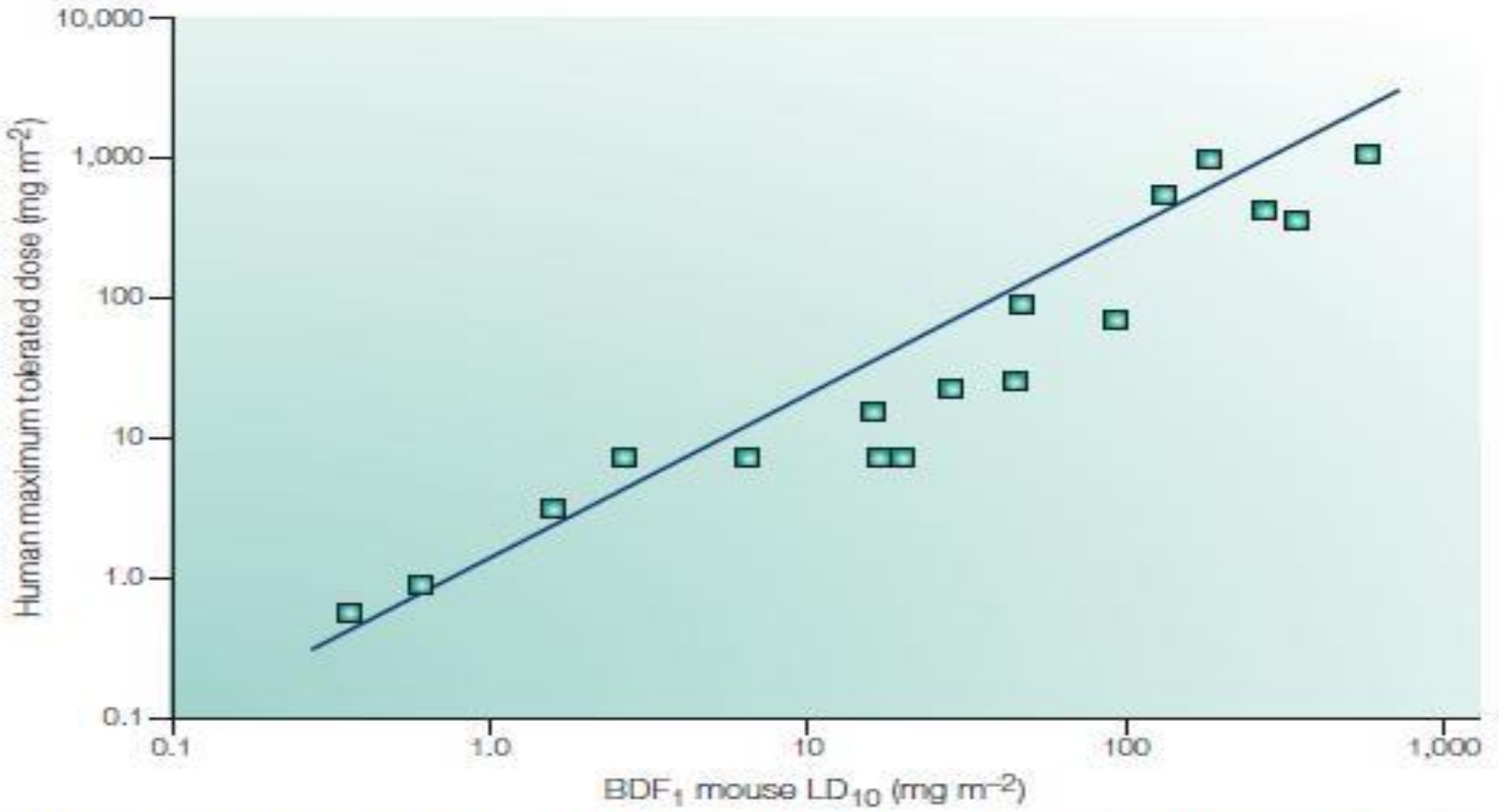



Figure 6 | **Correlation of lethal dose 10% ($LD_{10}$) in $BDF_1$ mice with the human maximum tolerated dose for anticancer drugs**[18]. The relationship between humans and mice (as well as rats, dogs and monkeys) are close to unity when compared on the basis of mg per $m^2$ rather than mg per kg.

# Limitations of preclinical studies

* Much of the data regarding this is quite old, particularly specifically concerning anticancer agents
  * Older data only classical cytotoxic agents
  * Little data regarding newer molecular entities, biologicals, immunomodulating drugs
  * Cautionary tale:  TGN1412

# Limitations of preclinical studies

* Concordance between animals and humans is not perfect
  * International Life Sciences Workshop 1999
  * 12 pharma companies, 150 compounds with 221 human toxicities
  * 43 % concordance with rodents alone
  * 63 % concordance with non-rodents alone
  * 71 % concordance with both

  * 30 % of toxicities in humans aren't predicted by animal models

# Limitations of preclinical studies

* Greatest concordance:
  * Hematological / bone marrow
  * Gastrointestinal (dogs >> monkeys, which don't vomit)
  * Cardiovascular

* Less concordance:
  * CNS
  * Dermatological / alopecia
  * Hepatotoxicity

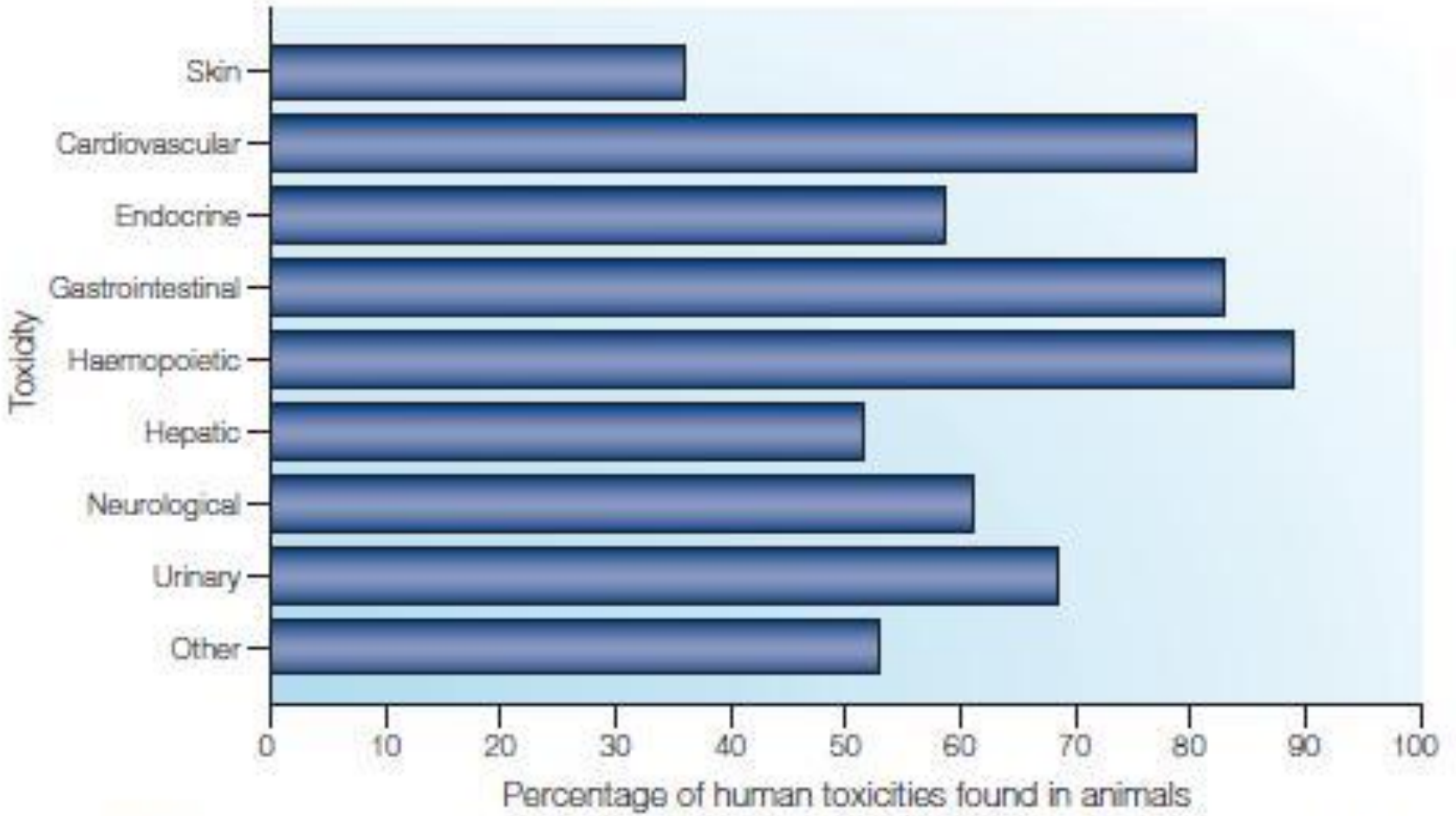



Figure 4 | **Percentage concordance between animal and human toxicities, grouped by organ.** Similarly to data on anticancer drugs, correlation is better for toxicities in the gastrointestinal tract, and haemopoietic and cardiovascular systems. Modified, with permission, from REF. 12 © (2002) Elsevier Science.

# Limitations of preclinical studies

Table 1 | **Cross-species comparison of adverse effects of 21 anticancer drugs[17]**

| Type of toxicity | Number showing toxicity in humans | Number showing toxicity in rodent/ number tested | Number showing toxicity in dogs/ number tested | Number showing toxicity in monkey/ number tested |
|---|---|---|---|---|
| Gastrointestinal | 13 | 9/11 | 12/13* | 6/7 |
| Bone marrow including thrombocytopaenia | 13* | 9/12* | 11/13* | 6/6 |
| Hepatic | 6 | 5/6‡ | 6/6 | None tested |
| Renal | 3 | 3/3 | 3/3 | 3/3 |
| Nervous system | 7 | 2/6* | 2/7 | 2/3 |
| Alopecia or dermatitis | 6 | 0/6 | 0/6 | 0/1 |

*One positive finding deemed borderline; ‡two positive findings deemed borderline.

# Limitations of preclinical studies

* Animals cannot communicate subjective symptoms:
  * Nausea
  * Dizziness
  * Pain, Injection site discomfort
  * Visual, auditory disturbance
    * Eg crizotinib

# Conclusions

* Preclinical data help inform phase I trial design
  * Go / no go decision
  * Schedule of administration
  * Monitoring for toxicities in phase I
* Evidence for the current standards is old, has significant limitations, but is the best we have