# Prerequisites for Therapeutic Studies

## What do you need to know before going into the clinic?

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# Clinical Scenario

- A scientist from a lab in your University approaches you about a drug he has discovered by high throughput screening of agents that targets the product of a new oncogene CUREALL-1
- Works amazingly *in vitro* and *in vivo* in a cancer cell line
- No effects on benign fibroblasts
- No bad effects on the mice during the *in vivo* experiments
- They have 1 kg of the stuff ready to go
- Wants you to take drug into humans now

# What do you do?

- Say “Yes, of course!” because you should always say “yes” as a new investigator
- Say “No” because you’ve already said “yes” to too many things
- Say “Maybe…”

# Prerequisites for Therapeutic Studies

- Drug development process
- What do you need to know before going into the clinic?
  - The target
  - The drug
  - Efficacy studies
  - Safety studies
  - Biomarker assays

# The Drug Development Process

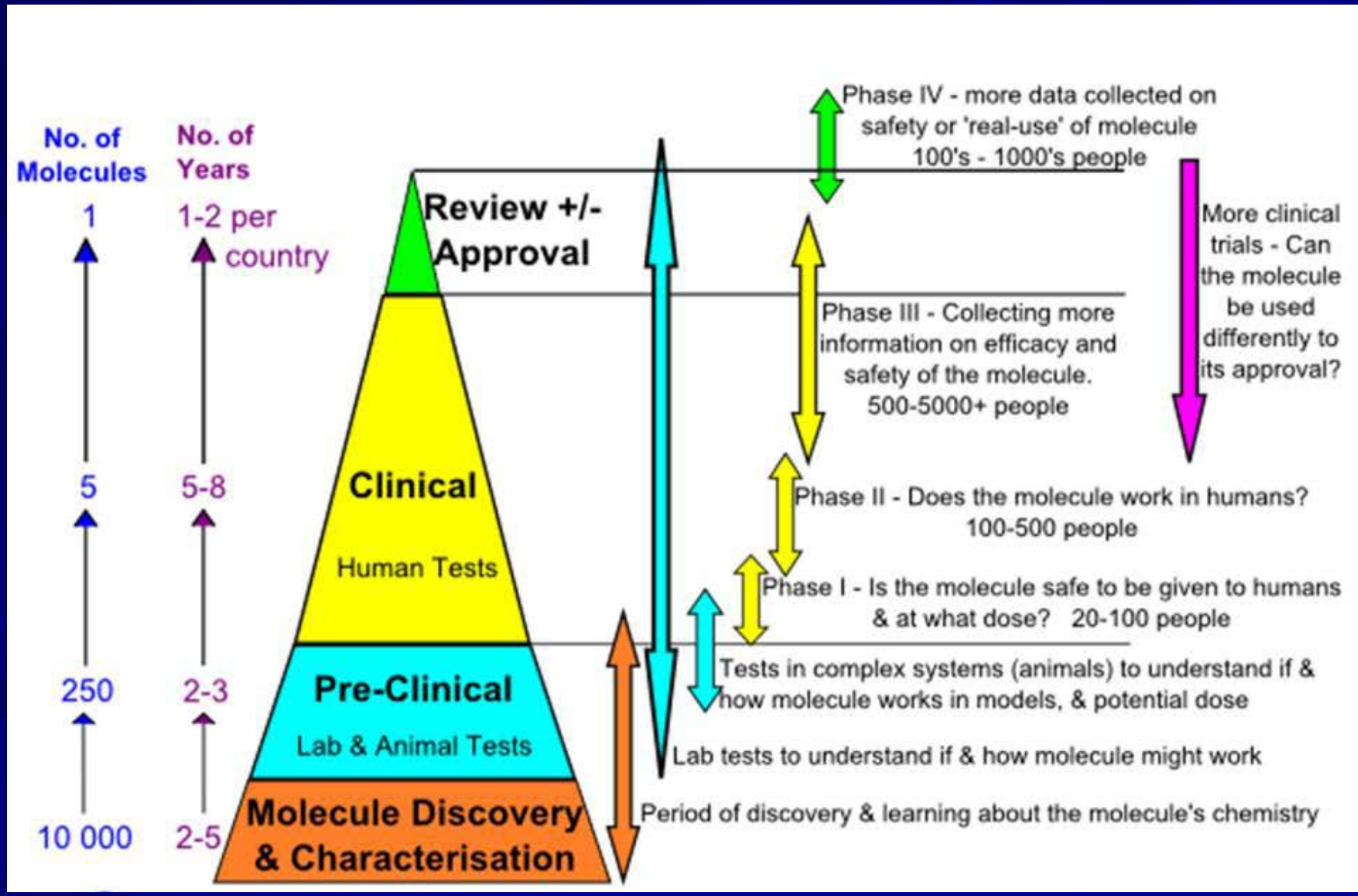
- 502 new drugs approved between 1990-2005
- 68 new oncology compounds

**Table 1.** New Oncology Compounds Approved in the United States, 1990-2005

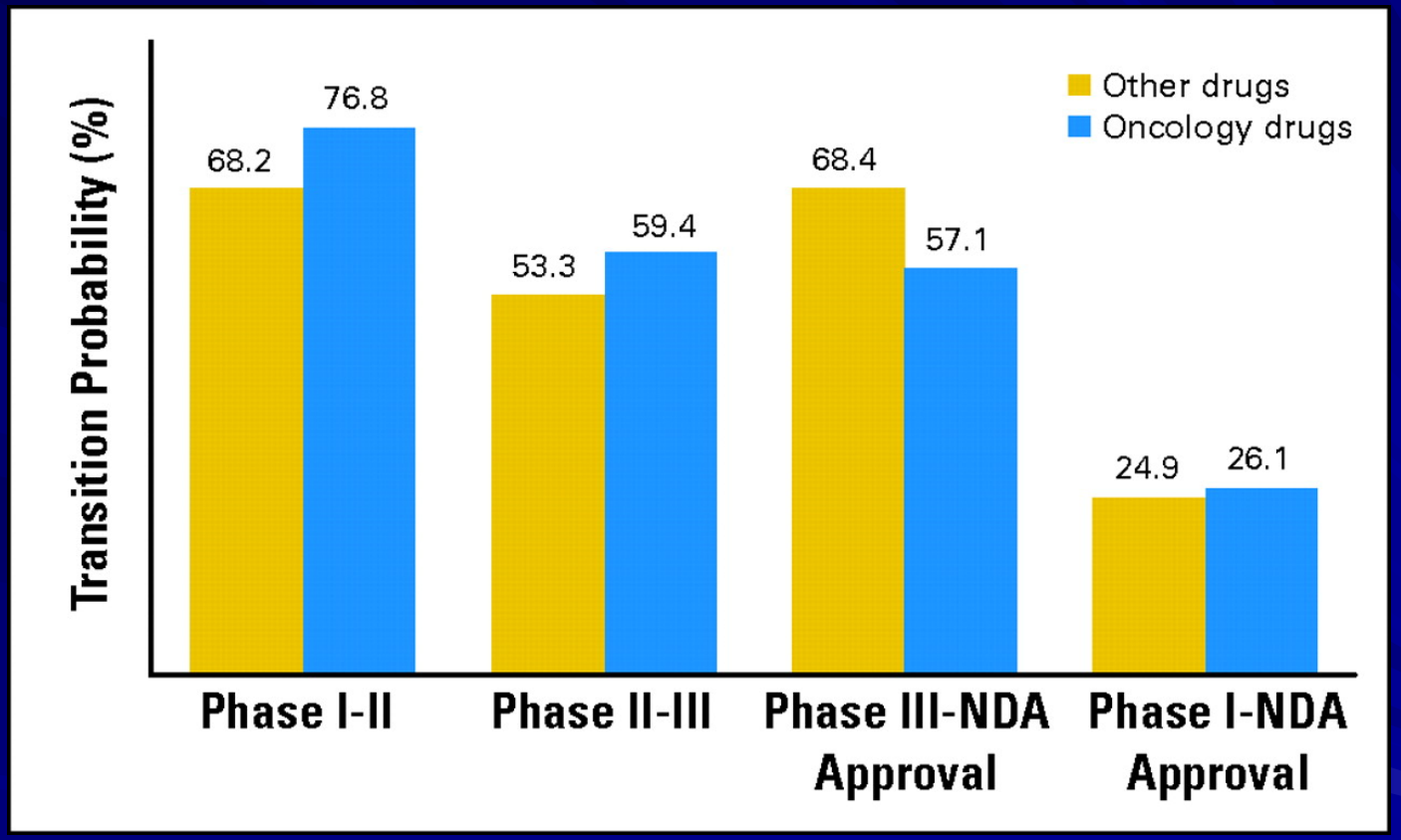
| Generic Name | Trade Name | Sponsor | NDA Submission Date | NDA Approval Date |
|---|---|---|---|---|
| Abarelix | Plenaxis | Praecis | 12/12/2000 | 11/25/2003 |
| Aldesleukin | Proleukin | Chiron | 12/1/1988 | 5/5/1992 |
| Alemtuzumab | Campath | Berlex | 12/23/1999 | 5/7/2001 |
| Alfuzosin | Uroxatral | Sanofi-Synthelabo | 12/8/2000 | 6/12/2003 |
| Alitretinoin | Panretin | Ligand | 5/27/1998 | 2/2/1999 |
| Altretamine | Hexalen | U.S. Bioscience | 12/19/1988 | 12/26/1990 |
| Amifostine | Ethyol | U.S. Bioscience | 9/30/1991 | 12/8/1995 |
| Aminolevulinic acid | Levulan Kerastick | Dusa | 7/1/1998 | 12/3/1999 |
| Anastrozole | Arimidex | Zeneca | 3/29/1995 | 12/27/1995 |
| Aprepitant | Emend | Merck | 9/27/2002 | 3/26/2003 |
| Arsenic trioxide | Trisenox | Cell Therapeutics | 3/28/2000 | 9/25/2000 |
| Azacitidine | Vidaza | Pharmion | 12/29/2003 | 5/19/2004 |
| Bcg, live | Pacis | Biochem Pharma | 4/21/1995 | 3/9/2000 |
| Bevacizumab | Avastin | Genentech | 9/30/2003 | 2/26/2004 |
| Bexarotene | Targretin | Ligand | 6/23/1999 | 12/29/1999 |
| Bicalutamide | Casodex | Zeneca | 9/14/1994 | 10/4/1995 |
| Bortezomib | Velcade | Millennium | 1/21/2003 | 5/13/2003 |
| Capecitabine | Xeloda | Roche | 10/31/1997 | 4/30/1998 |
| Cetuximab | Erbitux | Imclone | 8/14/2003 | 2/12/2004 |
| Cladribine | Leustatin | Ortho | 12/31/1991 | 2/26/1993 |
| Clofarabine | Clolar | Genzyme | 3/30/2004 | 12/28/2004 |
| Denileukin diftotox | Ontak | Ligand Pharmaceuticals | 12/9/1997 | 2/5/1999 |
| Dexrazoxane | Zinecard | Pharmacia | 2/10/1992 | 5/26/1995 |
| Docetaxel | Taxotere | Rhone-Poulenc Rorer | 7/27/1994 | 5/14/1996 |
| Dolasetron mesylate | Anzemet | Hoechst Marion Roussel | 9/29/1995 | 9/11/1997 |
| Dutasteride | Avodart | Glaxo Wellcome | 12/21/2000 | 11/20/2001 |
| Epirubicin | Ellence | Pharmacia & Upjohn | 12/15/1998 | 9/15/1999 |
| Erlotinib | Tarceva | Osi/Genentech | 7/30/2004 | 11/18/2004 |
| Exemestane | Aromasin | Pharmacia & Upjohn | 12/21/1998 | 10/21/1999 |
| Finasteride | Proscar | Merck | 4/15/1991 | 6/19/1992 |
| Fludarabine phosphate | Fludara | Berlex | 11/24/1989 | 4/18/1991 |
| Fulvestrant | Faslodex | Astrazeneca | 3/28/2001 | 4/25/2002 |
| Gefitinib | Iressa | Astrazeneca | 8/5/2002 | 5/5/2003 |
| Gemcitabine hydrochloride | Gemzar | Lilly | 2/2/1995 | 5/15/1996 |
| Gemtuzumab ozogamicin | Mylotarg | Wyeth-Ayerst | 10/29/1999 | 5/17/2000 |
| Granisetron hydrochloride | Kytril | Smithkline Beecham | 4/14/1992 | 12/29/1993 |
| Ibritumomab tiuxetan | Zevalin | Idec | 11/1/2000 | 2/19/2002 |
| Idarubicin hydrochloride | Idamycin | Adria Labs | 8/31/1989 | 9/27/1990 |
| Imatinib mesylate | Gleevec | Novartis | 2/27/2001 | 5/10/2001 |
| Irinotecan hydrochloride | Camptosar | Pharmacia & Upjohn | 12/28/1995 | 6/14/1996 |
| Lenalidomide | Revlimid | Celgene | 4/7/2005 | 12/27/2005 |
| Letrozole | Femara | Novartis | 7/25/1996 | 7/25/1997 |
| Levamisole hydrochloride | Ergamisol | Janssen | 11/1/1989 | 6/18/1990 |
| Masoprocol cream, 10% | Actinex | Chemex/Reed & Carnick | 4/10/1989 | 9/4/1992 |
| Nelarabine | Arranon | Glaxosmithkline | 4/29/2005 | 10/28/2005 |
| Nilutamide | Nilandron | Hoechst Marion Roussel | 3/7/1994 | 9/19/1996 |
| Oxaliplatin | Eloxatin | Sanofi | 6/24/2002 | 8/9/2002 |
| Paclitaxel | Taxol | Bristol-Myers Squibb | 7/22/1992 | 12/29/1992 |
| Palifermin (kgf) | Kepivance | Amgen | 6/24/2004 | 12/15/2004 |
| Palonosetron | Aloxi | Helsinn Healthcare | 9/27/2002 | 7/25/2003 |
| Pegaspargase | Oncospar | Enzon | 1/1/1991 | 2/1/1994 |
| Pemetrexed | Alimta | Eli Lilly | 9/30/2003 | 2/4/2004 |
| Pentostatin | Nipent | Warner-Lambert | 2/11/1991 | 10/11/1991 |
| Porfimer | Photofrin | Qlt | 4/13/1994 | 12/27/1995 |
| Rasburicase | Elitek | Sanofi-Synthelabo | 12/16/1999 | 7/12/2002 |
| Rituximab | Rituxan | Genentech | 2/28/1997 | 11/26/1997 |
| Samarium sm 153 lexidronam | Quadramet | Cytogen | 6/13/1995 | 3/28/1997 |
| Sorafenib | Nexavar | Bayer/Onyx | 7/8/2005 | 12/20/2005 |
| Temozolomide | Temodar | Schering-Plough | 8/13/1998 | 8/11/1999 |
| Teniposide | Vumon | Bristol-Myers Squibb | 9/28/1990 | 7/14/1992 |
| Topotecan hydrochloride | Hycamtin | Smithkline Beecham | 12/22/1995 | 5/28/1996 |
| Toremifene citrate | Fareston | Orion/Schering | 1/3/1995 | 5/29/1997 |
| Tositumomab-i131 | Bexxar | Corixa | 9/15/2000 | 6/27/2003 |
| Trastuzumab | Herceptin | Genentech | 5/4/1998 | 9/25/1998 |
| Triptorelin pamoate | Trelstar Depot | Pharmacia | 6/26/1996 | 6/15/2000 |
| Valrubicin | Valstar | Anthra Pharmaceuticals | 12/31/1997 | 9/25/1998 |
| Vinorelbine tartrate | Navelbine | Burroughs Wellcome | 8/27/1993 | 12/23/1994 |
| Zoledronic acid | Zometa | Novartis | 12/21/1999 | 8/20/2001 |

Abbreviation: NDA, new drug application.

# The Drug Development Process: Attrition



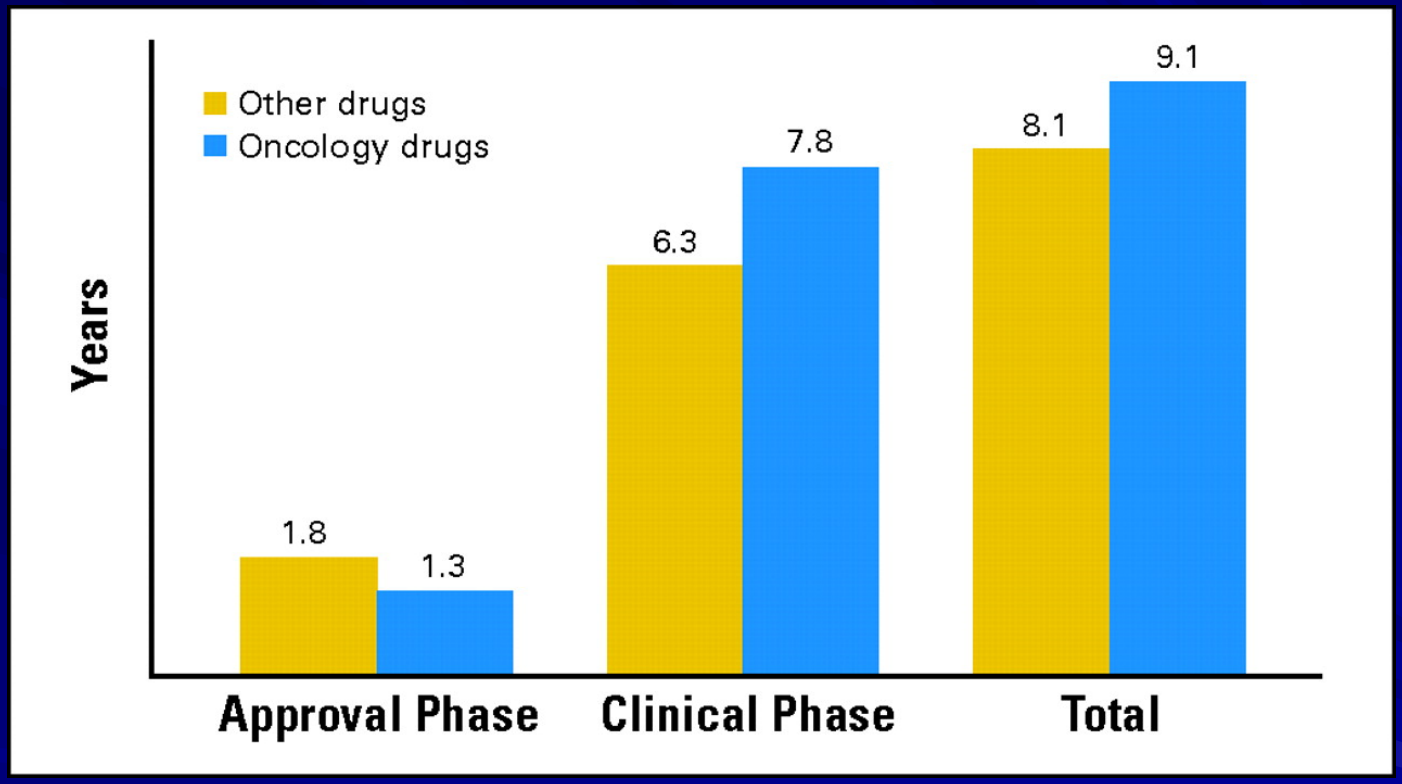
# The Drug Development Process: Time




**Clinical phase transition probabilities for investigational oncology and all compounds for the 20 largest firms by pharmaceutical sales for compounds that first entered clinical testing during 1993-2002**

DiMasi JA, JCO, 25:209, 2007

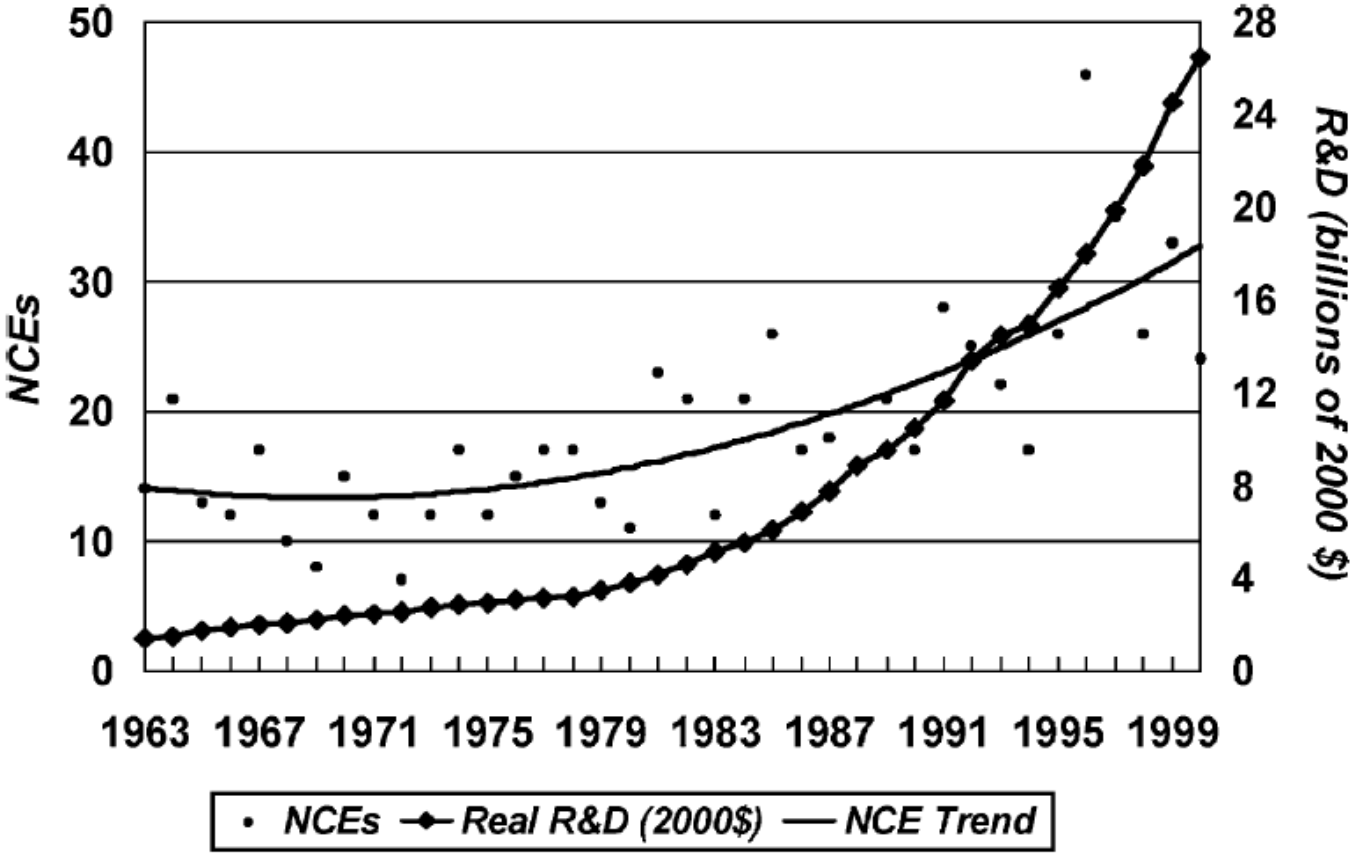
# The Drug Development Process: Time




**Mean clinical development and regulatory approval times for new oncology and other therapeutic molecular entities approved by the US Food and Drug Administration from 1990 to 2005**

DiMasi JA, JCO, 25:209, 2007

# The Drug Development Process: Money




DiMasi JA, J Health Economics, 22:151, 2003

# The Drug Development Process: Money

**EXHIBIT 5**
**Probability Of Market Entry, Durations, And Costs For New Drugs, By Disorder And Primary Indication**

| | | Entry probability (%) | | | Duration (months) | | | |
|---|---|---|---|---|---|---|---|---|
| **Disorder** | **N** | **Phase II** | **Phase III** | **Approval** | **Phase I** | **Phase II** | **Phase III** | **Cost ($)** |
| Blood | 163 | 60 | 57 | 25 | 18 | 32 | 33 | 906 |
| Cardiovascular | 280 | 69 | 42 | 22 | 14 | 35 | 30 | 887 |
| Cancer | 681 | 78 | 46 | 20 | 21 | 30 | 29 | 1,042 |
| Musculoskeletal | 134 | 73 | 41 | 22 | 19 | 39 | 30 | 946 |
| Neurological | 192 | 73 | 47 | 22 | 20 | 39 | 32 | 1,016 |
| Antiparasitic | 20 | 100 | 67 | 53 | 18 | 33 | 13 | 454 |
| Respiratory | 165 | 68 | 31 | 16 | 18 | 30 | 36 | 1,134 |
| Sensory | 53 | 88 | 60 | 40 | 11 | 44 | 30 | 648 |
| **Primary indication** | | | | | | | | |
| Alzheimer's disease | 46 | 65 | 46 | 25 | 17 | 37 | 18 | 903 |
| Rheumatoid arthritis | 51 | 91 | 33 | 23 | 18 | 36 | 39 | 936 |
| Asthma | 74 | 81 | 36 | 26 | 18 | 33 | 31 | 740 |
| Breast cancer | 54 | 96 | 58 | 44 | 17 | 37 | 37 | 610 |
| HIV/AIDS | 89 | 83 | 56 | 44 | 22 | 22 | 19 | 479 |

**SOURCE:** Authors' calculations.

**NOTES:** Phases are for human clinical trials. New drug application (NDA) durations are as for the average drug. Cost is the total expected capitalized cost per new drug (in millions of 2000 dollars).

Adams CP, Health Affairs, 25:420, 2006

# Prerequisites for Therapeutic Studies

- Drug development process
- What do you need to know before going into the clinic?
  - The target
  - The drug
  - Efficacy studies
  - Safety studies
  - Biomarker assays

# The Target

- Biologically plausible: evidence that the target is important
  - Effects of knock-in/knock-out experiments
  - Role in pathogenesis of the disease
    - E.g. Bcr-Abl, c-KIT, VHL
  - Expression in clinical specimens
    - Which cancers, what percentage, what pattern
  - Prognostic/predictive
  - Previously successful drugging of target/pathway

# The Target

- Can be known and important but not specifically relevant to cancer biology
  - Microtubules
- May not be known
  - Mechanism of action was imprecisely known for many currently used chemotherapy agents
  - High-throughput screening of natural compounds for cytotoxic/cytostatic activity

# The Target

- Impacts on trial design
  - Go/No Go
    - Potentially worthwhile to take forward?
    - Well defined biology
    - Me too target
  - Patient population
    - All comers vs. enriched for tumour or target
    - Resistant vs. naive populations

# The Drug

- Production
  - GMP (Good Manufacturing Practise)
    - Minimum set of standards for manufacturing
  - Sufficient quantities, practical dosage forms
- Chemistry
  - Chemical class of the agent
    - E.g. Small molecule, antibody, antisense, peptides, natural product, analogue
    - Implications for preclinical testing
      - Toxicity
      - Efficacy
  - Formulation issues

# The Drug

- Absorption
  - Oral, IV
- Distribution
  - Sites of action
  - Tissue concentrations: reservoirs, blood brain barrier
- Metabolism and Excretion
  - CYP enzymes, metabolites, route/organs of excretion
- Pharmacokinetic profile
  - Maximum concentration ($C_{MAX}$), Exposure (AUC), Half-life (blood, tissue), Distribution
  - Accumulation and multiple dose effects
  - PK-Toxicity associations
  - PK-Efficacy associations

# The Drug

- Impacts on trial design
  - Route and method of administration
  - Schedule
  - Eligibility criteria
    - Renal and hepatic function
  - Concomitant medications
  - Selection of RP2D
    - MTD
    - PK
    - Efficacy

# Efficacy Studies

- Will it work? Does the agent effect the target?
  - *in silica, in vitro, in vivo*
  - Target/pathway: expression, phosphorylation
  - Downstream effect: apoptosis, angiogenesis, proliferation
  - Dose/plasma level vs. target/pathway inhibition vs. downstream effects
  - Compare to other agents especially if analogue or similar mechanism of action
  - Combination studies

# Efficacy Studies

- In vitro
  - Broad array of well characterized cell lines (e.g. US NCI 60-cell line panel)
  - Determine concentration and exposure effects (IC50)
    - Proliferation (e.g. colony forming assay)
    - Viability (e.g. MTT assay)
  - Explore mechanisms of resistance

# In Vivo Models/Parameters

| ***Parameter*** | ***Variables*** |
|---|---|
| Murine host | Immune competent mouse<br>Immune deficient mouse (nude or SCID mouse)<br>Transgenic mouse |
| Type of Tumour | Allograft cell line<br>Human Xenograft cell line<br>Spontaneous (e.g. in transgenic mouse) |
| Tumour Profile | Characterised with respect to key targets<br>Not characterised |
| Tumour location | Subcutaneous<br>Intraperitoneal<br>Orthotopic<br>Subrenal capsule<br>Hollow fibre |
| Drug route of administration | Oral<br>Intravenous<br>Intraperitoneal<br>Intratumoural |

# In Vivo Models/Parameters

| ***Parameter*** | ***Variables*** |
|---|---|
| Drug schedule | Continuous (daily)<br>Single dose<br>Intermittent (e.g. days 1, 5, 9)<br>Repeat dose (e.g. days 1-5) |
| Drug Dose | Single or multiple dose levels<br>Include MTD for each schedule or other doses |
| Timing of drug administration | At same time as tumour implantation<br>After implanted tumour is established/palpable<br>After implanted tumour has micrometastases<br>After implanted tumour has macrometastases<br>After resection of implanted tumour (“adjuvant”) |
| Measures of efficacy | Tumour regression<br>Tumour growth delay (%T/C)<br>Animal survival<br>Animal cures (or proportion long term survival) |

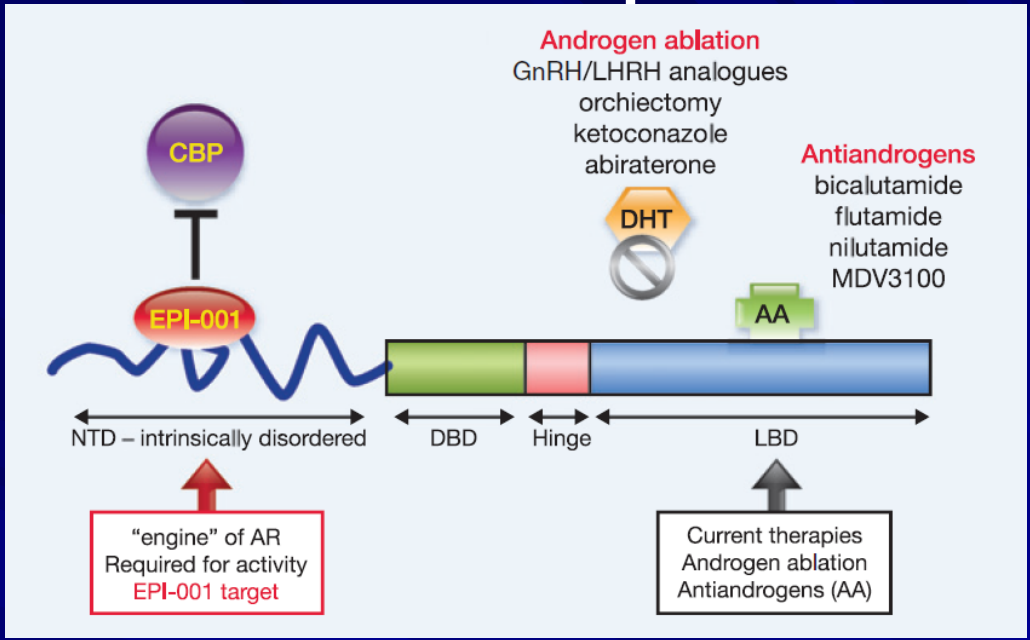
# Efficacy: General Considerations

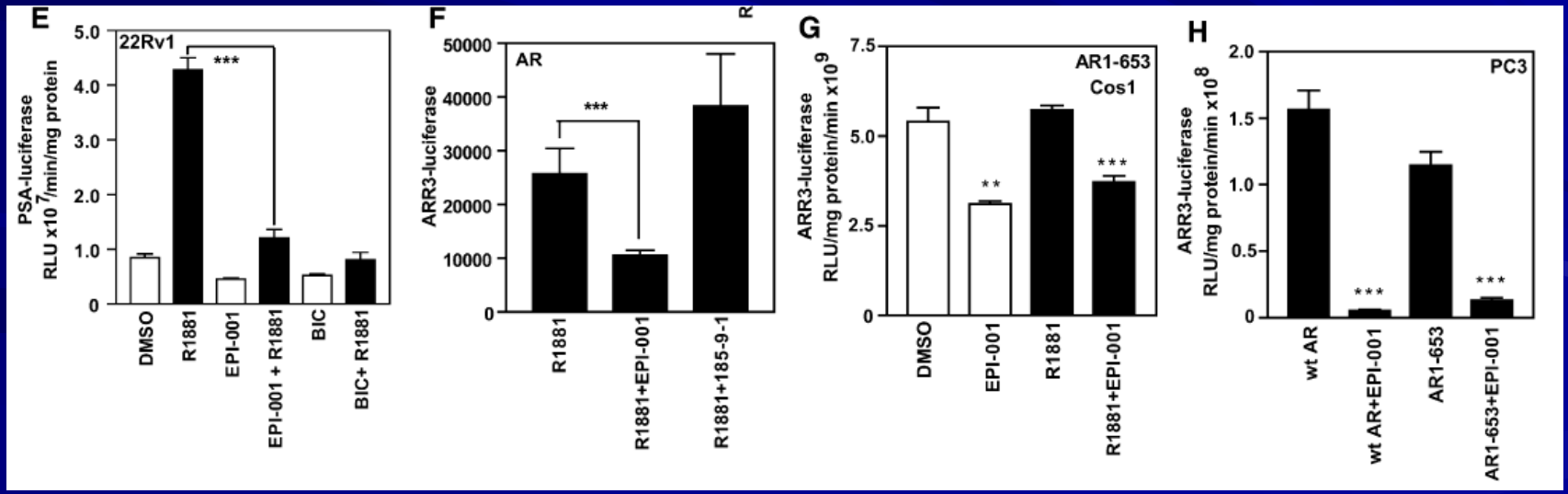
- No mandated studies
  - Up to the company and investigators
- Not predictive of success
  - Immortal, stable, homogenous, rapidly proliferating
  - But a high negative predictive value
- Want to have:
  - Multiple xenograft models (>2)
  - Models that establish the tumour +/- metastases prior to treatment
  - Models that use IV or PO administration
  - Dose response effects: plasma level–target–tumour
  - Comparisons, combinations

# Efficacy Studies

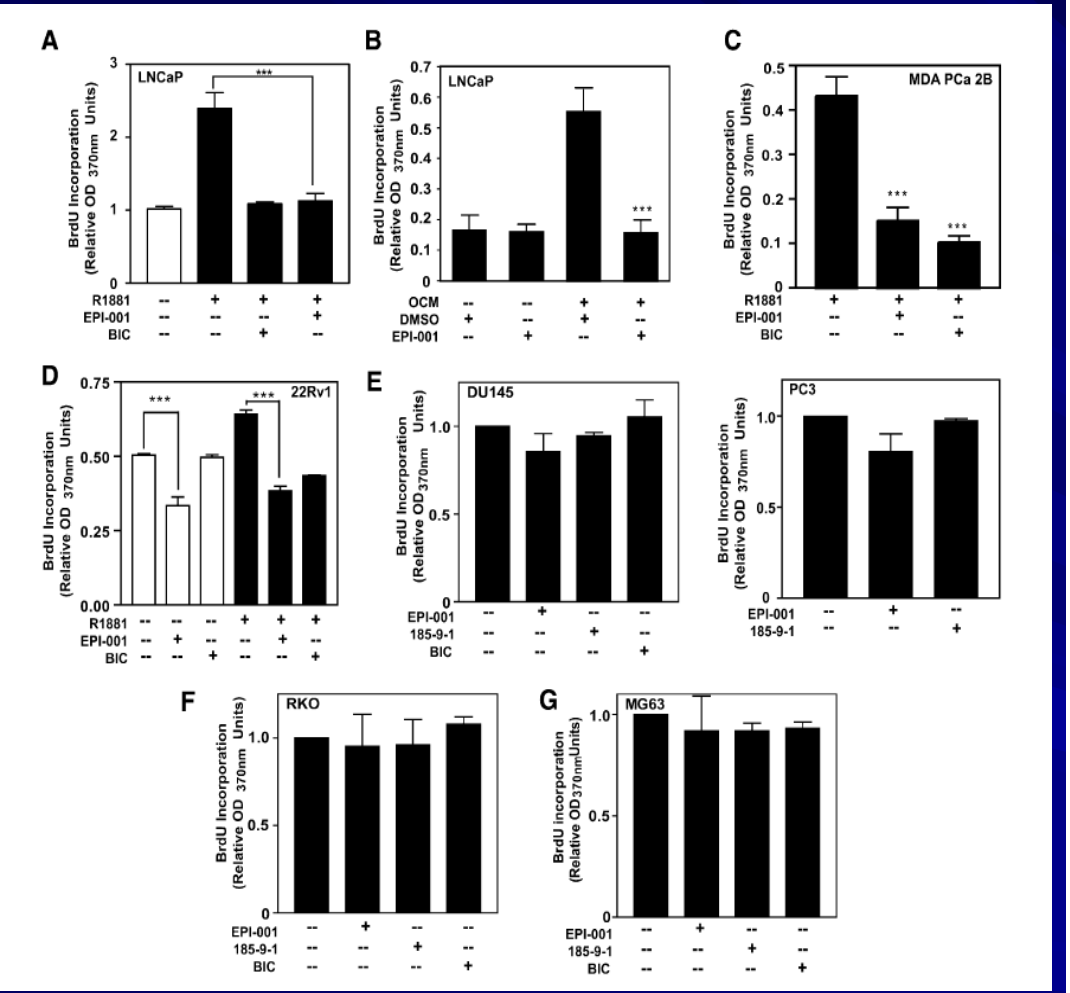
- Impact on trial design
  - Go/No Go:
    - Interesting enough to take forward?
    - Best compound to take forward?
    - Better than current standard?
  - Drug combinations
  - Tumour types

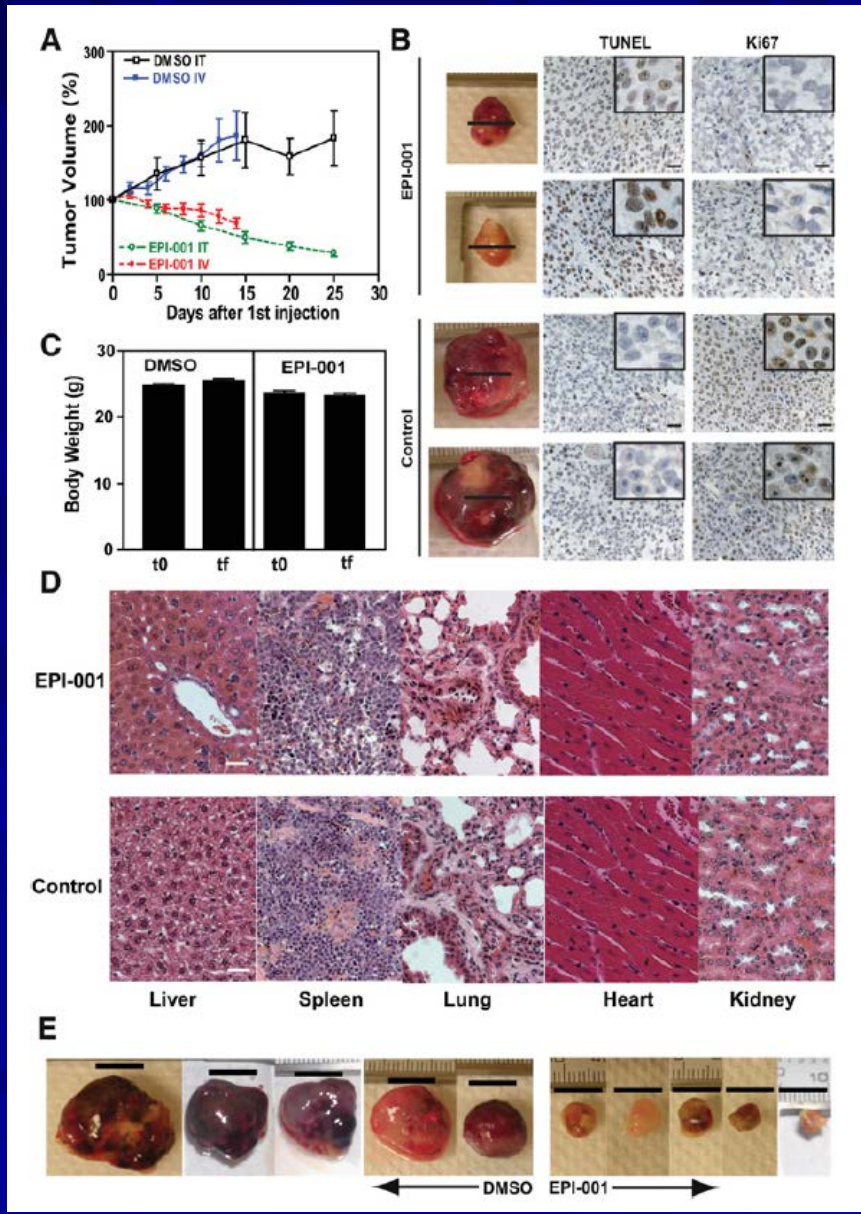
# An Example…




*MD Sadar, Cancer Res 71: 1208, 2011; RJ Andersen, Cancer Cell 17:535, 2010*




*MD Sadar, Cancer Res 71: 1208, 2011; RJ Andersen, Cancer Cell 17:535, 2010*

# The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- Previously major variations in the requirements for starting human clinical trials between regions
- ICH guidelines
  - Brings together health regulatory authorities from USA, Europe, Japan
  - Objective: economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health

http://www.ich.org/cache/compo/276-254-1.html

# Required Toxicology

| Type of toxicology | Requirements |
|---|---|
| Single Dose | • 2 species: rodent & non-rodent<br>• Clinical formulation<br>• Several doses studied<br>• Determine toxicity and organ effects<br>  • NOAEL, LD10<br>• PK for relationship to exposure and effects<br>• Species specific if required<br>  • Target<br>  • Toxic effects |
| Repeat dose | • 2 species: rodent & non-rodent<br>• Clinical formulation, dose and schedule<br>• Several dose levels<br>• Duration of treatment same as planned treatment duration in clinic<br>• Determine highest doses that can be safely administered, organ effects, severity and reversibility<br>• Species specific if required |

# Required Toxicology

| Type of toxicology | Requirements |
|---|---|
| Chronic Toxicity | • 2 species: rodent and non-rodent<br>• Clinical formulation, dose and schedule<br>• Duration of treatment:<br>  • Rodents: 6 months<br>  • Non-rodents: 9-12 months<br>• Determine chronic or late effects of treatment and their severity, reversibility<br>• May not be necessary prior to phase I |
| Safety pharmacology | • Evaluation for specific major organ effects<br>• Test system depends on organ system of concern or interest.<br>• Basic battery: cardiovascular, respiratory, CNS |
| Genotoxicity | • In vitro tests for mutations and chromosomal damage from the experimental agent. |
| Local toxicity | • Assessment of local tolerance using routes relevant to method of administration |

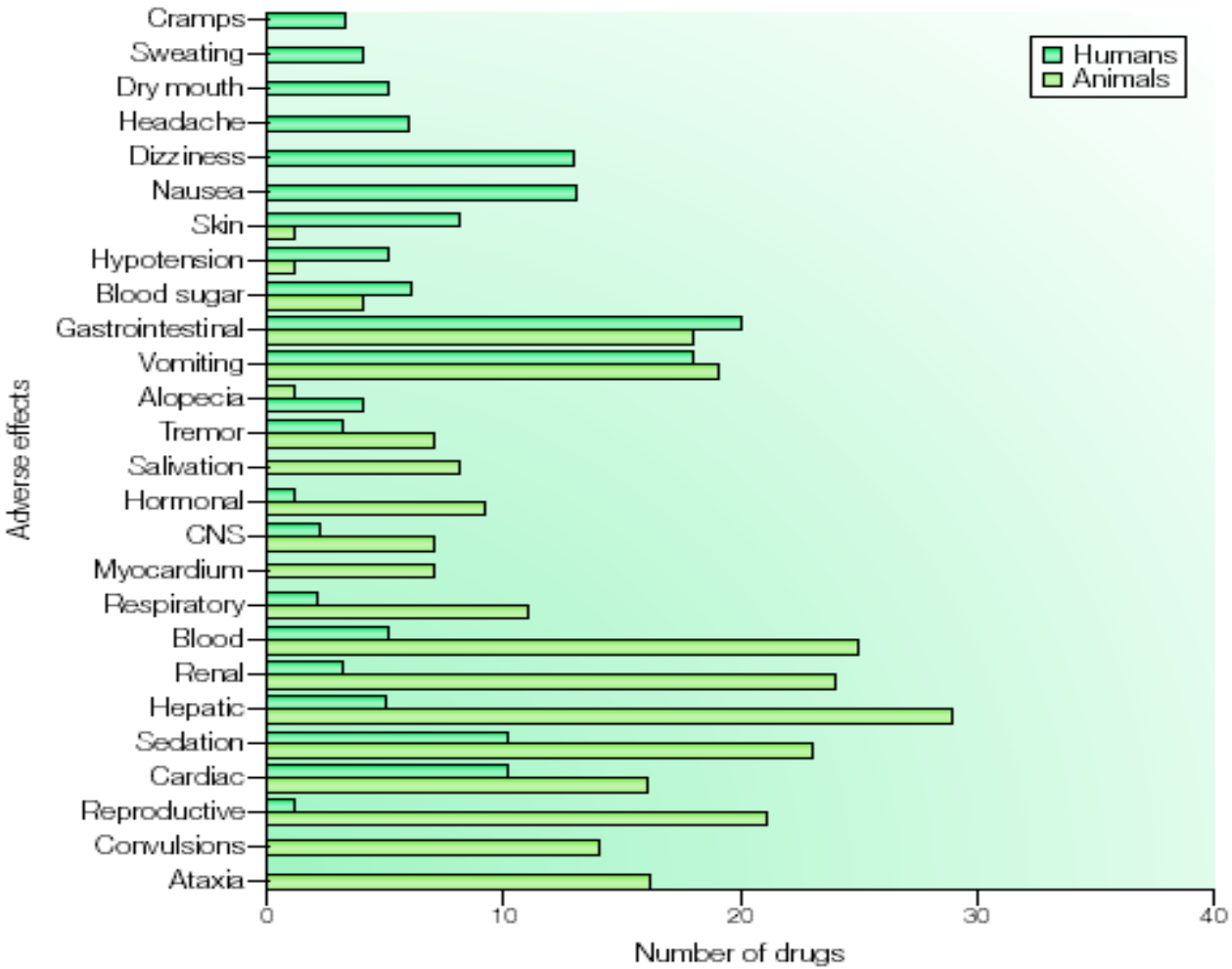



Figure 1 | **Animal and human toxicities of 45 drugs assessed by the Committee on Safety of Medicines in the United Kingdom during the eight or nine months prior to publication in 1978** (REF. 11). Data are for drugs of diverse therapeutic classes, including several cardiovascular and central nervous system drugs but only one anticancer agent. The six uppermost adverse effects were observed in humans but not in animals; the two adverse effects at the bottom of the graph were observed in animals but not in humans. For most adverse effects there is a degree of over- or under-prediction. CNS, central nervous system.

Greaves, Nature Drug Discovery, 2003

# Toxicology Studies

- Impact on trial design
  - Potential for toxicity in the clinical study
    - Therapeutic index
    - Eligibility criteria
    - Safety monitoring
    - Additional safety testing (ECG QT prolongation)
  - Selection of starting dose
    - 1/10$^{th}$ LD10 in rodents
    - 1/3-1/6 the TDL (Toxic Dose Low) in most sensitive species
  - Schedule and administration

# Biomarker Assay

- Biomarker
  - Factor that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

# Biomarker Assay

- Is it “valid”?
  - Analytical validation: does the assay measure what its supposed to measure in a reproducible and accurate fashion?
  - Clinical qualification: process of linking a biomarker with biological processes and clinical endpoints
  - Often initially developed in research laboratories under ideal conditions with ideal specimens. Clinical trial situation more complex:
    - Multi-centre, multi-personnel
    - Collection, handling and storage conditions
    - Practical issues: e.g. repeated fresh tissue biopsy

# Biomarker Assay

- Biomarkers in clinical trials
  - Proof of principal biologic activity on target in a patient
  - Optimization of dose and schedule (vs. MTD or PK)
  - Predictive marker for selection/stratification
  - Surrogate endpoint of clinical benefit

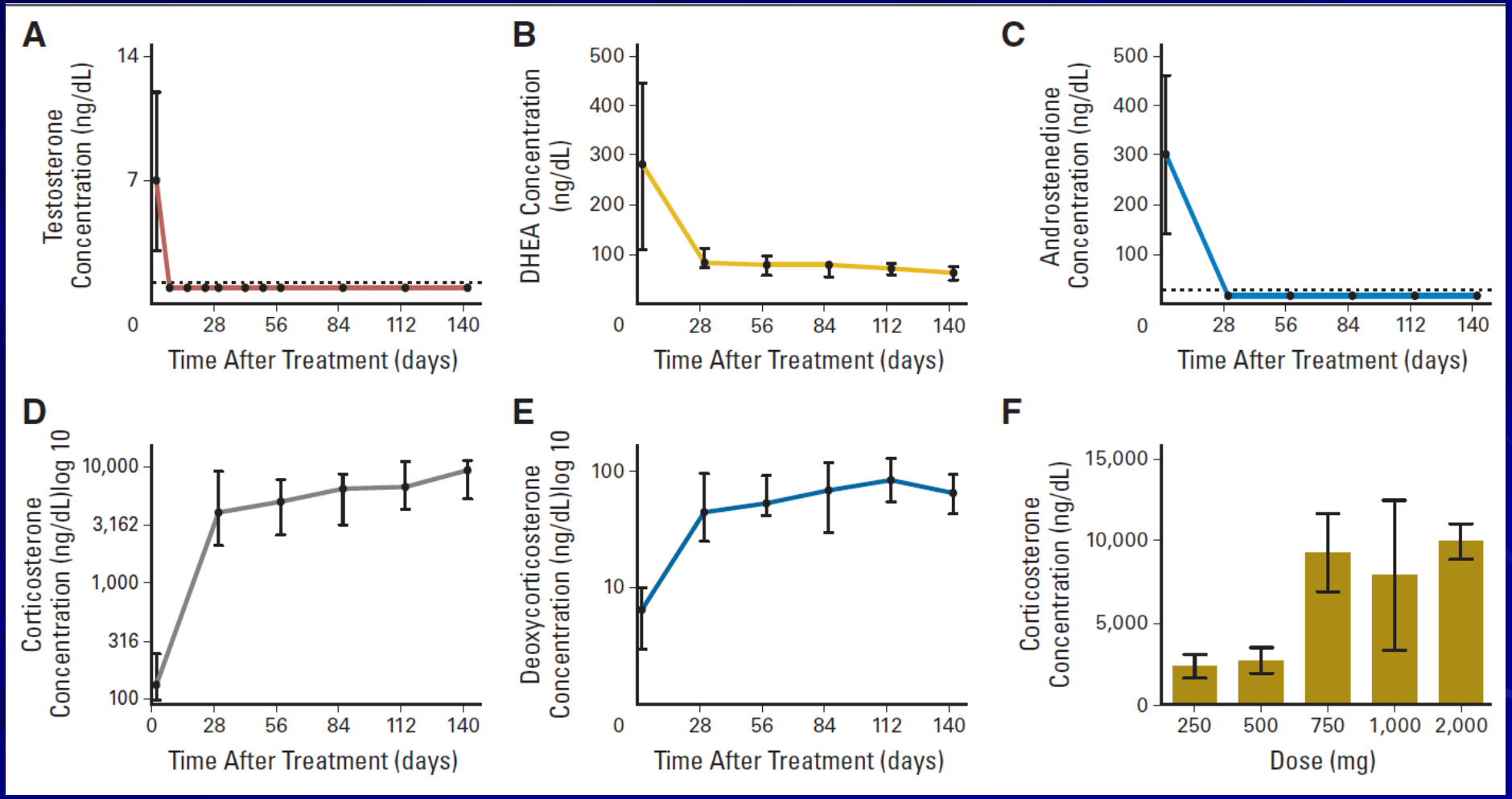
# Biomarker Assay

- Considerations
  - Assay performance
    - Accuracy, reproducibility
    - Qualitative vs. quantitative
    - Limits of detection
    - Handling processes optimized and characterized
  - Relationship between biomarker assay vs. dose/PK vs. anti-tumour efficacy
  - Time course: duration, recovery
  - Tumour vs. other tissues

# Biomarker Assay

- Impact on clinical trial design
  - To do or not to do? Will it provide useful information?
    - Increased complexity and cost
    - Limited patient numbers
    - Assay performance
  - Selection of patients
  - Timing of studies
  - Tissues to be sampled
  - Dose levels to include
    - All dose levels vs. 1 or 2 dose levels

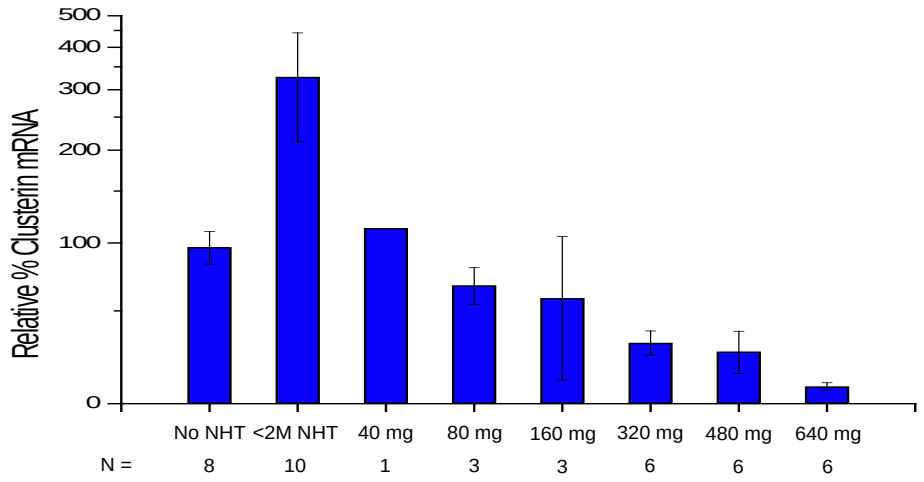
# Example: Simple



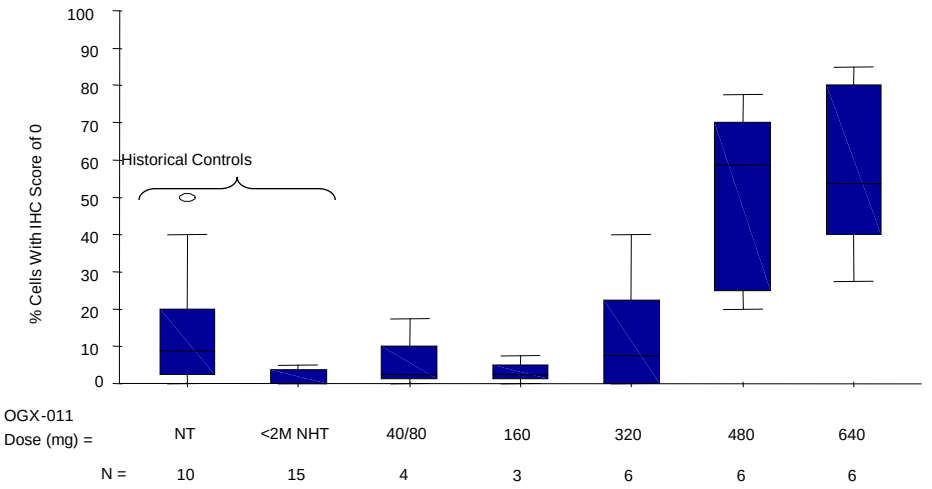

Attard, J Clin Oncol, 2008

# Example: Complex

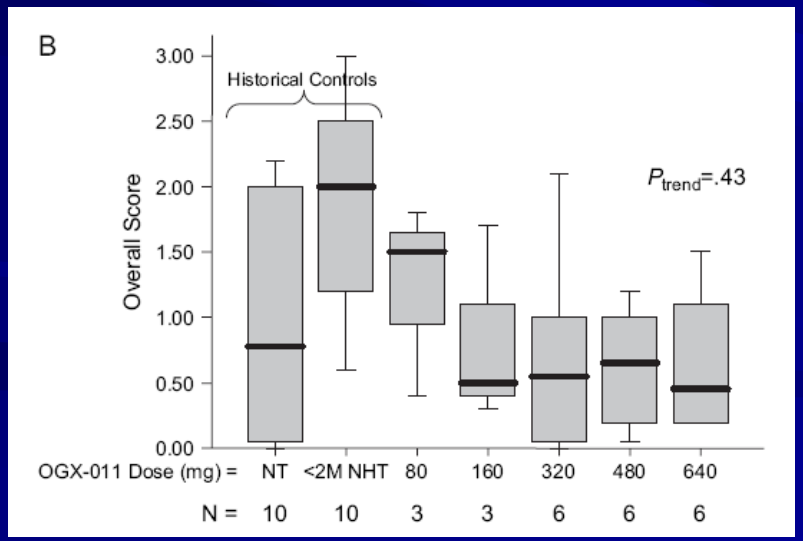
Inhibition of Clusterin mRNA: QRT-PCR



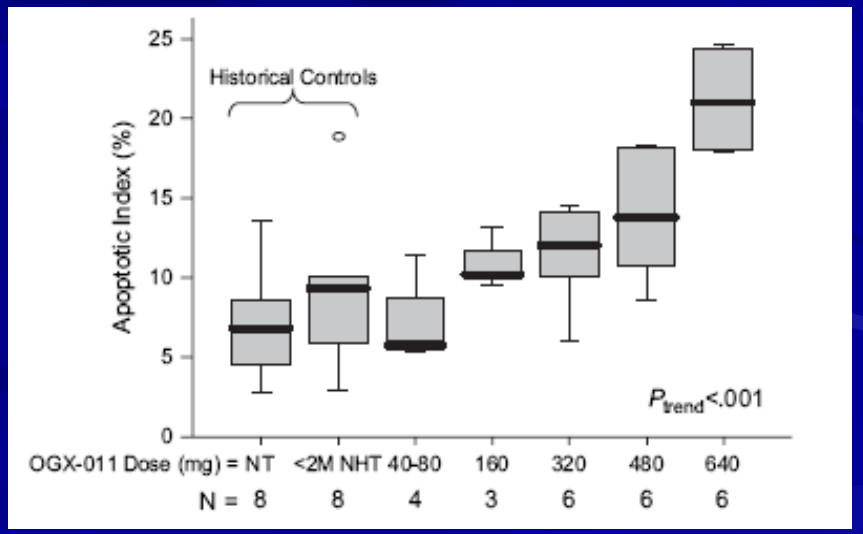

Inhibition of Clusterin Protein: IHC Score=0




Inhibition of Clusterin Protein: IHC Score




Apoptosis Index




Chi, J Natl Cancer Inst, 2005

# Investigator's Brochure

| *Major Headings* | *Details/content* |
|---|---|
| **Summary** | Highlight of significant physical, chemical pharmaceutical, pharmacological, toxicological, pharmacokinetic and clinical information |
| **Introduction** | Summary of chemical name, active ingredients, pharmacological class of drug, rationale for performing research and likely indications. Include at the end a summary of the approach to the clinical evaluation |
| **Physical, Chemical, Pharmaceutical properties and formulation** | |
| **Non-Clinical Studies** | Pharmacology: efficacy and mechanistic studies<br>Other studies: e.g. biomarker development<br>Pharmacokinetics and product metabolism<br>Relationship of PK to efficacy and toxicological findings<br>Toxicology |
| **Effects in Humans (If available)** | Pharmacokinetics and metabolism in humans<br>Safety and Efficacy<br>Marketing experience |
| **Summary of Data** | Guidance for the investigator |
| **References** | Publications and Reports |

# Ready to go!

1. Understanding of the drug development process
2. Understand the importance of considering preclinical data for protocol design
3. Understand the preclinical evaluation of novel therapeutics for efficacy, toxicology, biomarker development
4. Understand the regulatory requirements required to support phase I studies