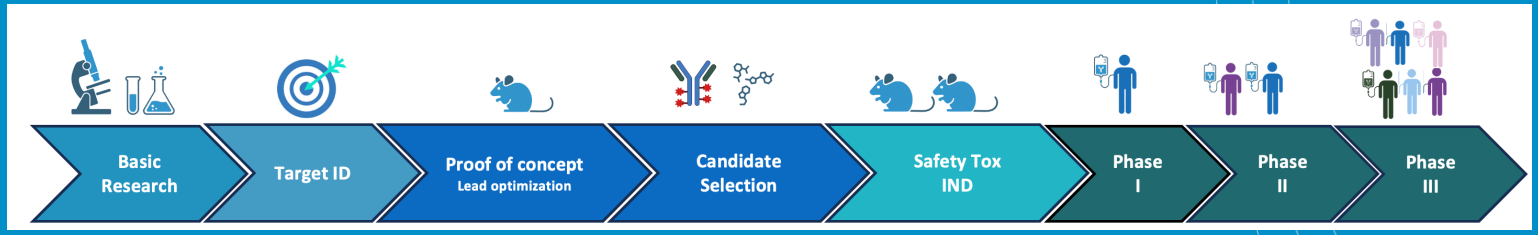
Memorial Sloan Kettering Cancer Center

INVESTIGATIONAL NEW DRUGS:
From preclinical development to first in human



Elisa de Stanchina, PhD

Steps in drugs development



Discovery – Early Development

- In vitro activity
- Selectivity
- Solubility
- Permeability
- Metabolic Stability
- Clearance
- Protein Binding
- CYP450 inhibition
- hERG inhibition

Late Preclinical Development

- In vivo activity
- Dosing regimen
- Pharmacology
- Toxicology
- Clinical study design
- Drug Formulation
- Manufacturing

Clinical Development

- Safety
- PK profiles
- Efficacy
- Clinical decision
- Market formulation

- Product label
- Scale-up manufacturing
- Regulatory compliance
- Post-approval monitoring

Memorial Sloan Kettering Cancer Center

Steps in drugs development



Discovery – Early Development

- In vitro activity
- Selectivity
- ✓ Solubility
- Permeability
- Metabolic Stability
- Clearance
- Protein Binding
- CYP450 inhibition
- hERG inhibition

Late Preclinical Development

- ✓ In vivo activity
- ✓ Dosing regimen
- ✓ Pharmacology
- ✓ Toxicology
- Clinical study design
- Clinical drug formulation
- Manufacturing

Clinical Development

- Safety
- ✓ PK profiles
- Efficacy
- Clinical decision
- Market formulation

- Product label
- Scale-up manufacturing
- Regulatory compliance
- Post-approval monitoring

Antitumor Assessment Core at MSK

Memorial Sloan Kettering Cancer Center

Late preclinical drug development stages

Animal models are extensively used in late drug development:



- To demonstrate in vivo target engagement
- To demonstrate effect on a disease-relevant endpoint
- To assess PK/TK parameters
- To assess safety/toxicity
- To model and predict human dose
- To inform therapeutic index
- To determine possible interactions with other drugs

Late preclinical drug development stages



Mice

- May be used in PKs
- May be used in safety toxicology, when deemed the most adequate model
- Used primarily to assess target engagement and in vivo efficacy
- Both GEMMs and transplantation models (cell xeno- and allografts, PDXs) are used to assess cancer therapeutics



GEMMs

- Innate immune system
- Intact tumor stroma
- Orthotopic tumor growth
- Native vasculature
- Defined molecular subtypes
- Limited intratumor heterogeneity
- Often rely on the expression of a single oncogene



PDXs

- Severely limited immune system
- Admixed murine/human tumor stroma
- Orthotopic and sc tumor growth
- Murine vasculature
- Full range of molecular subtypes
- Higher intratumor heterogeneity
- Can recapitulate clinical pattern of metastasis/drug resistance

* The Antitumor Assessment Core large PDX library is available to MSK Investigators

Memorial Sloan Kettering Cancer Center

Late preclinical drug development stages



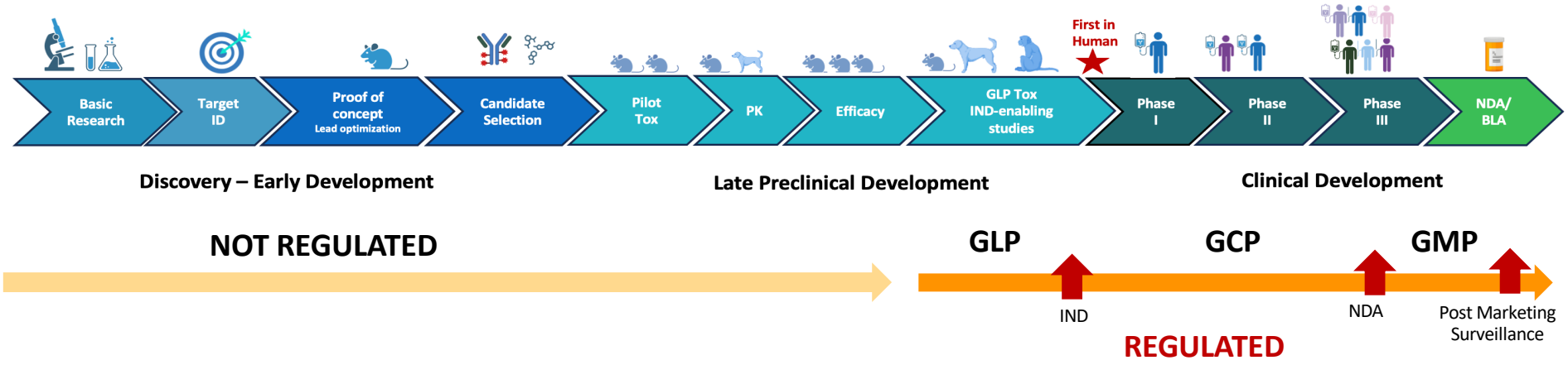
Rats
- Preferred rodent species to assess PK and toxicology

Dogs
- Preferred non-rodent species to assess PK and toxicology, to predict human dose and possible toxicity

NHP
- May be required to assess safety/toxicity/PK when other species are not adequate

Pigs
Rabbits
Others
- May be required to assess safety/toxicity if considered the most appropriate model

Drug Development and Regulation



GLP: Good Laboratory Practice - Applies to nonclinical safety studies
GCP: Good Clinical Practice - Applies to clinical trial and correlative studies
GMP: Good Manufacturing Practice - Applies to product

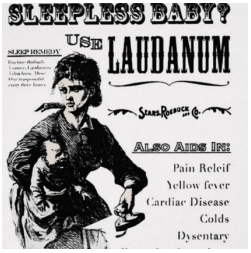
Memorial Sloan Kettering Cancer Center

Drug Development and Regulation

Pharma started out as a largely unregulated industry, but became more and more regulated over time







1906: The original Pure Food and Drugs Act prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs.

1938: The Federal Food, Drug, and Cosmetic Act of 1938 contained provisions requiring new drugs to be shown to be safe before marketing.

1951: The Durham-Humphrey Amendment defined which drugs require medical supervision and require prescription by a licensed practitioner.

1964: The Declaration of Helsinki by the World Medical Association clarifies the Nuremberg Code and defines the clinical research process

Pre-1900 | 1900s | 1910s | 1920s | 1930s | 1940s | 1950s | 1960s | 1970s | 1980s | 1990s | 2000s | 2010s

FDA

1930: The name of the Food, Drug, and Insecticide Administration is shortened to the Food and Drug Administration (FDA).

1947: The Nuremberg Code outlines 10 points to ensure ethically conducted human trials.

1962: Kefauver-Harris Drug Amendments require drug manufacturers to prove to the FDA the effectiveness of their products before marketing them.

1979: The Belmont Report defines the essential components of ethical research: respect for persons, beneficence, and justice.

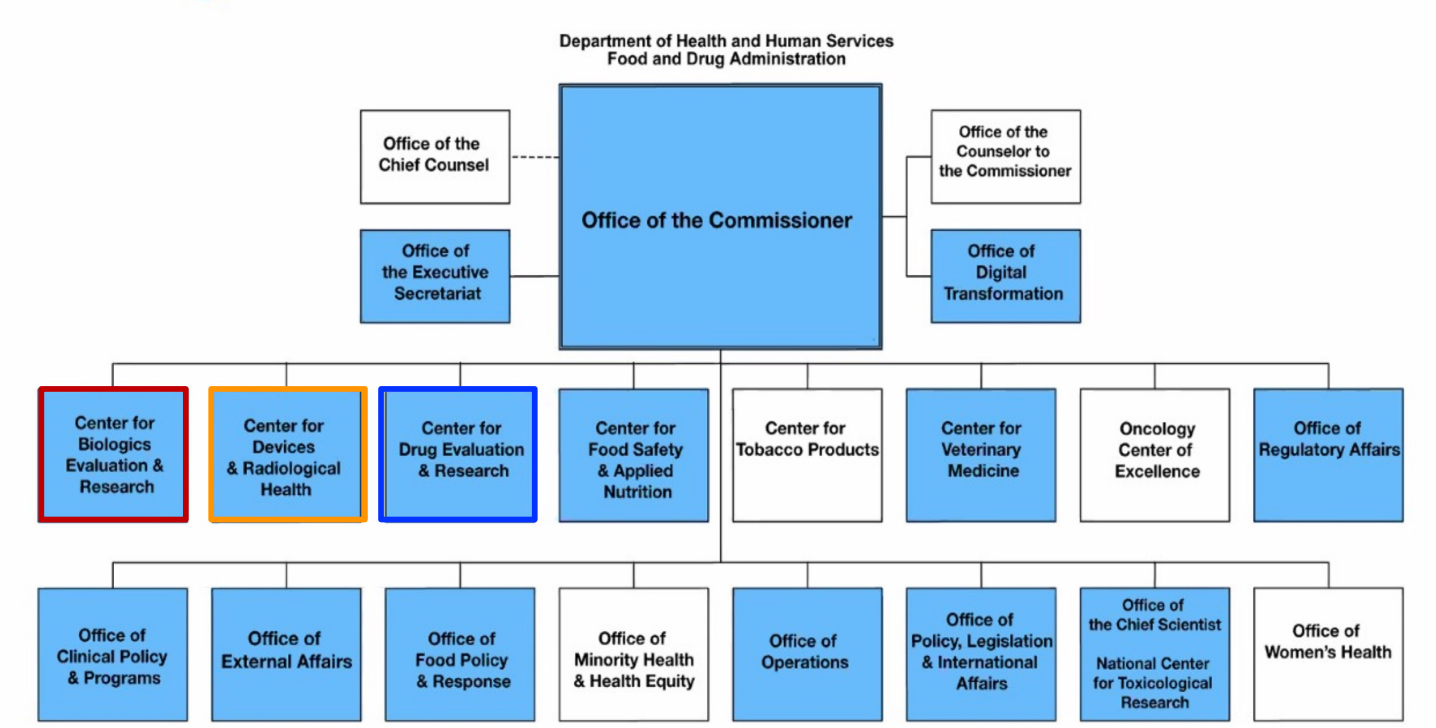
Drug Development and Regulation

The FDA is the Drug Regulatory body in the US and is organized into Centers and Offices by Area of Expertise

The Center for Drug Evaluation and Research (**CEDER**) is the primary interface for drug and therapeutic biologics development

The Center for Biologics Evaluation and Research (**CBER**) is the primary interface for cell and gene therapy, vaccines, and blood products development

The Center for Devices and Radiological Health (**CDRH**) is the primary interface for Devices and radiological products



Drug Development and Regulation: GMP

GMP: Good **Manufacturing** Practice

- Applies to **PRODUCT**

- Assures identity, strength, quality, and purity of drug products through design, monitoring and controls, as per:

  - 21 CFR PART 211 cGMP For Finished Pharmaceuticals
  - 21 CFR PART 212 cGMP For Positron Emission Tomography Drugs

- FDA Guidance cGMP for **Phase 1** Investigational Drugs (2008) indicates that Investigational New Drugs (IND) used in phase 1 clinical trials, including biological drugs, **are exempt** from complying with 21 CFR part 211

Drug Development and Regulation: GCP

GCP: Good **Clinical** Practice

- Applies to **CLINICAL TRIALS** and correlative studies
- Is a **Quality Standard**
- Provided by the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Us*e (ICH), an international body that defines a set of standards, which governments can then transpose into regulations for clinical trials involving human subjects
- GCP guidelines include standards on how clinical trials should be conducted, define the roles and responsibilities of Institutional Review Boards (IRB), clinical research investigators, clinical trial sponsors, and monitors.
- 13 core principles involve:
  - Study sponsor
  - IRB
  - Patients
  - Regulatory Authorities
  - Investigators
  - Monitors
  - Pharmacists

Drug Development and Regulation: GLP

GLP: Good **Laboratory** Practice



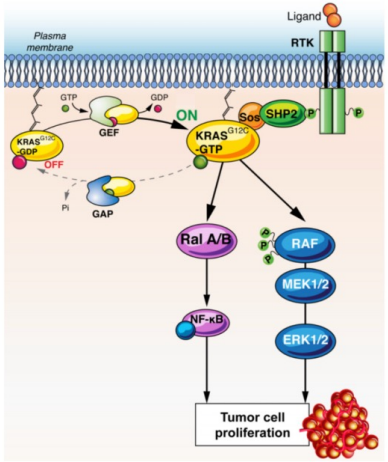
- Applies to **NON-CLINICAL SAFETY** studies
- GLP is mandated by Law (21 CFR 58). It is a formal regulation that was created by the FDA in 1978 , following the report of cases of poor laboratory practice and fraud in preclinical studies that were supposed to determine the safety of drugs prior to their use in the clinic.
- Although GLP originated in the United States , it had a worldwide impact. In 1981 the Organization for Economic Cooperation and Development (OECD) produced international standards for GLP principles
- All non-clinical studies performed to evaluate **SAFETY** of a product need to be conducted **under GLP**

✗ Proof-of-concept efficacy	✓ General Toxicology
✗ ADME	✓ Safety Pharmacology
✗ Biodistribution (for radiopharmaceuticals)	✓ Toxicokinetic

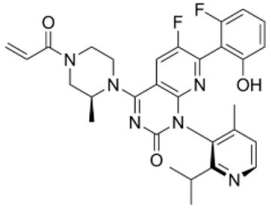
The Antitumor Assessment Core can conduct GLP-compliant toxicology studies at MSK

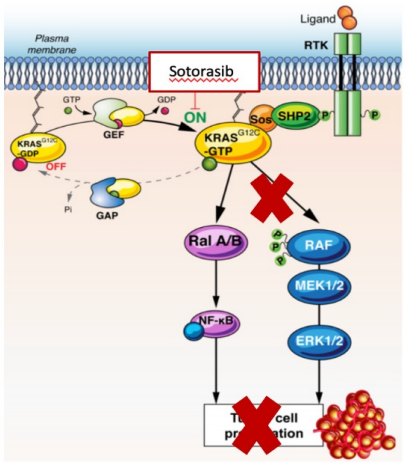
In vivo Pharmacology – non GLP

Ras Signaling Pathway



Sotorasib
Kras G12C inhibitor

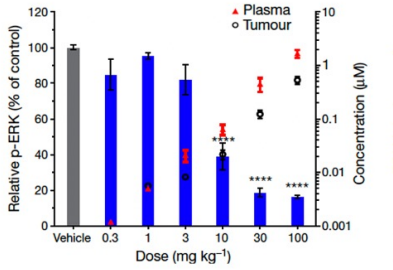


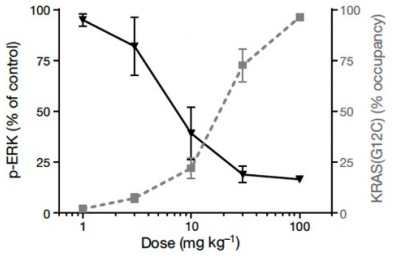


Target Engagement

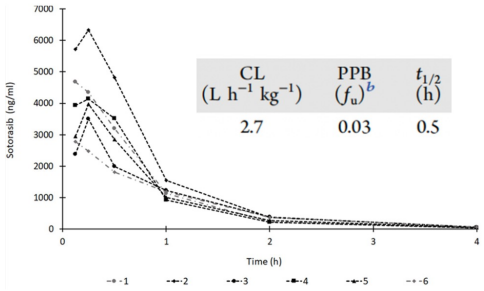


Vehicle
Sotorasib 0.3-100 mg/kg





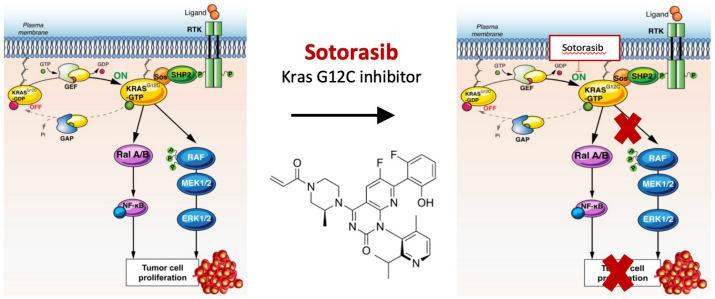
PK Profile



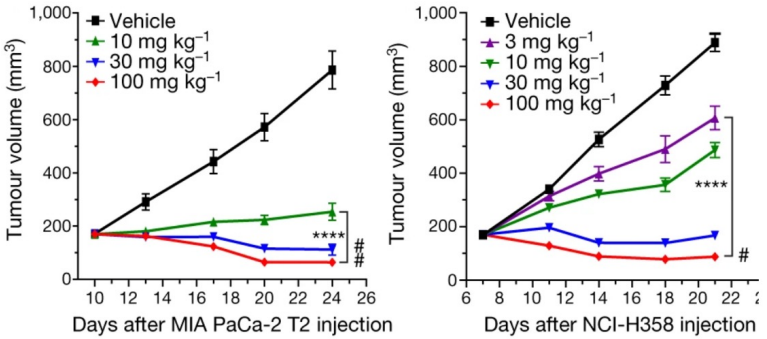
CL (L h^{-1} kg^{-1})	PPB (f_u)^b	$t_{1/2}$ (h)
2.7	0.03	0.5

Canon J et al, Nature 2019
Lanman BA, et al, J Med Chem 2020
Retmana et al, J Chromatography 2021

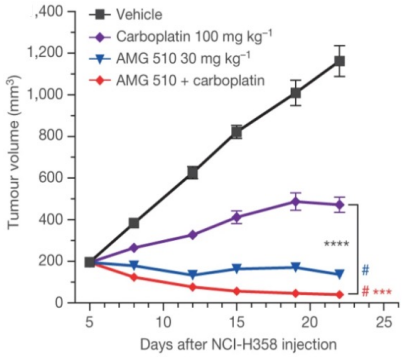
In vivo Pharmacology – non GLP

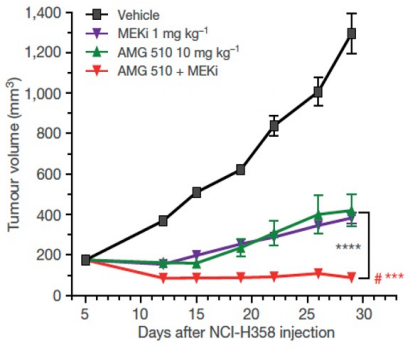


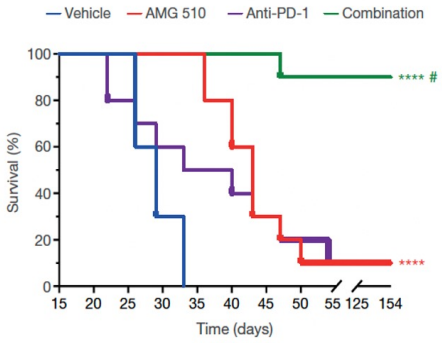
Dose-dependent Efficacy



Synergy with other therapeutics





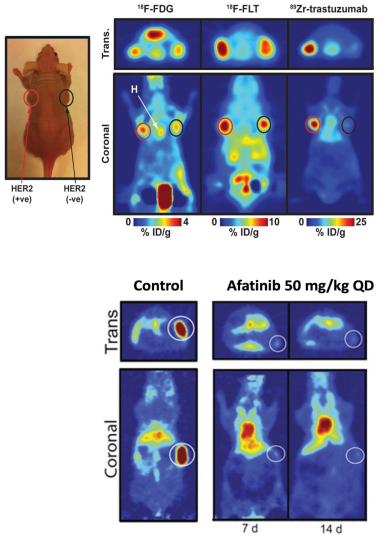


Canon J et al, Nature 2019
Lanman BA, et al, J Med Chem 2020

In vivo Pharmacology – non GLP

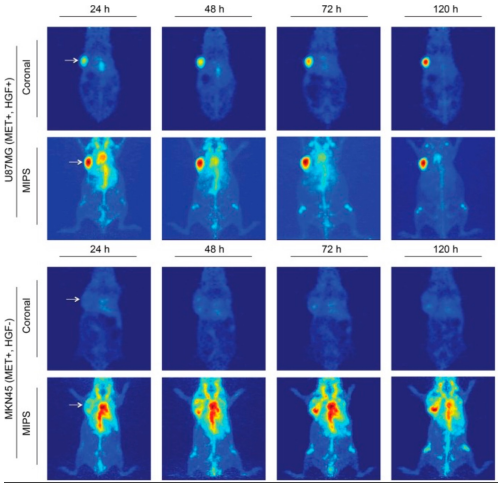
Immuno-PET Agents

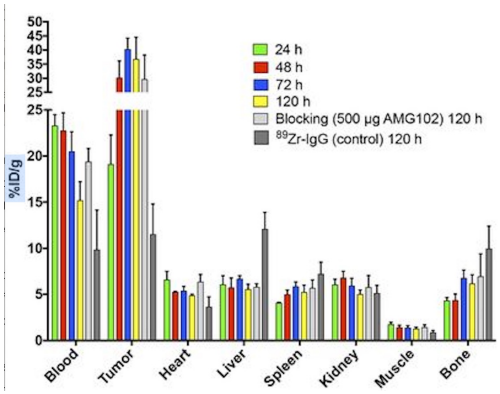
^{89}Zr-Trastuzumab: Target Engagement



Janjigian YY et al, J Nucl Med 2013

^{89}Zr-DFO-AMG102 Target Engagement and Biodistribution





Price et al, J Nucl Med 2017

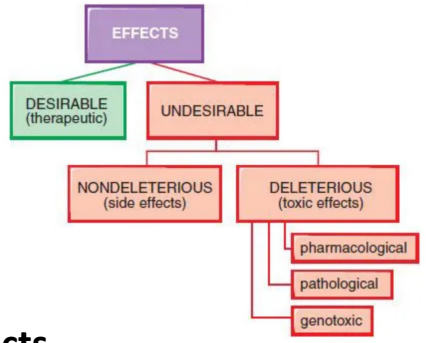
Safety Pharmacology and Toxicology - GLP compliant

Goals

- ✓ Evaluate pharmacologic properties
- ✓ Evaluate toxicological and toxicokinetic profiles
- ✓ Identification of target organs
  - Dose limiting- toxicities
  - Relationship to exposure
  - Potential reversibility
- ✓ Assess potential toxicities that cannot be identified in clinical trials

Information is used to

- ➢ Inform an initial safe starting dose and dose range for the human trials
- ➢ Identify parameters for clinical monitoring for potential adverse effects.



Studies should be thorough enough to adequately characterize **potential Adverse Effects** that might occur under the conditions of the clinical trial to be supported

Safety Pharmacology and Toxicology: what is required

- Toxicokinetic and Pharmacokinetic studies
- Safety Pharmacology studies
- General Toxicity studies (single/repeat dose, rodent + non-rodent, as dictated by proposed trial)
- Genotoxicity studies (in vitro mutagenesis studies) for trials in healthy volunteers
- Reproduction Toxicity studies

Cancer therapeutics have **limited requirements** for:

- Safety pharmacology
- Reproduction toxicity
- Genotoxicity

Pharmacokinetics/Toxicokinetics

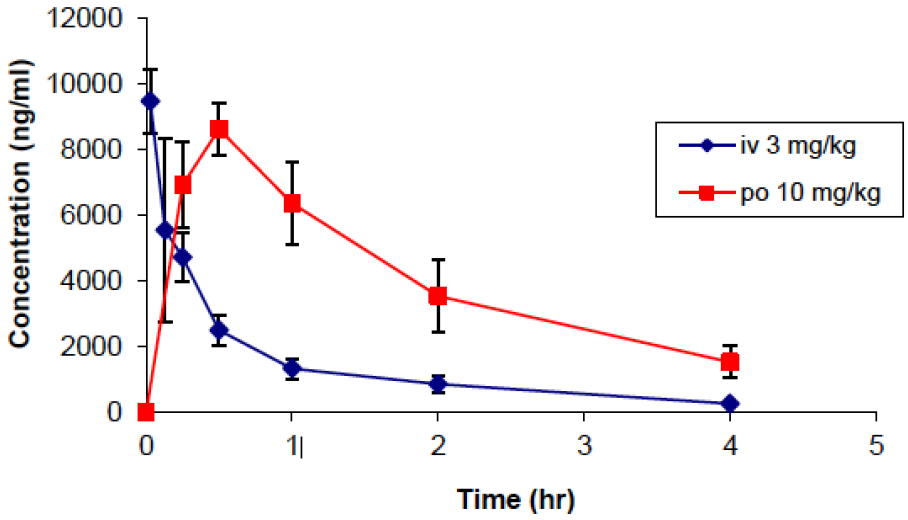
Crucial to demonstrate exposure levels in toxicology studies – human starting doses and dosing schedules are based on these data

PK - Pharmacokinetics

PK profile of efficacious doses

TK – Toxicokinetics

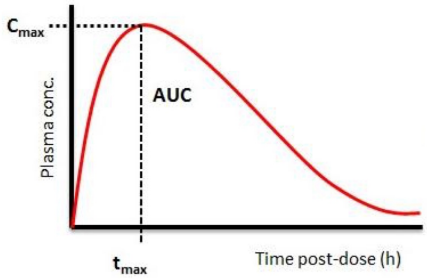
PK profile at high doses

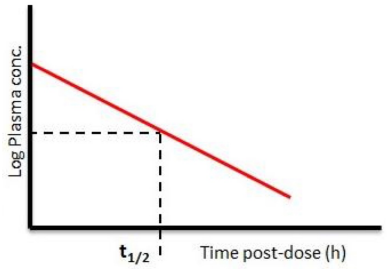


Pharmacokinetics/Toxicokinetics

PK Endpoints

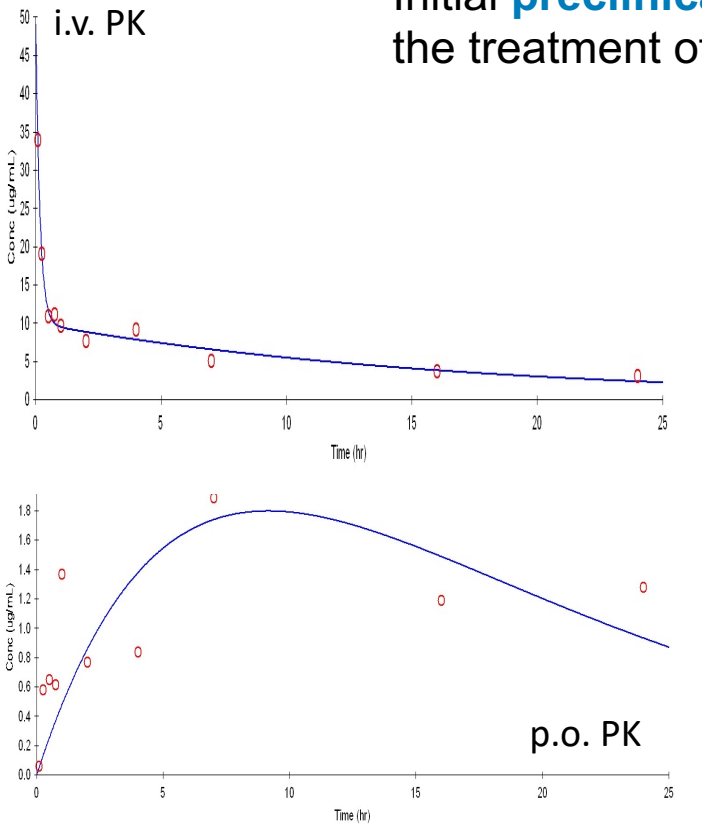
- **C_{max}**: The peak plasma concentration of a drug after administration
- **T_{max}** Time to reach C_{max}
- **AUC** (area under the curve): represents the total amount of drug absorbed
- **Clearance**: The volume of plasma cleared of the drug per unit time
- **Volume of Distribution**: The apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).
- **t1/2 (elimination half-life)** the time taken for the plasma concentration to fall by half its original value
- **Bioavailability**: percent of drug that is absorbed relative to the maximum absorbed seen after IV dosing



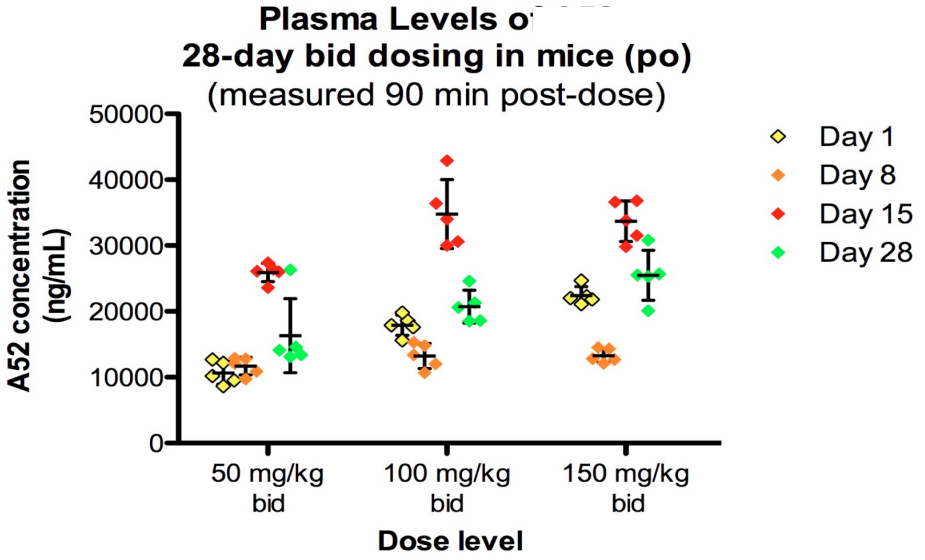


Pharmacokinetics/Toxicokinetics

Initial **preclinical development or ARN-509**, now FDA approved for the treatment of castration resistant prostate cancer (Apalutamide)



Clegg et al., Cancer Res. 2012



Safety Pharmacology: what is required

- Focuses on identifying the potential undesirable pharmacodynamic effects of a substance on vital organ functions in relation to exposure in the therapeutic range and above
- Usually single-dose studies

Rat



CNS

- Motor Activity
- Behavior
- Coordination
- Sensory/Motor Reflexes
- Body Temperature



Respiratory

- Respiratory Rate
- Tidal Volume
- O_2 Saturation

Nonrodent



Cardiovascular

- BP & Heart Rate
- ECG
- Repolarization (APD)
- hERG (I_{Kr}) assay
- Conduction

Genetic Toxicity: what is required

- Conducted to identify rodent carcinogenic potential of small molecules
- Different types of DNA lesions require several complementary assays
  - **Ames test** to detect gene mutations
  - **Micronucleus test** to detect structural (clastogenicity) and numerical (aneugenicity) chromosomal changes in vitro and in vivo (bone marrow or peripheral blood)
  - **Comet assay** to detect DNA strand breaks as a consequence of direct DNA damage or repair

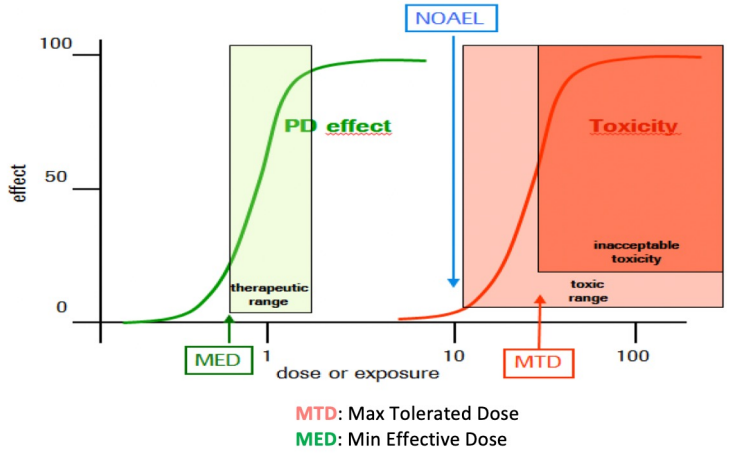
- Positive genotox data are a major developmental hurdle

Safety Toxicology Studies: what is required

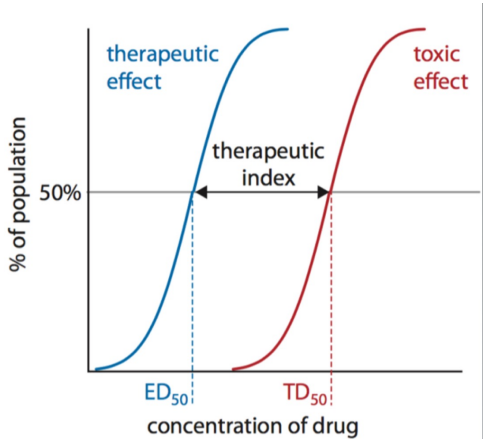
To evaluate the potential for risk in humans, one or more multidose animal studies are used to establish the highest level that does not produce adverse effects.

NOAEL (NO OBSERVED ADVERSE EFFECT LEVEL): the dose at which no harmful anatomical, biochemical, or functional changes are induced by test article administration in a specific study.

THERAPEUTIC INDEX: Exposure difference between toxicity and efficacy



MTD: Max Tolerated Dose
MED: Min Effective Dose



- in animals TI = $\frac{LD_{50}}{ED_{50}}$
- in humans TI = $\frac{TD_{50}}{ED_{50}}$

Safety Toxicology Studies: Study design considerations

Appropriate species

- One rodent, one second species (dog, pig or monkey generally)
- Good drug exposure
- Metabolism similar to human
- Same pharmacologic activity as humans (same target binding, effect in disease models, pharmacologic effects)

Exposure

Exposure achieved in test species should be sufficient to cover multiples of the intended human dose/exposure in order to establish a safety margin

- Higher doses to evaluate possible toxicities that could occur
- Administer compound long enough to support intended clinical study

Study Design

It should mimic as much as possible the design of the corresponding clinical trial

Rodent models for Toxicology Studies

MOUSE

Historical relevance:

Critical in developing treatment for polio and influenza
Key in research involving genetics and understanding the functions of the immune system
Most widely used animal with regards to molecular biology

Pros:
Availability of different genetic strains
Availability of tumor models

Cons:
Small size (small blood volumes/tissues)
Not very robust



RAT

Historical relevance:

Critical in studies of diabetes, high blood pressure, arthritis
Key in research studying reproductive biology
Learning and behavior studies
Organ transplants

Pros:
Availability of different genetic strains
More robust
More consistent physiological responses

Cons:
Non as many genetic and tumor models

Non-Rodent models for Toxicology Studies

DOG

Historical relevance:
Cardiovascular and pulmonary research
Predictive of compounds that will impact the stomach and intestine
Beagles are the most common

Pros:
Large size
Easy temperament
Ease of handling
Large historical database

Cons:
Variation in size
Social issues
Cost and maintenance
More test article
Availability

NON HUMAN PRIMATE

Historical relevance:
Heart disease
Viral disease: malaria, polio and AIDS
Brain research: Alzheimer's and Parkinson's
Reproductive biology, in vitro fertilization
Most of the work in **cynomolgus monkeys**

Pros:
Large size
Large historical database
Phylogenetic closeness

Cons:
Social issues
Cost and maintenance
Availability
Handling danger (Herpes B)

PIG

Historical relevance:
Cardiovascular anatomy and physiology
Model for human skin
GI system and digestion
Relatively new to toxicology as a non rodent model

Pros:
Large size
Large historical database

Cons:
Larger size
Social issues
Cost and maintenance
Availability
Handling

GLP Tox study Design

The study design needs to reflect the clinical trial requirements: route and frequency of administration should be the same as intended for humans

Example: drug will be administered orally once/day for 4 weeks

GLP TOX STUDY DESIGN:

Treatment Groups: 1 control + 3 dose levels (low/medium/high), males + females

Dosing Schedule: daily p.o. x 28 days

End points: 24 hours after the last dose, and after 2 week recovery period

Parameters:

- Toxicokinetics
- Clinical Observations
- Body weight and food consumption
- ECG
- Ophtalmoscopy
- Hematology
- Clinical Chemistry
- Urinalysis
- Organ weights
- Necropsy and macroscopic examination of organs
- Histopathologic evaluation of organs and tissues

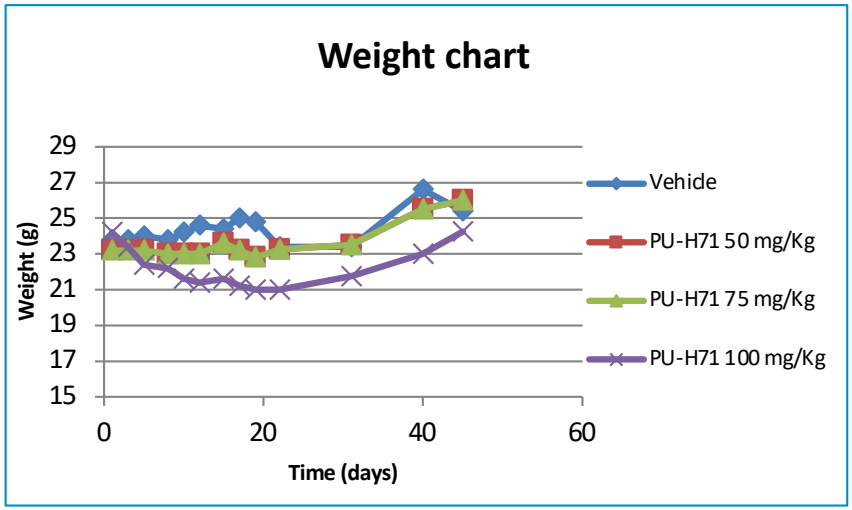
GLP Tox study Design

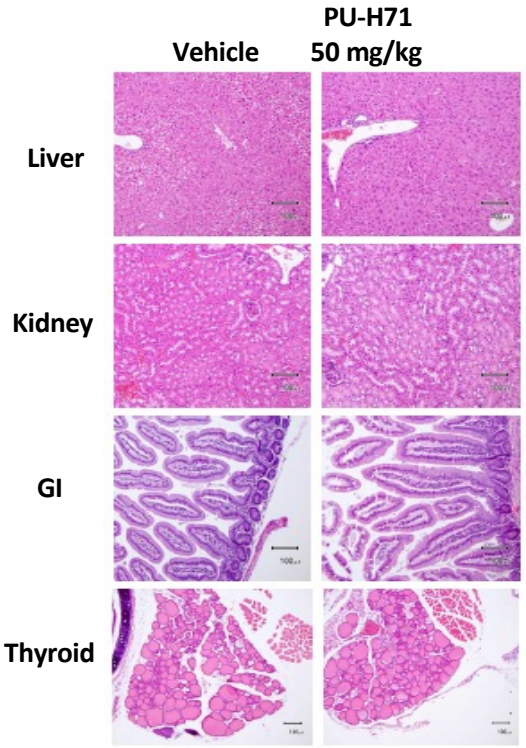
Recommendations for duration of animal studies based on intended duration of treatment in patients

Duration of Indicated Treatment	Rodent	Non-Rodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months	9 months

Safety Toxicology parameters

Preclinical development of the Hsp90 inhibitor PU-H71



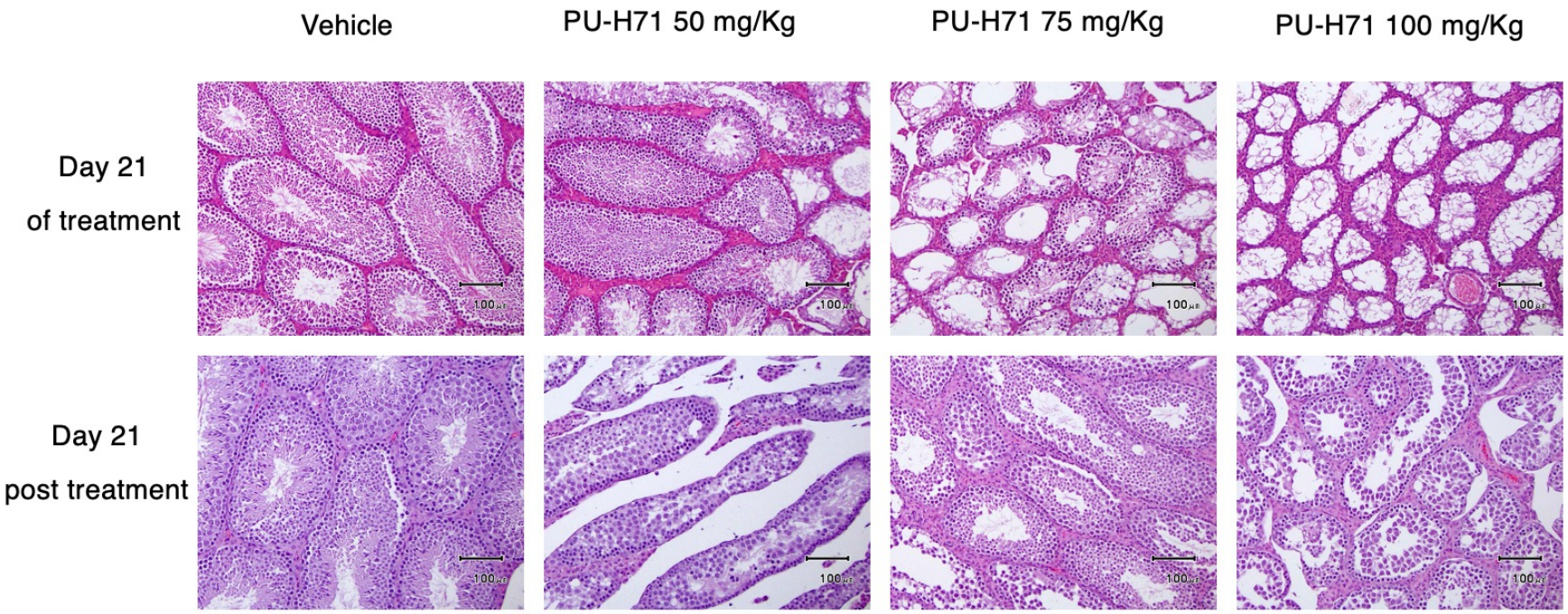


Parameter	Unit	Ref range	Vehicle	St.Dev	PU-H71 50mg/kg	St.Dev
WBC	K/uL	1.8-10.7	9.9	1.6	8.4	1.3
NEUTROPHILS	K/uL	0.1-2.4	2.2	0.3	2.8	0.8
LYMPHOCYTES	K/uL	0.9-9.3	6.9	1.5	5.1	1.0
MONOCYTES	K/uL	0.0-0.4	0.8	0.1	0.4	0.1
EOSINOPHILS	K/uL	0.0-0.2	0.0	0.0	0.0	0.0
BASOPHILS	K/uL	0.0-0.2	0.0	0.0	0.0	0.0
NE%	%	6.6-38.9	22.1	2.9	33.4	7.3
LY%	%	55.8-91.6	69.7	3.6	61.3	6.9
MO%	%	0.0-7.5	8.1	1.7	5.0	1.0
EO%	%	0.0-3.9	0.1	0.1	0.2	0.1
BA%	%	0.0-2.0	0.0	0.0	0.1	0.0
RBC	M/uL	6.36-9.42	10.2	0.9	10.6	0.4
HB	g/dL	11.0-15.1	13.9	0.6	14.2	0.5
HCT	%	35.1-45.4	47.6	2.4	48.1	2.1
MCV	fL	45.4-60.3	46.7	2.0	45.6	1.0
MCH	Pg	14.1-19.3	13.6	0.9	13.5	0.2
MCHC	g/dL	30.2-34.2	29.1	0.9	29.6	0.4
RDW	%	12.4-27.0	17.7	0.9	17.2	0.3
PLT	K/uL	592-2972	742.3	411.1	993.2	143.8
MPV	fL	5.0-20.0	4.4	0.1	4.5	0.1
ALP	IU/L	23-181	131.2	30.4	156.0	63.1
ALT (SGPT)	IU/L	16-58	105.8	65.3	51.8	22.9
AST (SGOT)	IU/L	36-102	195.4	68.0	144.4	54.7
GGT	IU/L	0-2	0.4	0.9	0.0	0.0
Total Bilirubin	mg/dl	0.0-0.3	0.2	0.0	0.2	0.0
Total Protein	g/dl	4.1-6.4	5.6	0.2	5.8	0.3
Albumin	g/dl	2.5-3.9	2.8	0.7	3.3	0.2
Blood Urea Nitrogen	mg/dl	14-32	14.0	4.1	17.4	1.8
Creatinine	mg/dl	0.1-0.6	0.2	0.1	0.2	0.0
Phosphorus	mg/dl	4.6-9.3	9.8	2.5	9.8	0.4
Calcium	mg/dl	7.6-10.7	9.7	0.2	9.9	0.1
Sodium	mEq/l	146-155	161.4	0.9	162.0	0.7
Chloride	mEq/l	103-115	115.0	0.0	115.0	0.0
Potassium	mEq/l	3.4-5.5	8.3	0.4	8.2	0.3
B/C Ratio		21-127	63.0	35.6	87.0	9.1
Na/K Ratio		26.7-42.1	19.4	1.0	16.3	7.8
T4, Total	µg/dL		3.6	1.7	5.4	0.8

Caldas Lopes et al., PNAS. 2009

Safety Toxicology parameters

- Chronic dosing of PU-H71 induces testicular degeneration in mice, an effect that was shown to be reversible



Caldas Lopes et al., PNAS. 2009

Human Starting Dose: Calculating HED

Animal toxicity data are used to calculate the starting dose in **FIRST IN HUMAN** (**FIH**) Phase I trials

Small molecules: convert animal dose to human dose on a mg/m^2 body surface area basis

1. Determine NOAEL for all toxicology species
2. Determine the most appropriate species
3. Convert NOAEL to **Animal Equivalent Dose (AED):** $\frac{mg}{m^2} = K_m \times \frac{mg}{kg}$
4. Convert AED to **Human Equivalent Dose (HED)**

Example: NOAEL in Monkey: 30 mg/Kg

- AED= 30 mg/kg *12 (Monkey K_m) = 360 mg/m^2
- HED = AED *1.6 (human BSA) = 360 mg/m^2 * 1.6m^2 = 576 mg

Conversion of Animal Doses to HED based on BSA

Species	Weight (kg)	BSA (m^2)	Km (factor)
Human			
Adult	60	1,6	37
Child	20	0,8	25
Baboon	12	0,6	20
Dog	10	0,5	20
Monkey	3	0,24	12
Rabbit	1,8	0,15	12
Guinea pig	0,4	0,05	8
Rat	0,15	0,025	6
Hamster	0,08	0,02	5
Mouse	0,02	0,007	3

Human Starting Dose: Safety Factor

the FDA recommends to apply a 10-fold **SAFETY FACTOR** as a standard for non-oncology drugs

Example: HED = 576 mg

- Apply 10X Safety factor
- Initial starting dose in humans: 576 mg/10= 57.6 mg

Higher safety factors may be warranted in special circumstances:

- Steep toxicity dose response curve
- Severe, irreversible toxicity
- Toxicity without pre-monitory signs
- Expected variable bioavailability in the clinic
- Unexplained mortality in the animal studies
- Nonlinear PK
- Inadequate dose response data
- Novel therapeutic target
- Animal models with limited utility

Non-Animal models for Toxicology Studies

New Approach Methodologies (NAMs) are a diverse suite of tools and technologies that can be used either alone or in combination with other methods to evaluate chemical and drug safety without relying on animal testing

IN VITRO METHODS
Using human cells, tissues, or organoids to model biological pathways and understand how chemicals interact with human systems

IN SILICO (COMPUTATIONAL) TOOLS
Employing computer models, like those based on Quantitative Structure-Activity Relationships (QSAR), to predict chemical toxicity based on their physical characteristics and molecular structures

MECHANISTIC UNDERSTANDING
Investigating the specific biological mechanisms by which a chemical causes toxicity, leading to a better understanding of its action and potential effects on human health

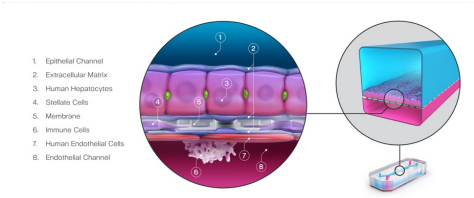


OMICS APPROACHES
Using high-throughput 'omics' technologies to gather comprehensive data on biological responses to chemical exposures

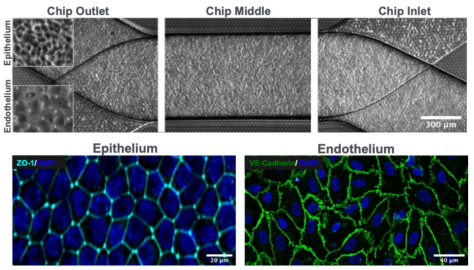
DATA INTEGRATION
Combining different types of NAM data with systems biology approaches to create more predictive and comprehensive models of chemical safety

Types of NAMs

IN VITRO MODELS to assess biological responses to compounds and pharmaceuticals:



- **2D cell cultures:** Widely used for basic toxicity screening
- **3D spheroids and organoids**: Offer more physiologically relevant structure and function
- **Organ-on-a-Chip models**: Microengineered systems that mimic organ-level functions, enabling dynamic studies of toxicity, pharmacokinetics, and mechanisms of action. They can replicate complex tissue-tissue interfaces, fluid flow, and mechanical forces, offering a powerful bridge between cell culture and whole-organism physiology



***IN SILICO* MODELS** to simulate biological responses or predict chemical properties based on existing data.

- **QSARs**: Quantitative Structure-Activity Relationships: Predict a chemical's activity based on its structure.
- **PBPK**: Physiologically Based Pharmacokinetic models: Model how chemicals are absorbed, distributed, metabolized, and excreted in the body
- **Machine Learning/AI**: Leverage big data to uncover novel patterns and make toxicity predictions across the pharmaceutical space

These tools can screen thousands of compounds *in silico* before any lab testing is done, helping prioritize candidates and reduce unnecessary experimentation

Types of NAMs

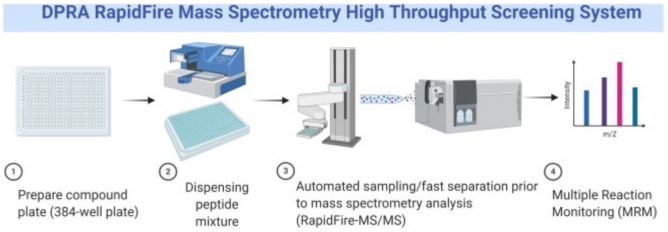
OMICS-BASED APPROACHES analyze large datasets from genomics, proteomics, metabolomics, and transcriptomics to identify molecular signatures of toxicity or disease. They offer:

- Mechanistic insights into how chemicals affect biological systems.
- Biomarker discovery for early indicators of adverse effects.
- Pathway-based analyses aligned with Adverse Outcome Pathways (AOPs).

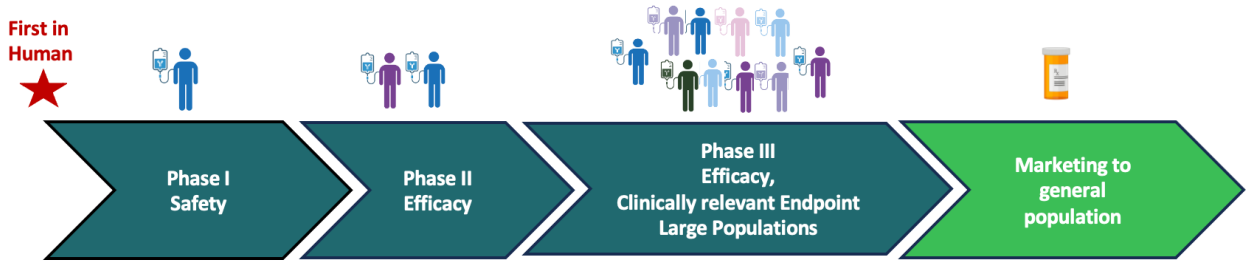
These methods support a shift toward mechanistic toxicology, focusing on early molecular events rather than late-stage pathology.

IN CHEMICO METHODS assess chemical reactivity without involving biological systems.

A common application is testing for skin sensitization, where the ability of a compound to bind to proteins is evaluated directly through assays like the Direct Peptide Reactivity Assay (**DPRA**), which quantifies cysteine- or lysine-containing peptide depletion following 24 hours incubation with the drug



The IND Application Process



- The goal of an Investigational New Drug Application (**IND**) is commercialization through a New Drug Application (**NDA**) or a Biologics License Application (**BLA**)
- The IND process is **regulated by the FDA** Part 312 - CFR - Code of Federal Regulations Title 21
- IND applications are submitted to the FDA to obtain authorization to begin **testing in humans** in clinical trials

The IND Application Process

INDs are required whenever clinical studies are initiated on:

- a **NEW** drug or biologic
- an **APPROVED** drug or biologic:
  - For a new indication
  - With a different route of administration
  - With a change of formulation that increases risk
  - With a significant change in dosing regimen
  - In a different population

- **SPONSOR**: the entity who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization
- **SUBJECTS**: Patients who participate in an investigation

The IND Application Process

The IND application is organized in 9 sections:

1. Form FDA 1571
2. Table of Contents
3. Introductory statement
4. General Investigational plan
5. Investigator's brochure
6. Clinical Protocol
    a. Study protocol
    b. Investigator data
    c. Facilities data
    d. Institutional Review Board data
7. Chemistry, manufacturing, and control data
8. Pharmacology and toxicology data
9. Previous human experience

- **Clinical Protocols and Investigator Information**: Detailed protocols for clinical studies, qualifications of investigators, and commitments to obtain informed consent

- **Manufacturing Information**: Information on the drug's composition, manufacturer, stability, and controls

- **Animal Pharmacology and Toxicology Studies**: Preclinical data to assess the drug's safety for human testing

The IND Application Process

After Submission:

- FDA sends letter acknowledging receipt of the submission and assigns the IND number
- Review period of 30 calendar days before initiating any clinical trials
- If there are no issues, the IND generally goes **into effect** 30 days after the *Date of Receipt* shown in letter – clinical study can proceed
- If there are issues, the IND goes on **Clinical hold** until issues are resolved

Clinical Hold:

- Subjects are exposed to unreasonable risk of illness or injury
- Investigator is not qualified
- Investigational Brochure is incorrect, misleading, or incomplete
- IND does not contain enough data to assess safety
- Protocol is deficient in meeting stated objectives

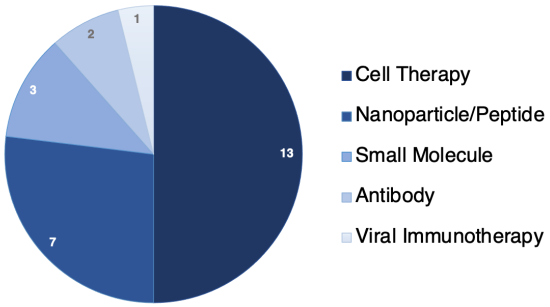
The Sponsor must request in writing that a clinical hold be removed, and FDA should respond within 30 days

Steps in cancer drugs development

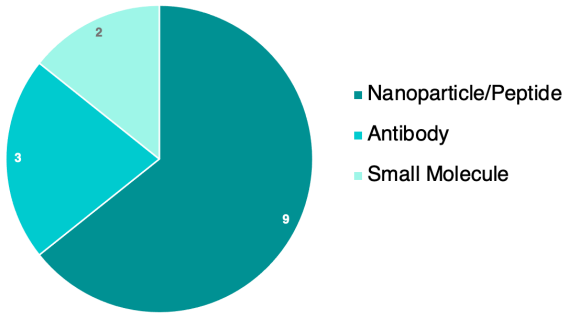
The **Antitumor Assessment Core** routinely conducts in GLP-compliant safety toxicology studies in support of IND applications sponsored by MSK investigators.

Test articles include both therapeutic and diagnostic agents.

Therapeutic Test articles

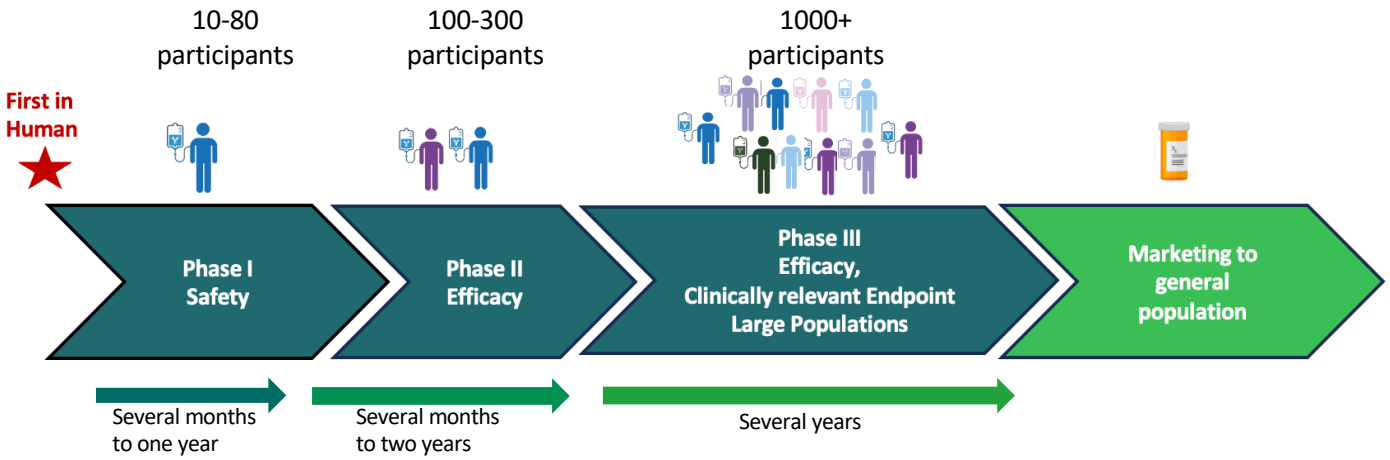


Diagnostic Test articles



GLP STUDIES 2017-2026	
Completed	35
In progress	5

Human Clinical Trial Phases



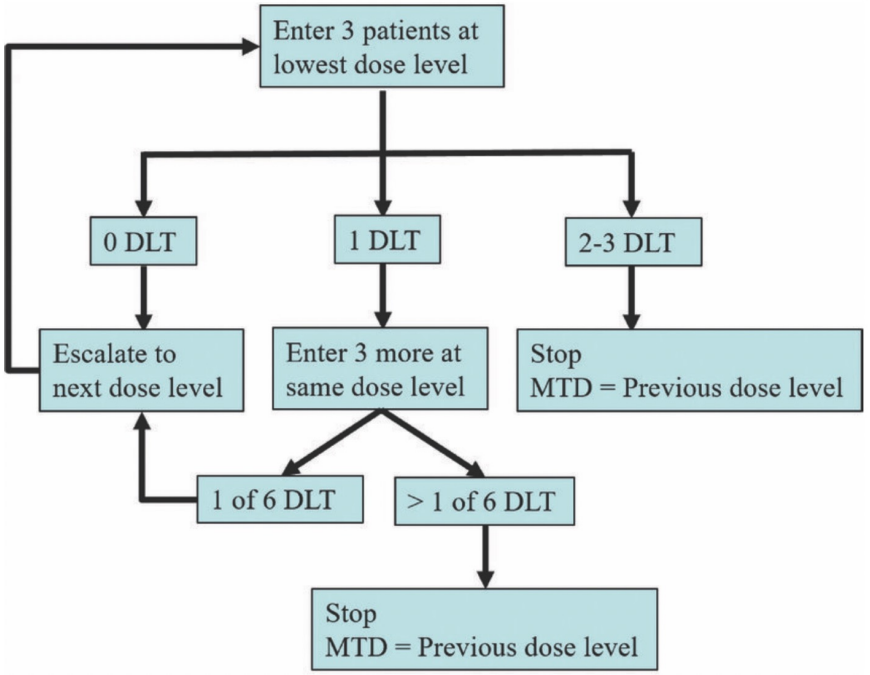
Human Clinical Trials: Phase I

Safety and Tolerability: define a safe clinical dose range
Human Pharmacology: right dose for the right patient

- Single and multiple doses
- Drug-Drug Interaction (DDI) studies
- Studies in reduced number of patients
- Special population studies

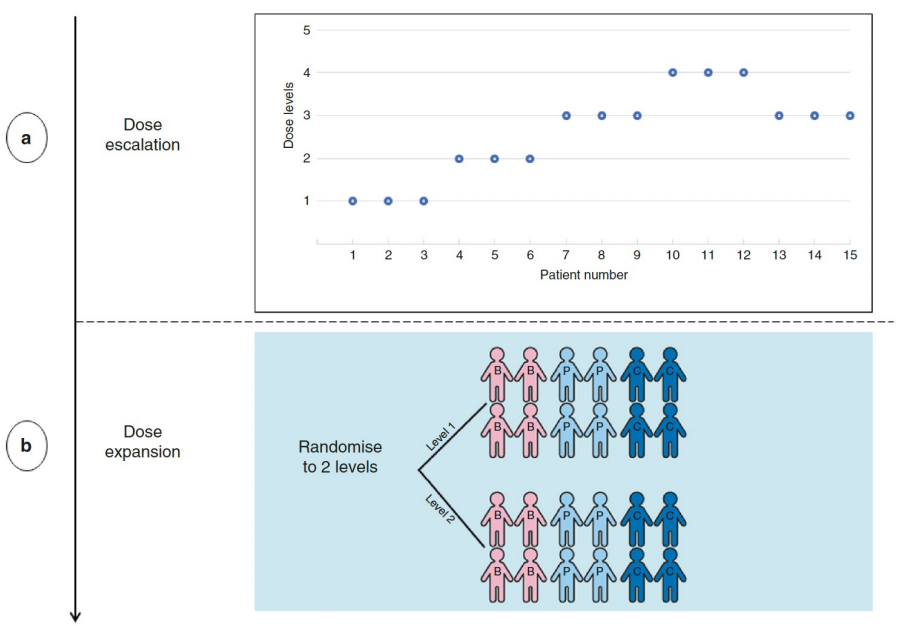
Dose escalation Protocols

3+3 Model: Dose escalation is carried out in cohorts of 3 patients until MTD has been determined.

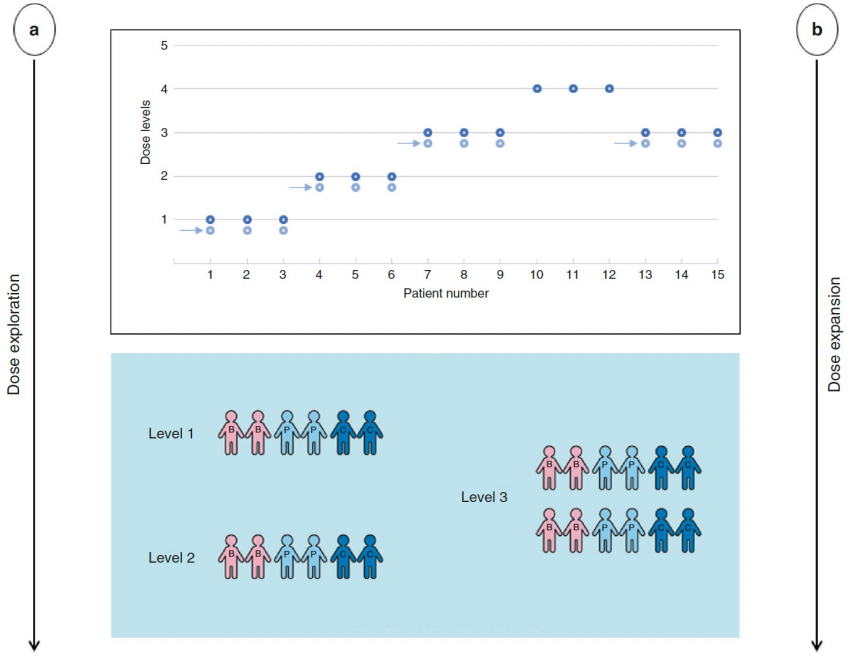


Human Clinical Trials: Phase I

Dose Escalation and Dose Expansion



Dose escalation followed **sequentially** by dose expansion after the MTD has been determined. Dose expansion randomizes subjects equally to two dose levels in molecular- or disease-specific patient populations



Dose escalation and dose expansion carried out **concurrently** prior to determination of the MTD. Dose expansion randomizes equally to three dose levels (levels 1, 2 and 3) in molecular- or disease-specific patient populations patients at levels 1, 2 or 3.

Human Clinical Trial: Phase II and III

Efficacy Assessment

Phase II

- Therapeutic Exploration
- Safety in the target population
- Proof of concept
- Use of Biomarkers
- Dose selection
- PK/PD

Phase III

- Therapeutic Confirmation
  -Pivotal studies
  - Larger group of patients
  - Usually multinational studies
- Evaluation of safety to define risk management in the post-marketing phase
- **Regulatory filing**

➢ **NDA Review**

The NDA/BLA Application

The **New Drug /Biologic Licensing Application** (**NDA/BLA**) is required for marketing approval

The goal of the submission is to provide enough information to permit the FDA to determine:

- whether the drug is safe and effective
- whether the benefits of the drug overweight the risk
- whether the drug's proposed labeling is appropriate and what it should contain
- whether the methods used in manufacturing the drugs and the controls used to maintain the drug's quality are adequate

The NDA/BLA Application

The **New Drug /Biologic Licensing Application** (**NDA/BLA**) is required for marketing approval

In response to the application, the FDA can issue:

- **Refuse to File letter**: The sponsor can resubmit once deficiencies are addressed
- **Approval letter**: Enables commercial distribution
- **Complete Response Letter**: describes why the agency will not approve the application in its present form. The sponsor can resubmit, withdraw or request meeting
- **Refuse to Approve Letter**: after sponsor's appeal

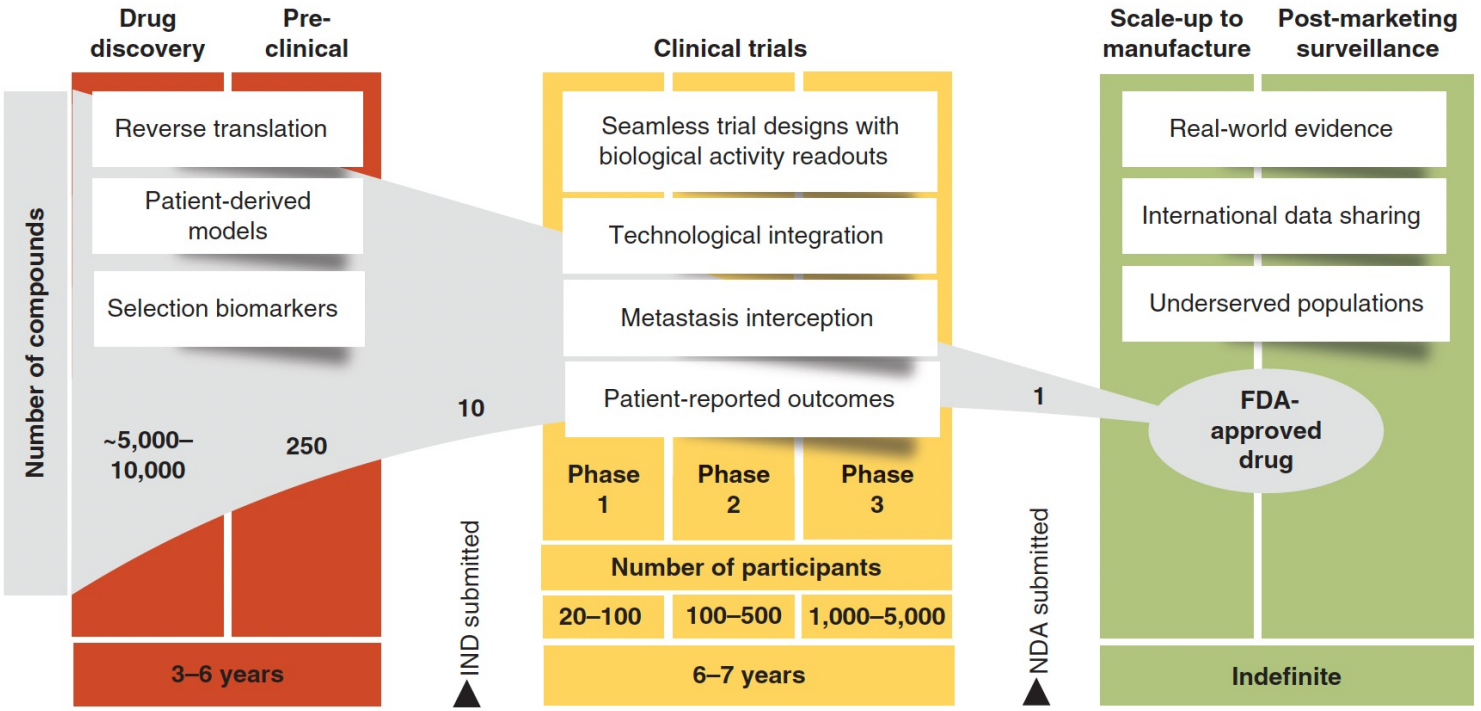
Human Clinical Trial: Phase IV (Post-approval)

Even after Approval, drug investigation and clinical trials can continue

- Therapeutic Use
- Post-registration Monitoring
- Further Exploration of safety and efficacy
- Real life experience
- Pharmacoeconomic evaluation
- Global expansion
- Novel indication
- Investigator-led studies
- Epidemiologic studies



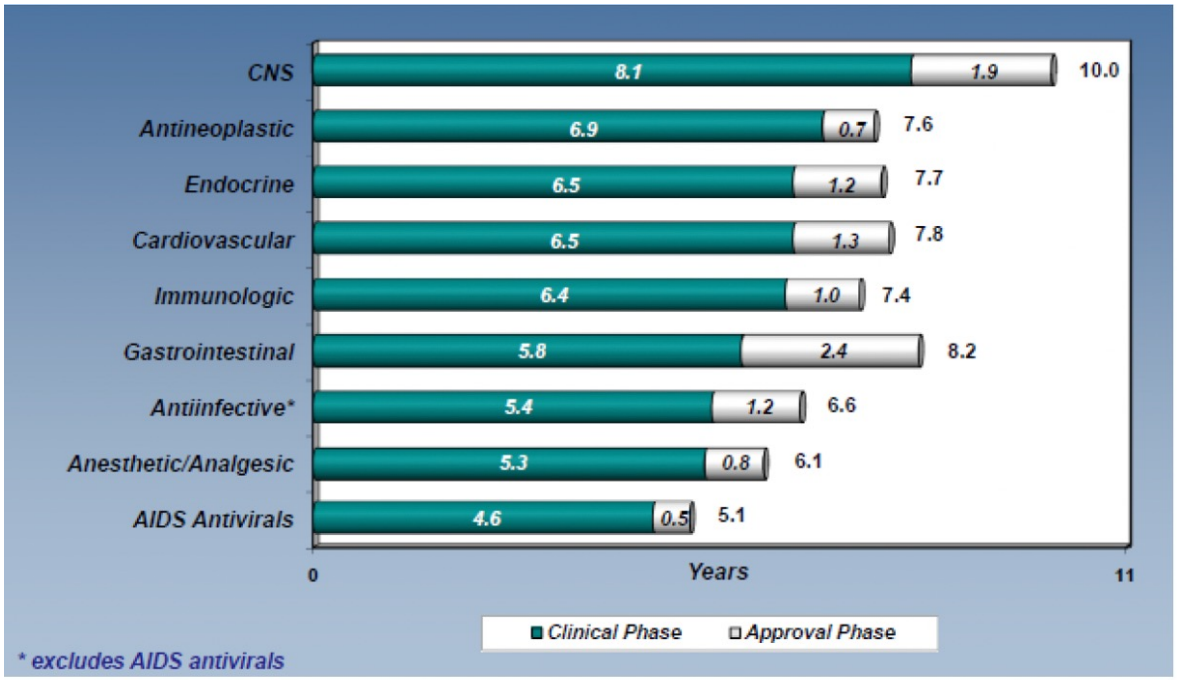
Drug Development timeline



Spreafico A et al, Cancer Discov 2021

Drug Development timeline

Drug approval times for different indications



2005-2009

Kaitin KI et al. Clin Pharmacol Ther. 2011;89(2):183–188

Drug Development timeline: expedite development

Expedited development pathway exists for products addressing unmet needs

Designation

BREAKTHROUGH THERAPY

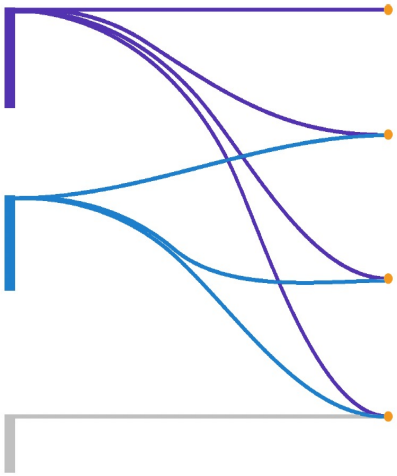
Drug makers can apply based on clinical data that indicate substantial improvement in one clinically significant endpoint over available medicines

FAST TRACK

Drug makers can apply based on pre-clinical or clinical data for a serious condition with a need for new medicines

PRIORITY REVIEW

The FDA grants priority review to drugs deemed major advancements



Key Elements

DEDICATED SENIOR MANAGEMENT TEAM

At the FDA helps companies streamline the clinical trial process

FREQUENT FDA MEETINGS

Help drug makers design clinical trials that are as efficient as possible and meet FDA expectations

ROLLING REVIEW

Allows drug makers to submit data as they become available

SHORTENED APPLICATION REVIEW TIME*

Shortens the FDA's review time by 4 months

**Breakthrough therapy and fast track designations have the possibility of shortened review times; they are not guaranteed.*

News | Articles | September 15, 2026

Daraxonrasib Receives FDA Breakthrough Therapy Status in 1L Metastatic PDAC

Development timeline for Enhertu

Date	Article
May 15, 2026	Approval Enhertu Approved in the US for Two New Indications for Patients with HER2 Positive Early Breast Cancer
Dec 15, 2025	Approval Enhertu Plus Pertuzumab Approved in the US as First New Treatment in a Decade for the First-Line Treatment of Patients with HER2-Positive Metastatic Breast Cancer
Jan 27, 2025	Approval Enhertu Approved as First HER2-Directed Therapy for Patients with HER2-Low or HER2-Ultralow Metastatic Breast Cancer
Apr 6, 2024	Approval Enhertu Approved in the US as First Tumor-Agnostic HER2-Directed Therapy for Previously Treated Patients with Metastatic HER2-Positive Solid Tumors
Aug 12, 2022	Approval Enhertu Approved in the US as the First HER2-Directed Therapy for Patients with Previously Treated HER2-Mutant Metastatic Non-Small Cell Lung Cancer
Aug 6, 2022	Approval Enhertu Approved in the US as the First HER2-Directed Therapy for Patients with HER2-Low Metastatic Breast Cancer
May 6, 2022	Approval Enhertu Approved in the US for Patients with HER2-Positive Metastatic Breast Cancer Treated with a Prior Anti-HER2-Based Regimen
Apr 27, 2022	Enhertu Granted Breakthrough Therapy Designation in U.S. for Patients with HER2 Low Metastatic Breast Cancer
Jan 15, 2021	Approval Enhertu Approved in the U.S. for the Treatment of Patients With Previously Treated HER2 Positive Advanced Gastric Cancer
Dec 20, 2019	Approval FDA Approves Enhertu (fam-trastuzumab deruxtecan-nxki) for HER2-Positive Unresectable or Metastatic Breast Cancer Following Two or More Prior Anti-HER2 Based Regimens
Oct 17, 2019	[Fam-] Trastuzumab Deruxtecan Granted FDA Priority Review for Treatment of Patients with HER2-positive Metastatic Breast Cancer

Drug Development timeline: expedite development

Legislation exists to incentivize drug development for rare diseases

Orphan Drug Act

Orphan Drug Act of 1983 provided incentives to facilitate development of products to treat rare diseases (affecting <200,000 patients in the United States), including:

- 7 years of **marketing exclusivity** granted at time of approval
- PDUFA filing **fees waived**
- **Peds (Pediatric Research Equity Act/PREA) waiver**
- **Tax benefits** in form of Orphan Drug Tax Credits for internal/external US clinical research activities from orphan drug designation to marketing approval

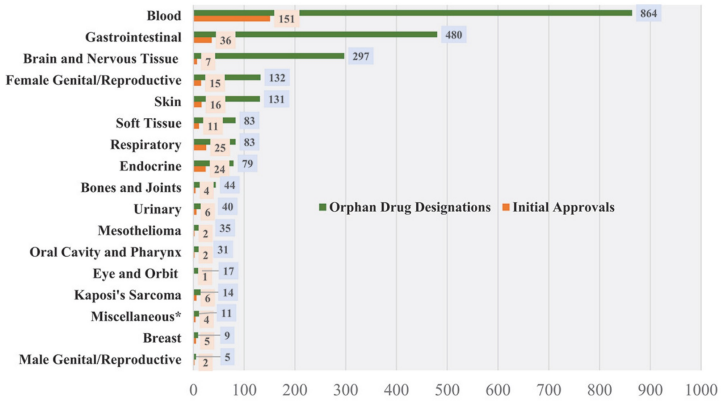
Rare Cancers

- Glioblastoma multiforme
- Esophageal cancer
- Gastric cancer
- Hepatocellular Carcinoma
- Small Cell lung cancer
- Sarcomas
- Most Leukemias and Lymphomas
- Uveal Melanomas
- Pediatric cancers

Orphan-approved Oncology drugs

- Ibrutinib (B-cell malignancies)
- Larotectinib (NTRK fusion solid tumors)
- Sotorasib (KRAS G12C-mutated NSCLC)
- Selpercatinib (RET fusion-positive NSCLC)
- Crizotinib (ALK+ and ROS1+ NSCLC)
- Imatinib (CML)

Oncologic orphan drug designations (and approvals) by organ system, 1983–2022



Ipe et al Expert Opinion on Orphan Drugs, 2024

Drug Development timeline: expedite development

Legislation exists to incentivize drug development for pediatric diseases

Best Pharmaceutical for Children Act

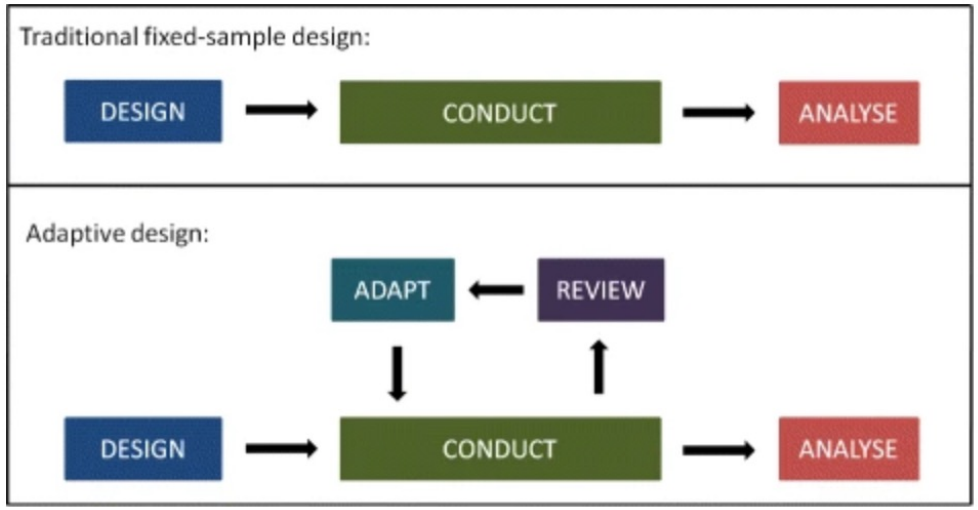
- The Best Pharmaceuticals for Children Act (BPCA), first enacted in 2002, provides an incentive for drug companies to conduct FDA-requested pediatric studies by granting an additional 6 months of marketing exclusivity
- PREA, first enacted in 2003, requires drug companies to study their products in children under certain circumstances
- **Before BPCA and PREA became law, more than 80% of the drugs approved for adult use were being used in children, even though the safety and effectiveness had not been established in children; today that number has been reduced to about 50%**

- **9 Products** have been approved with a pediatric oncology indication based on studies conducted under BPCA
  - Dasatinib, Nilotinib, Blinatumomab, Imatinib (Ph+ CML, ALL)
  - Tisagenlecleucel (CAR-T cell for refractory ALL)
  - Everolimus (SEGA)
  - Larotrectinib, Entrectinib (NTRK fusion solid tumors)
  - Ipilimumab (metastatic melanoma)
- **17 Products** have had pediatric safety/dosing information added to the label
- **24 Products** have been granted exclusivity
- **More than 30 Product** are currently being investigated under BPCA

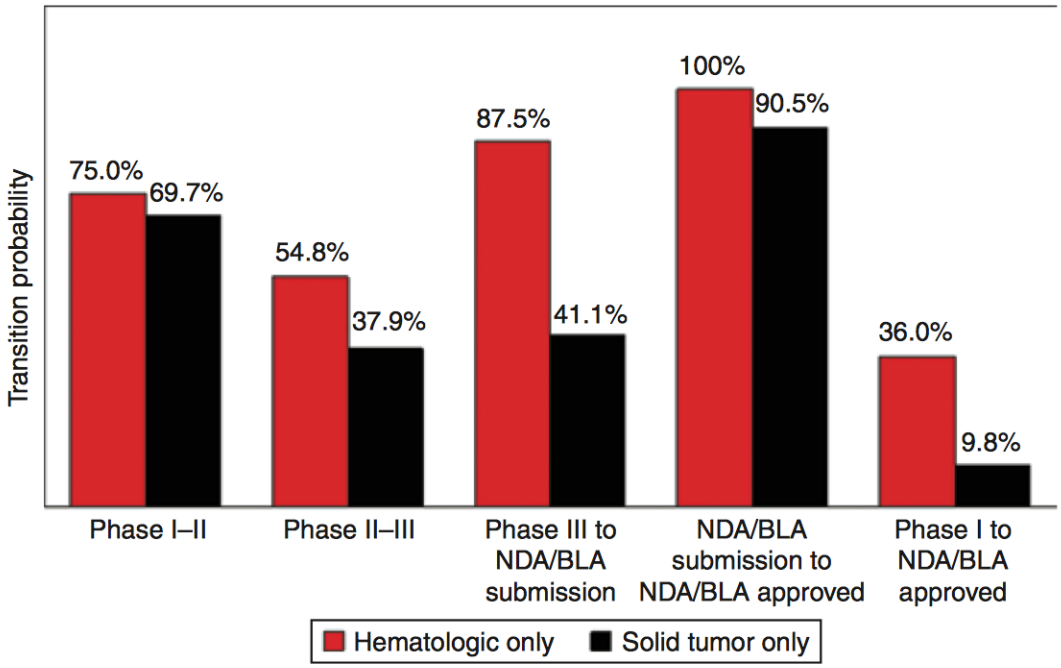
Drug Development timeline: Novel Trial designs

Current trends in Clinical Development:

- Avoid long, linear drug development
- Seamless development programs
- Integrate Phase I-II
- Move from Phase I to Phase III
- Adaptive Clinical Studies
- Staggered enrollment and interim analysis
- Target Population in earlier studies
- Use of Biomarkers
- Predictivity of non-clinical models



Drug Development Attrition

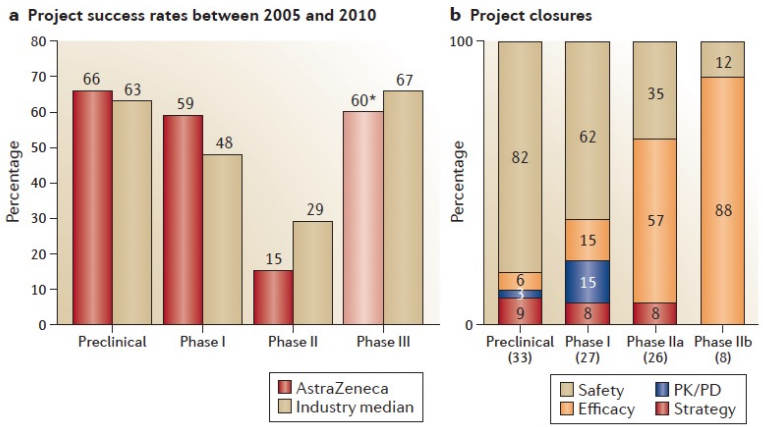


Less than 10% of anticancer compounds with encouraging preclinical efficacy demonstrate robust clinical performance and gain FDA approval

DiMasi et al, Clin Pharmacol Ther. 2013

Drug Development Attrition

Review of Astra Zeneca pipeline



Most drugs failed for lack of efficacy

The 5 Rs Framework

Right target
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients
- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Right commercial potential
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

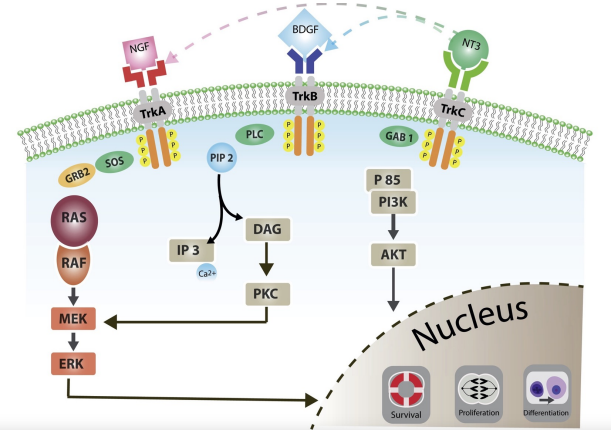
Cook et al, Nat Rev Drug Discov 2014

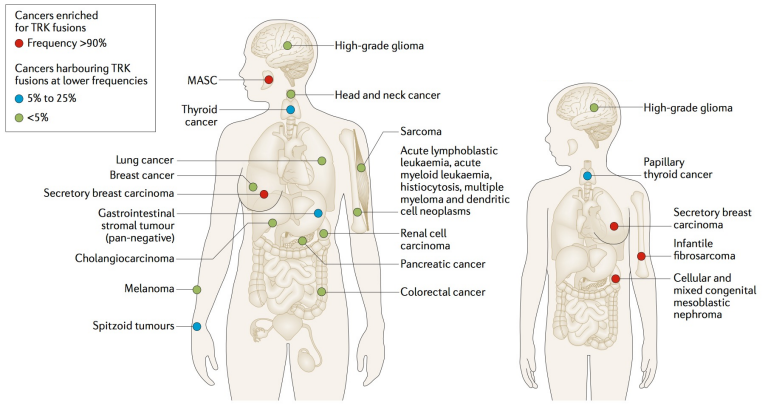
Drug Development – Basket Trials

In **BASKET TRIALS**, patients are grouped not by tumor site but by **genetic signature**

The Neurothropic Tyrosine Receptor Kinases (NTRK) play an important role in the development and function of the nervous system.

NTRK fusions, encoding TRK fusion proteins, are oncogenic drivers of a **wide variety of adult and pediatric tumors**, and activate well-known signal transduction pathways like the MAPK-ERK pathway.





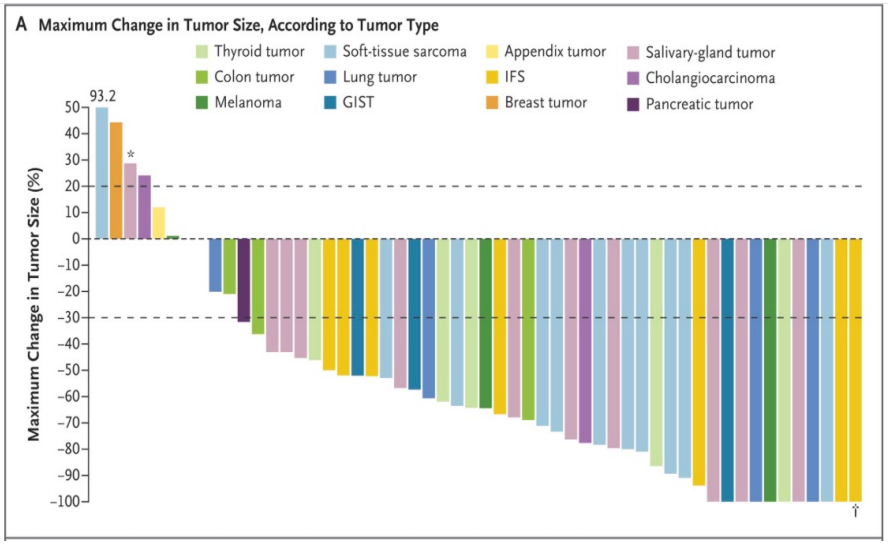
Markl et al, Pathol Res Pract 2019

Drilon et al, New England J. 2018

Drug Development – Basket Trials

Patients were enrolled in TRK inhibitors basket trials solely based on the fact their tumors harbored NTRK fusions, independently of tumor type or patient age

First generation TRK inhibitors demonstrated histology- agnostic and age-independent activity in adult and pediatric patients with diverse cancers harboring NTRK fusions



Drilon et al, New England J. 2018

This led to approval of the first oncology drug not based on tumor type but genetic mutations

FDA News Release

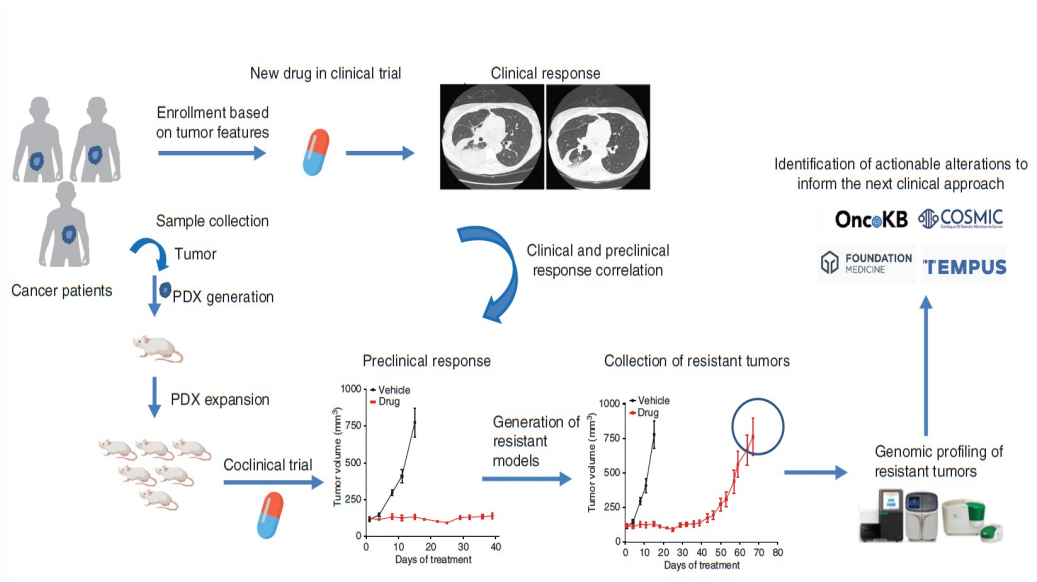
FDA approves an oncology drug that targets a key genetic driver of cancer, rather than a specific type of tumor

New drug Vitrakvi targets specific receptor kinase that promotes tumors

For Immediate Release

November 26, 2018

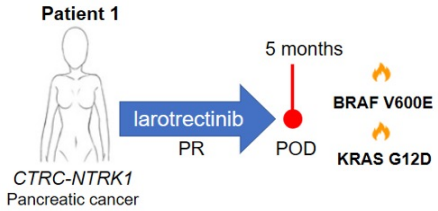
Modeling Drug resistance in Co-clinical Trials

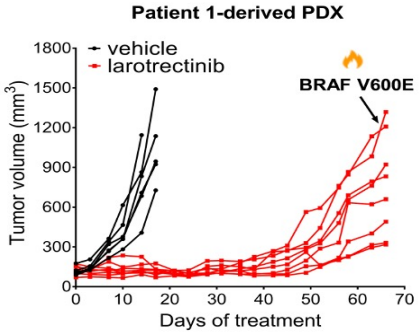


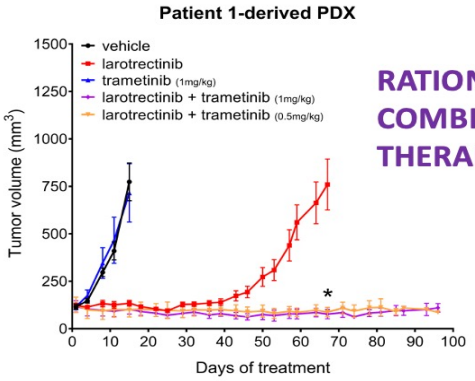
- Stratification of patients based on their genetic make up
- Trials in mice (GEMMs or PDXs) carried out in parallel with ongoing Phase I/II trials
- Collection, comparison and integration of murine and human tumors (mutation analysis, responsiveness to therapeutic agents, tumor RNA, protein and metabolic profiles, etc.)
- Resistance to therapy in the murine system is investigated, and information is used to inform patient treatment and novel combination trials

Cocco and de Stanchina, Cold Spring Harb Perspect Med. 2023

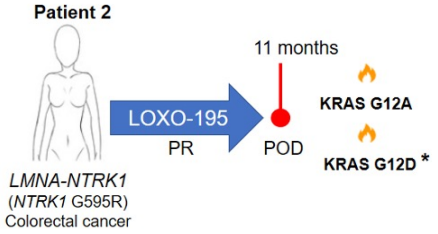
Modeling Drug resistance in Co-clinical Trials

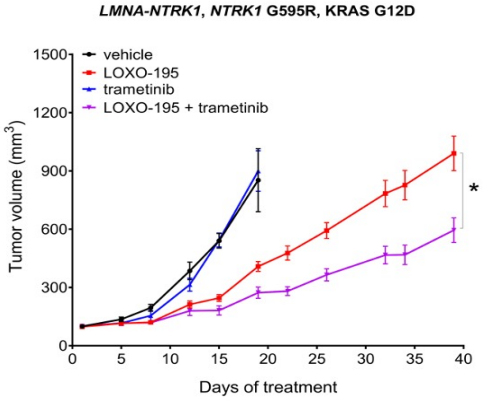


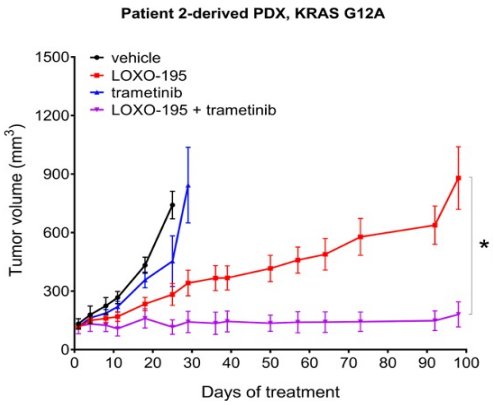




RATIONAL COMBINATION THERAPIES

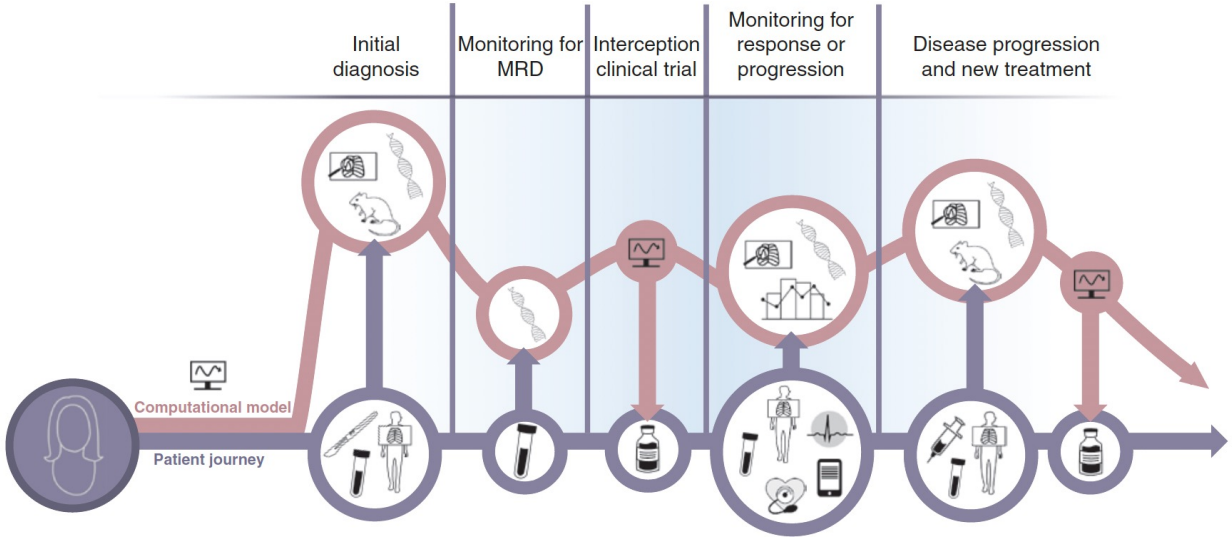






Cocco et al, Nature Medicine 2019

Future of clinical trials



- Clinical trials have shifted from traditional studies evaluating cytotoxic chemotherapy in largely histology-based populations to become adaptively designed.
- They often include **biomarker-driven** evaluations of molecularly targeted agents and immune therapies in **selected patient subsets**.
- Next-generation clinical trials will offer more and more individualized strategies.

Spreafico A et al, Cancer Discov 2021