An overview on early clinical trial and innovative clinical trial designs in oncology drug development

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February 23rd, 2023

University of Brescia (virtual presentation)
PhD Artificial Intelligence in Medicine and Innovation in Clinical Research and Methodology

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Disclosure

- I am a Novartis full time employee and a Novartis shareholder

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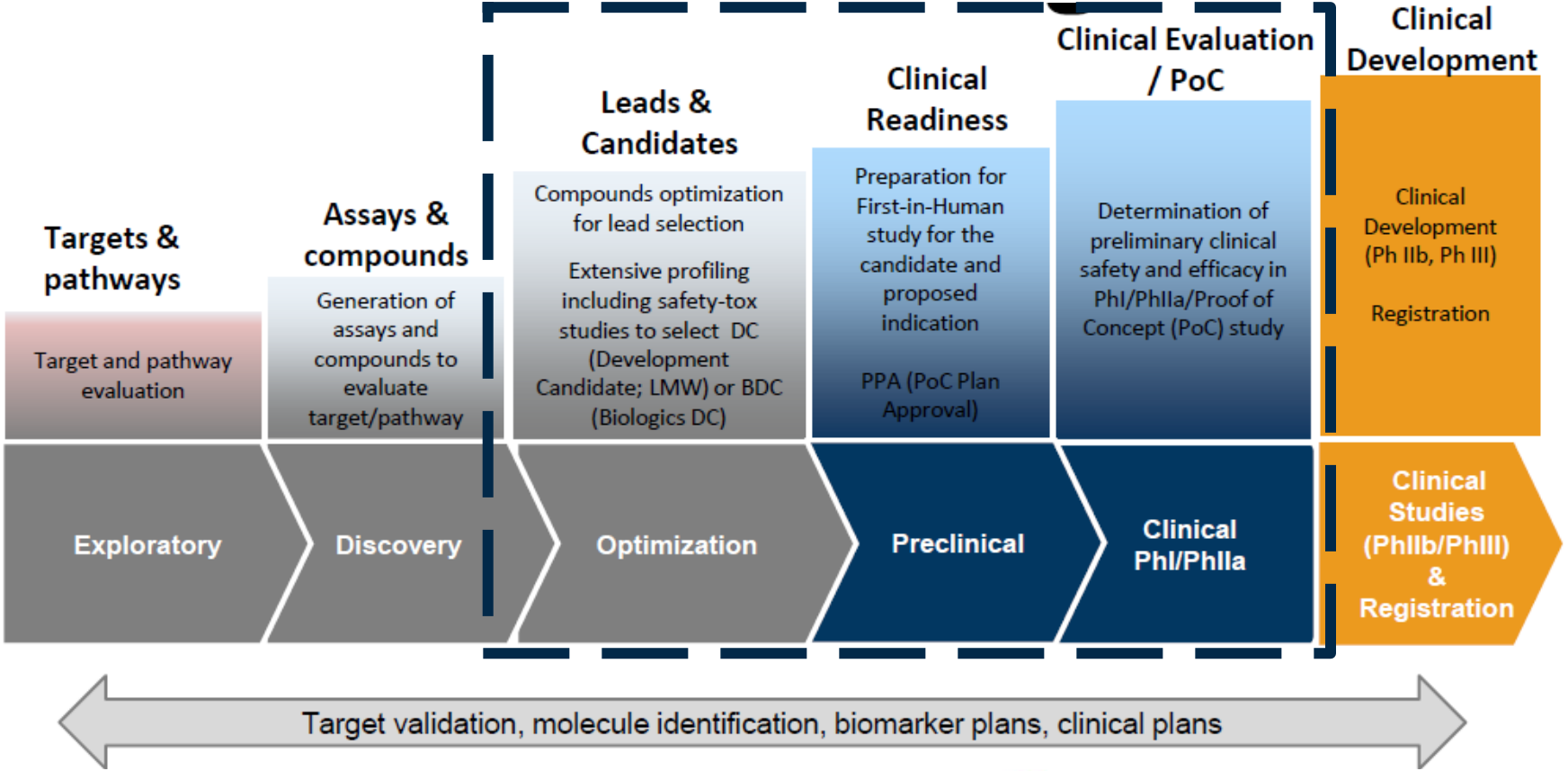
How we develop a new drug – a complex endeavor



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The benefit of participating in Phase 1 Oncology trials is increasing

SPECIAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002

March 3, 2005
N Engl J Med 2005; 352:895-904
DOI: 10.1056/NEJMsa042220

All phase 1 oncology trials sponsored by the National Cancer Institute between 1991 and 2002. The overall response rate for "classic* Phase I trial" was of 4.6% (it increase to 10% considering all phase I trials).

CORRESPONDENCE

The NEW ENGLAND JOURNAL of MEDICINE

Encouraging Trends in Modern Phase 1 Oncology Trials

June 7, 2018
N Engl J Med 2018; 378:2242-2243
DOI: 10.1056/NEJMc1803837
Metrics

A PubMed research to identify phase 1 trials that were published from January 1, 2014, through June 30, 2015. The overall response rate (CR + PR) was 19.8%.

I suspect a more recent analysis would lead to an even better results

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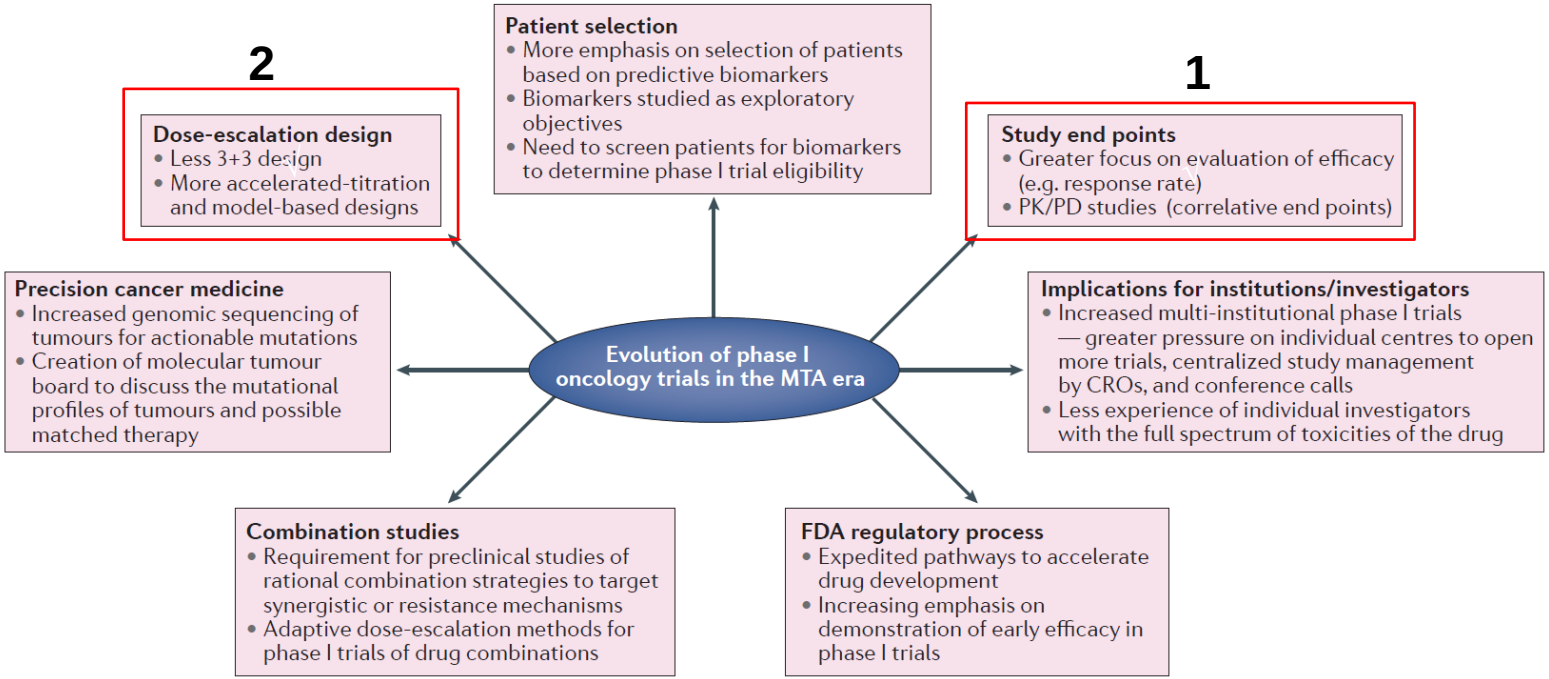
Evolution of Phase 1 trials in the era of MTA, immunotherapy (IO), cell therapy..



Wong et al. Nat Rev Clin Oncol. 2016 Feb;13(2):106-17

MTA: molecular targeted agents

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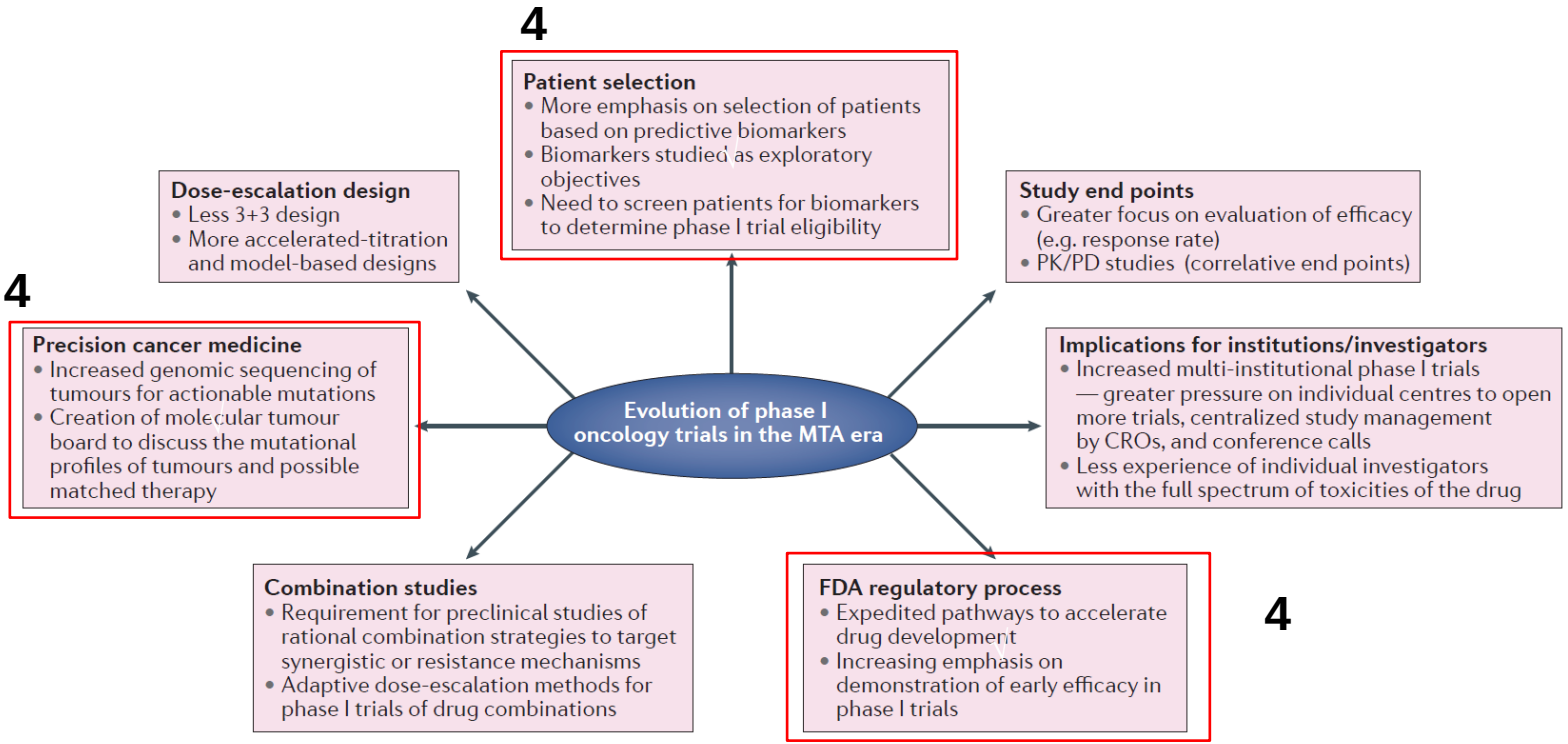
Evolution of Phase 1 trials in the era of MTA, immunotherapy (IO), cell therapy..



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MTA: molecular targeted agent

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Evolution of Phase 1 trials in the era of MTA, immunotherapy (IO), cell therapy..

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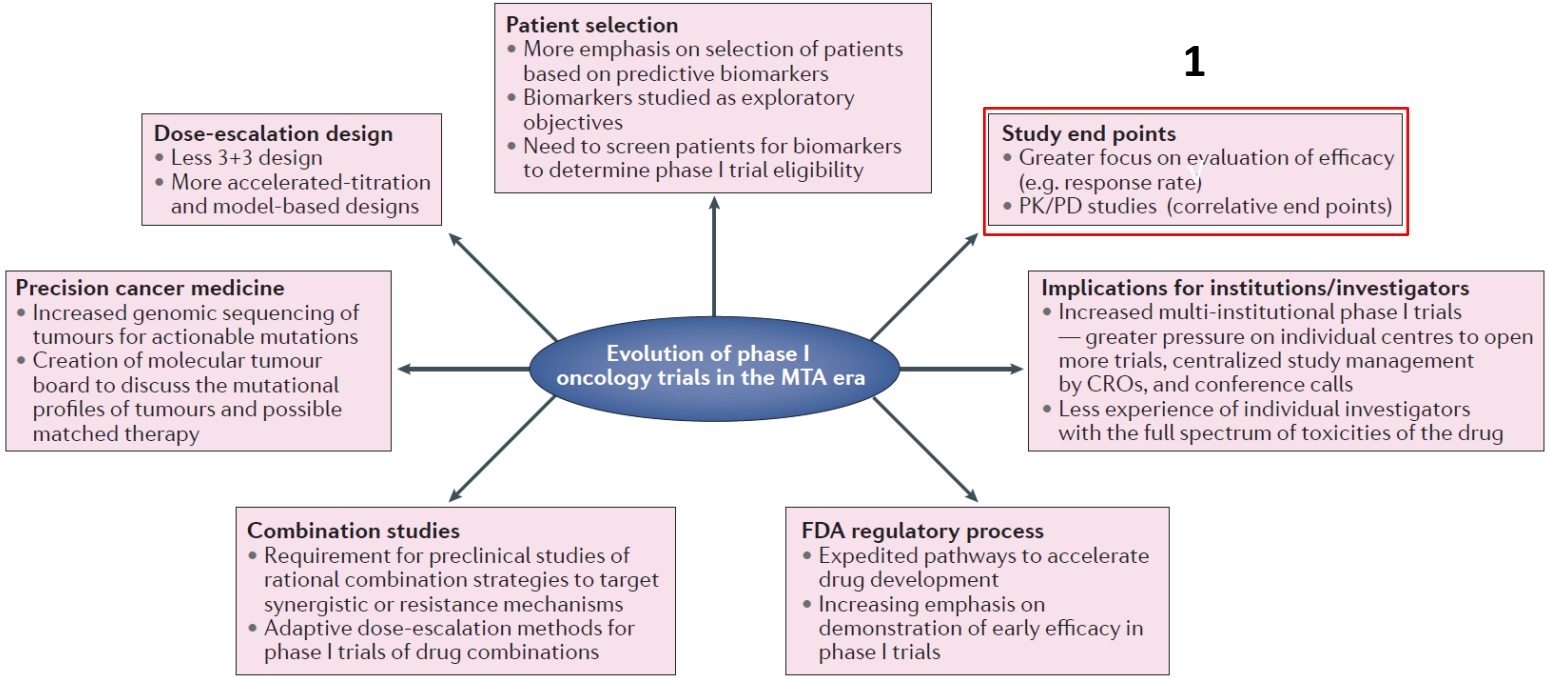

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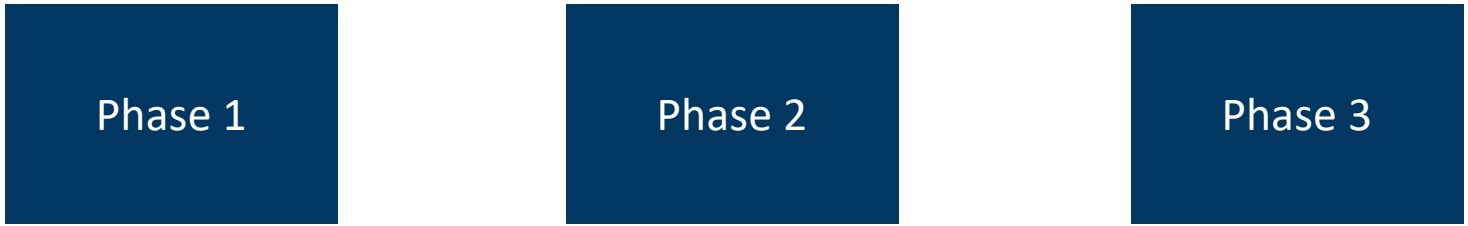
The current clinical drug development phases



Key words:
PK: Pharmacokinetic
RP2D: Recommended phase 2 dose
POC: Proof of Concept
POM: Proof of mechanism

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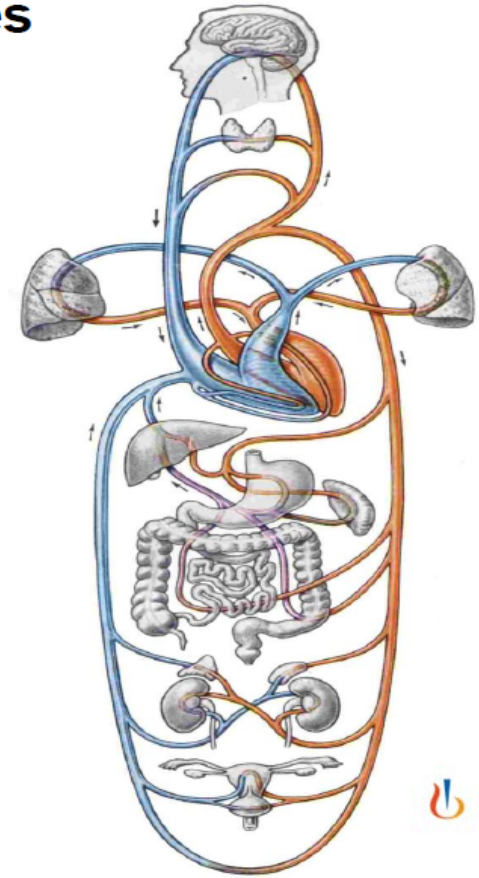
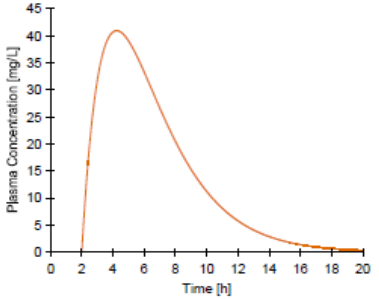
What is pharmacokinetics (PK)?

…PK is what the body does to the drug…

- **Pharmacokinetics**
  - Kinetics of drug absorption, distribution and elimination (excretion and metabolism)
  - Drug disposition = distribution and elimination
- **ADME**
  - **Absorption**
  - **Distribution**
  - **Metabolism**
  - **Elimination**





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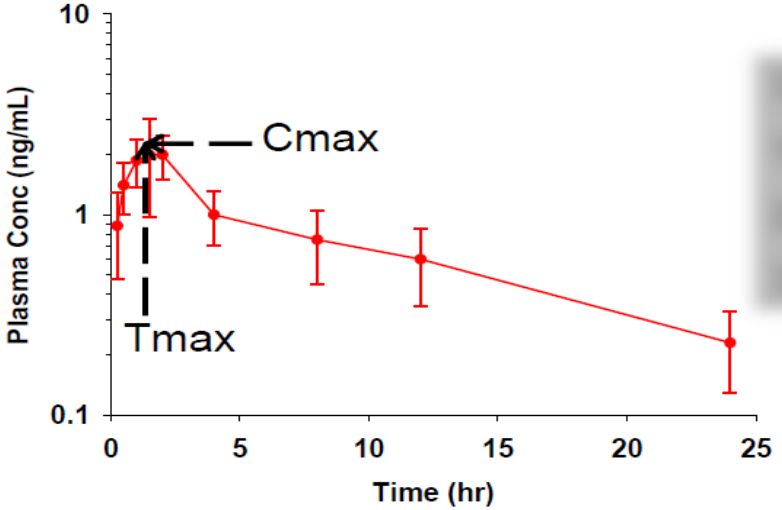
Concentration-time profile

Single oral (PO) administration



3 Key Phases:

1. **Absorption**
2. **Distribution**
3. **Elimination**

Cmax = Highest concentration of drug observed

Cmin = Minimum concentration of drug observed

Tmax = Time at which the highest concentration of drug is observed

AUC(0-t) = The area under the curve (trapezoidal rule) calculated to the last quantifiable concentration or a specific time point

Bioavailability (%F) = Fraction of extravascular dose that reaches systemic circulation

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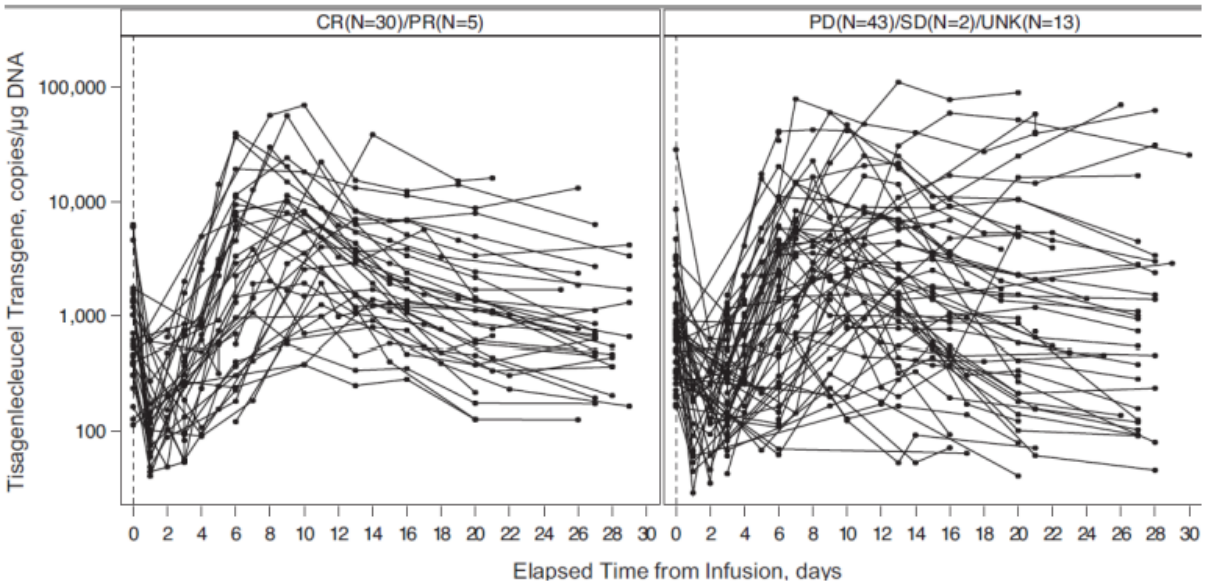
Understanding PK profile of new drug modalities like cell therapies

A. Individual concentration-time profiles up to day 28 in responding (left panel) and nonresponding patients (right panel).



How to set the dose of a drug that auto-proliferates?

How to account for variability of patient cell products?

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Schuster er all N Engl J Med 2019; 380:45-56

What is pharmacodynamics (PD)?

…PD is what the drug does to the body…

- PD describes the time-course of the biological effects of drugs
- Studied with the use of biomarkers
  - Measurable physiological or biochemical signals that reflect some PD activity of the drug
- Evidence of drug- target interaction
  - Leading to efficacy (clinical effects) or
  - toxicity (chemical toxicity, on-target, off-target or downstream)

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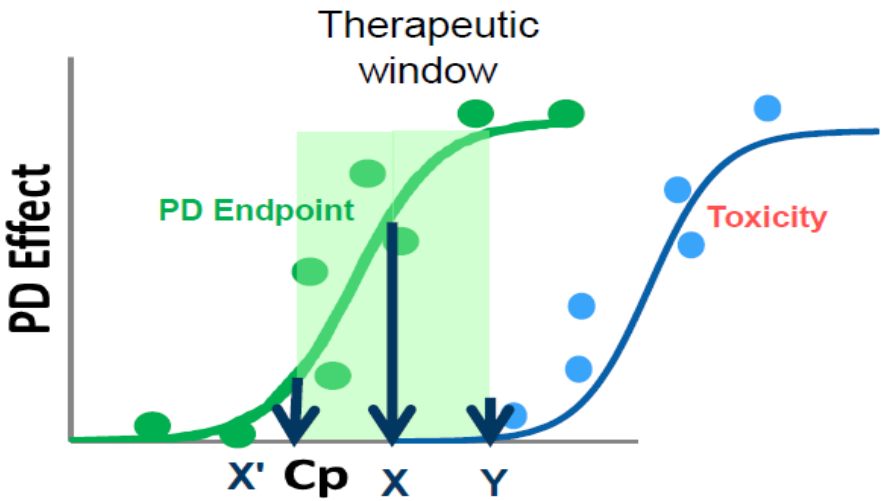
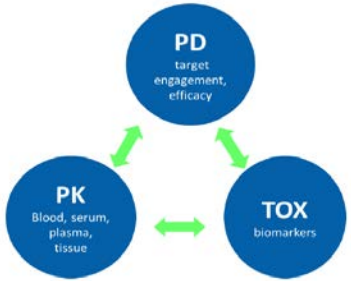
PKPD modeling and integration with toxicity endpoints





PD and toxicity endpoints may be obtained from a single or a different set of experiments, and within same or different species

Therapeutic index or safety margin = $\frac{\text{Y (Drug exposure with safety end point)}}{\text{X or X' (Drug exposure with desired pharmacology end point)}}$

Exposures can be defined by Cmax, AUC, Cave, IC_{50} , IC_{90} etc. or another surrogate for drug concentration

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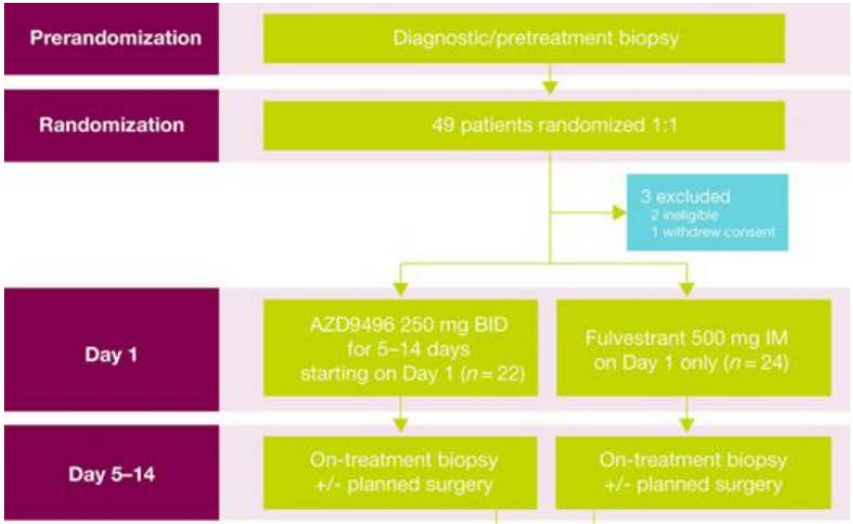
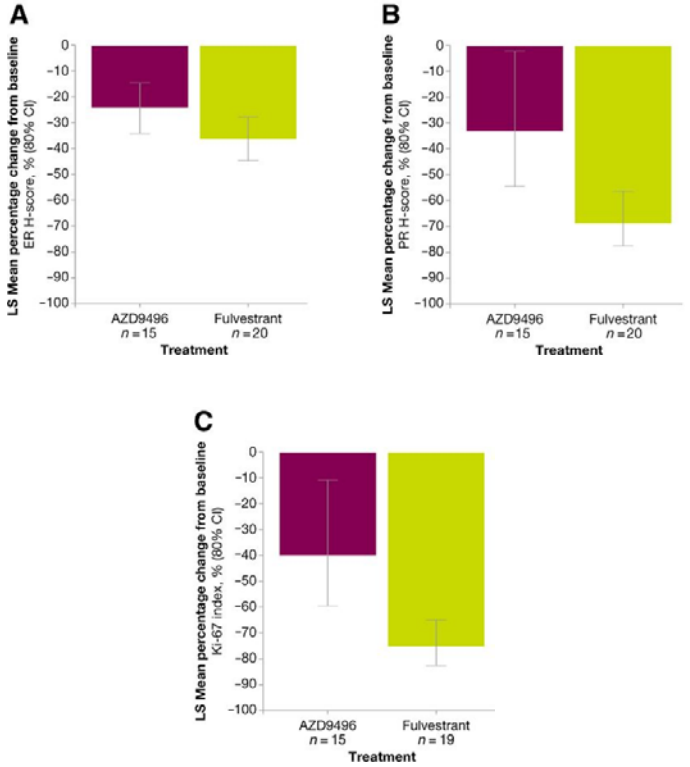
A Randomized, Open-label, Presurgical, Window-of-Opportunity Study Comparing the Pharmacodynamic Effects of the Novel Oral SERD AZD9496 with Fulvestrant in Patients with Newly Diagnosed ER^{+} HER2^{-} Primary Breast Cancer FREE

John F.R. Robertson ; Abigail Evans; Stephan Henschen ; Cliona C. Kirwan ; Ali Jahan; Laura M. Kenny; J. Michael Dixon; Peter Schmid; Ashutosh Kothari; Omar Mohamed; Peter A. Fasching ; Kwok-Leung Cheung ; Rachel Wuerstlein; Danielle Carroll; Teresa Klinowska; Justin P.O. Lindemann ; Alexander MacDonald; Richard Mather; Rhiannon Maudsley; Michele Moschetta; Myria Nikolaou; Martine P. Roudier; Tinnu Sarvotham; Gaia Schiavon; Diansong Zhou ; Li Zhou ; Nadia Harbeck

Figure 1.





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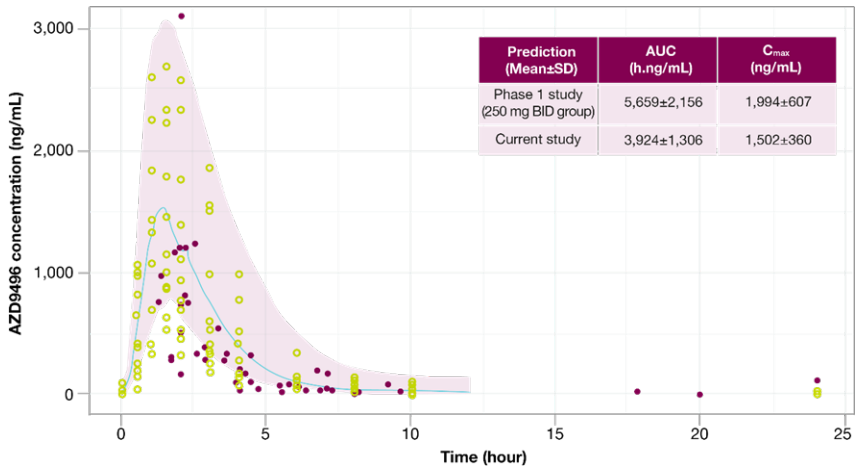
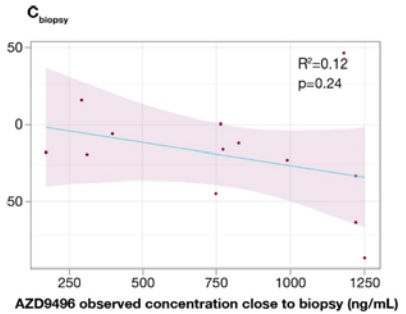
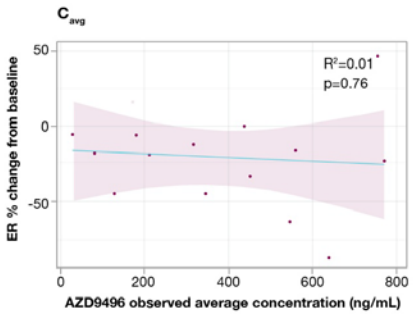
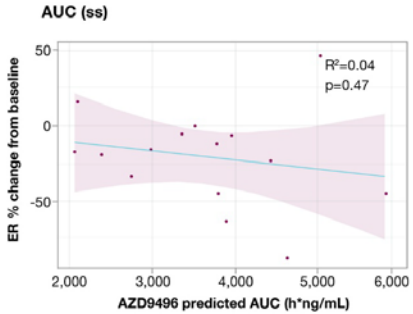
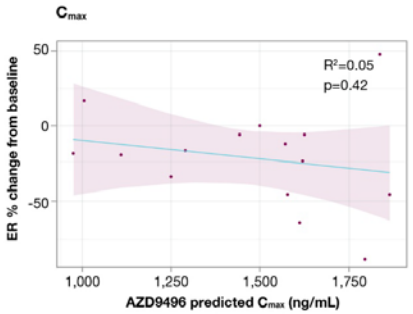


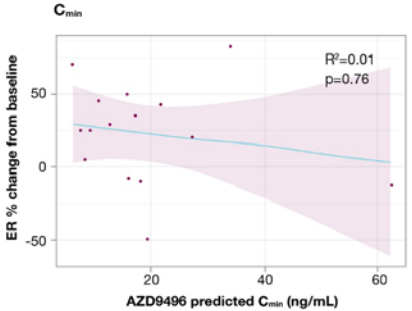
Prediction (Mean±SD)	AUC (h.ng/mL)	C_{max} (ng/mL)
Phase 1 study (250 mg BID group)	5,659±2,156	1,994±607
Current study	3,924±1,306	1,502±360



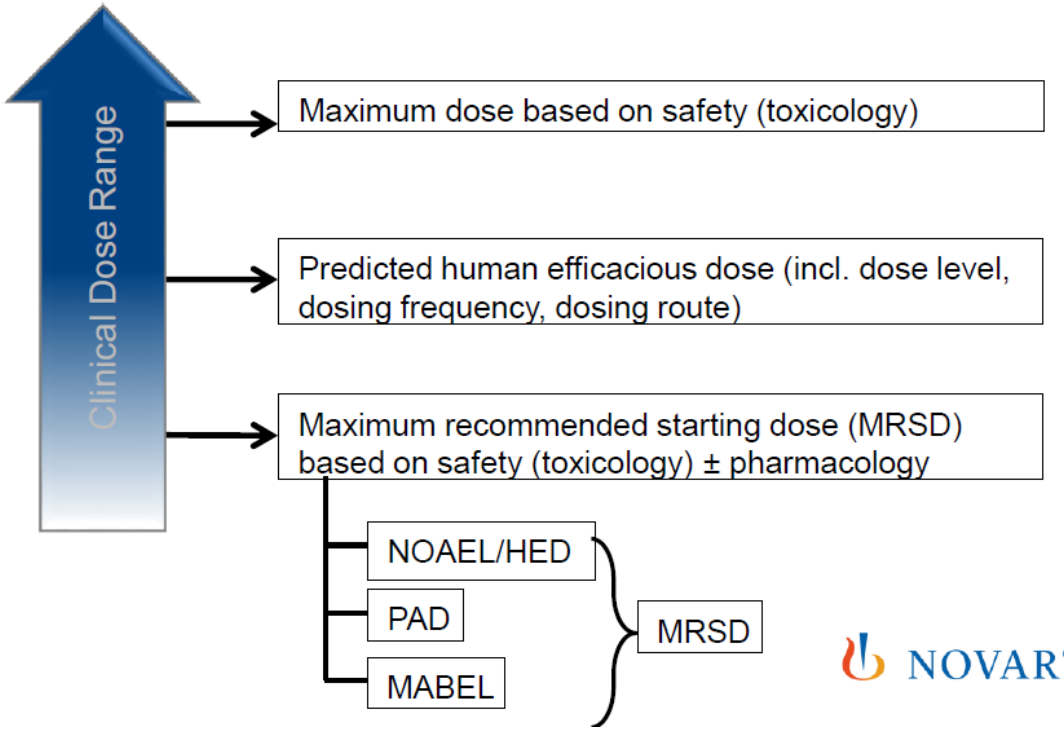








Defining a clinical dose range requires both starting dose and maximum dose predictions



NOAEL/HED	No observed adverse effect level/Human equivalent dose
PAD	Pharmacologically active dose
MABEL	Minimum anticipated biological effect level

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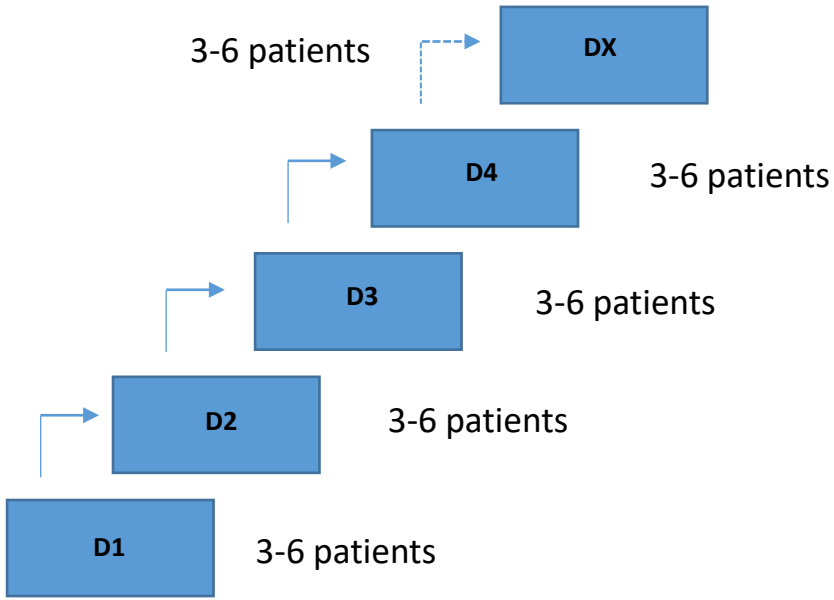
Classical versus novel Phase 1 clinical trials

All comer patient population

Safety/Tolerability/PK/ MTD/RP2D



FTIH
(First time in human)
Starting dose

Classical=max 30-50 pts

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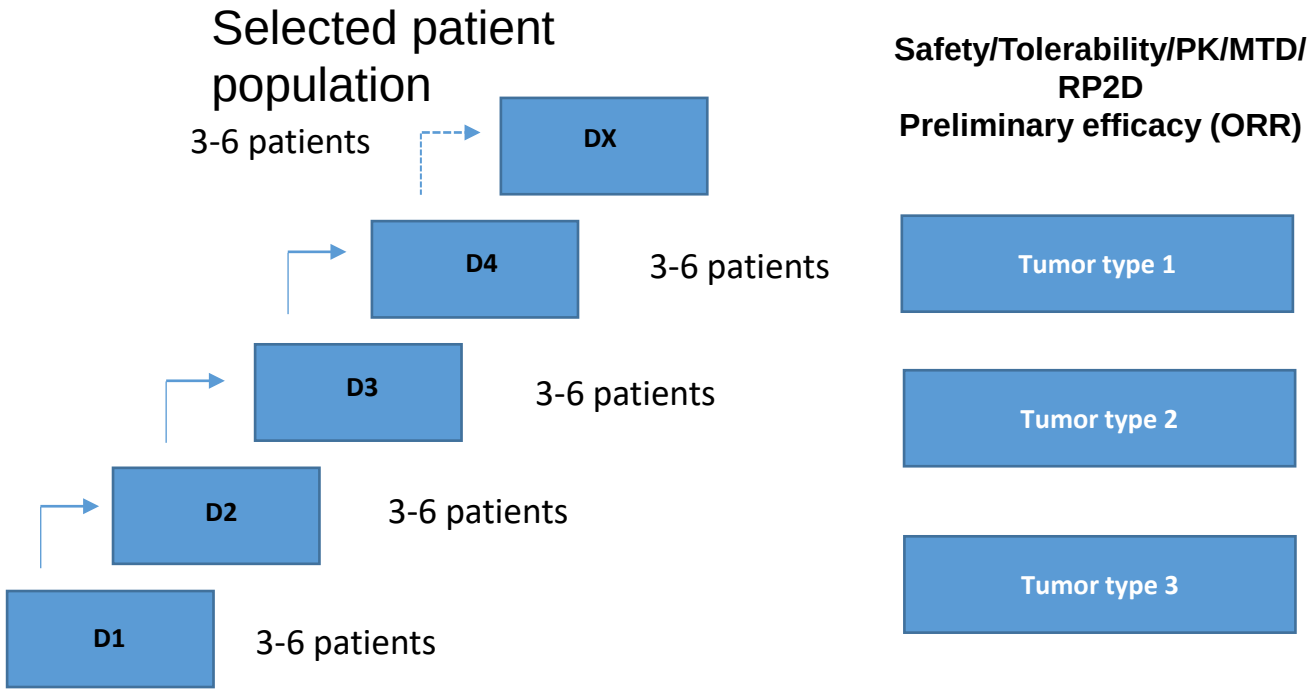
Classical versus novel Phase 1 clinical trials



FTIH
(First time in human)
Starting dose

Novel Phase 1/2a=max 100-200 pts

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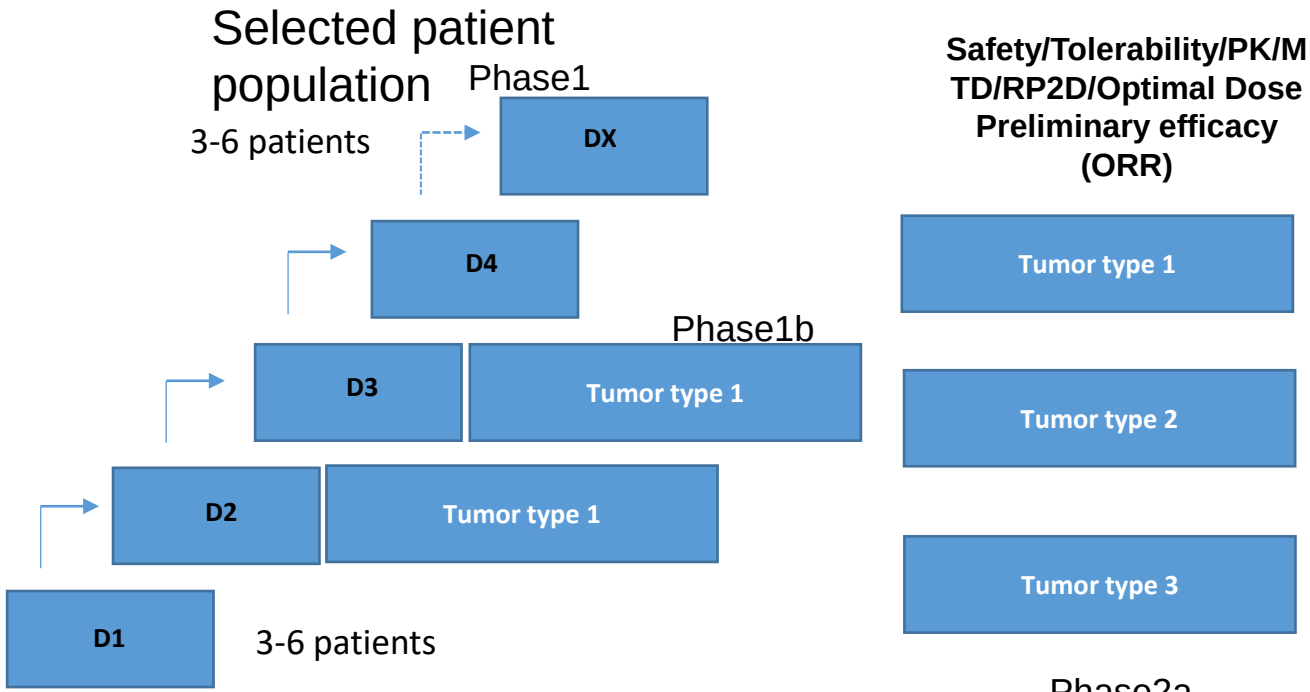
Classical versus novel Phase 1 clinical trials



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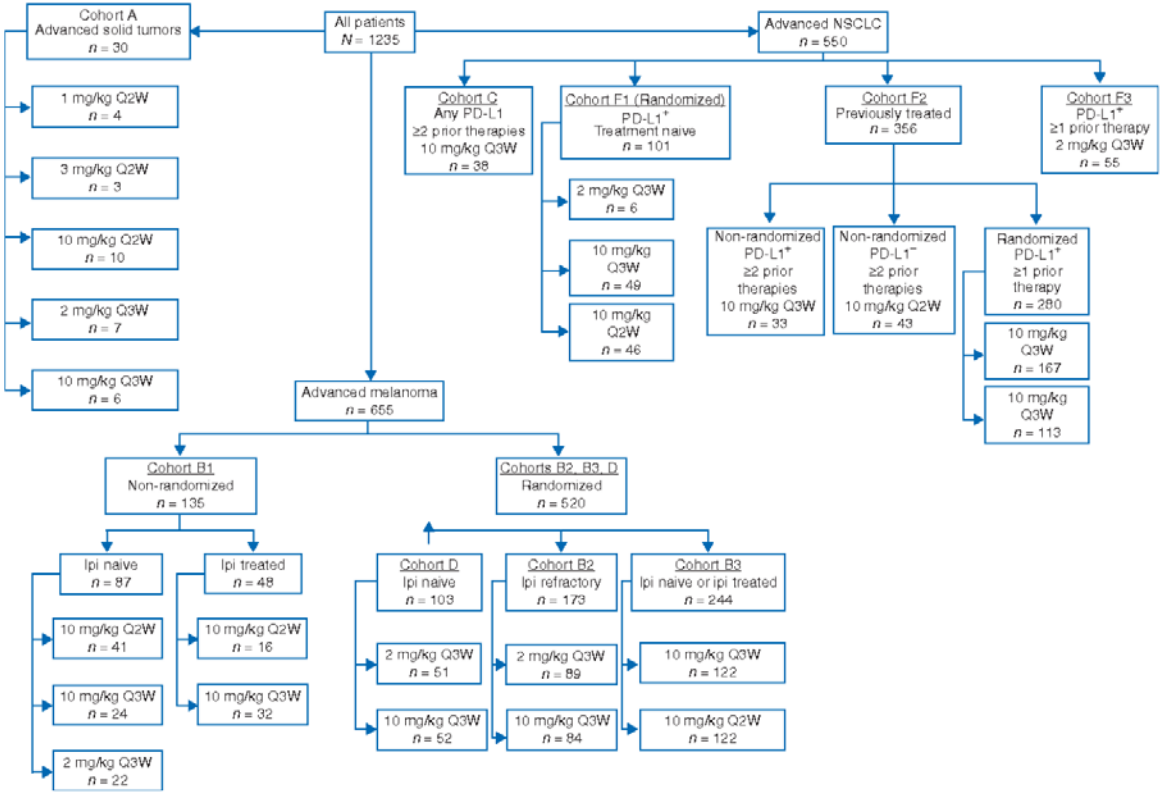
Classical versus novel Phase 1 clinical trials



Safety/Tolerability/PK/MTD/RP2D/Optimal Dose/POC/POM
Accelerated Registration

KEYNOTE001

Novel>1200 pts

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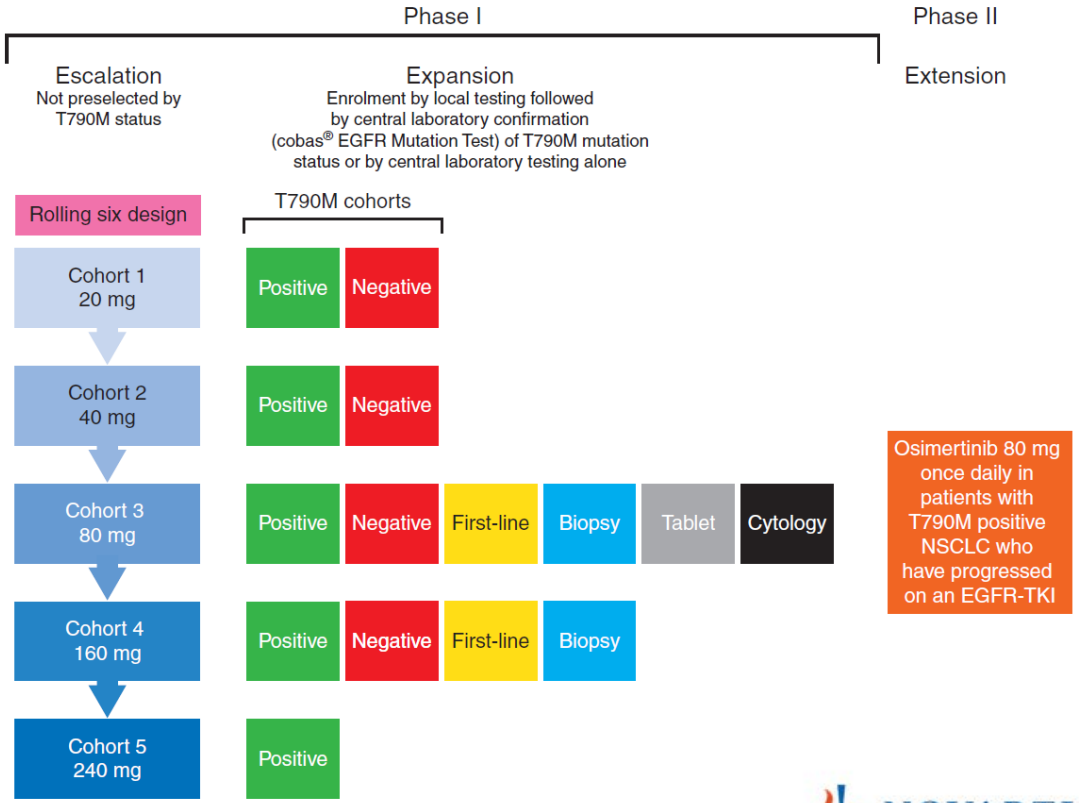
Classical versus novel Phase 1 clinical trials

industry corner

Annals of Oncology



Safety/Tolerability/PK/MTD/RP2D/Optimal Dose/POC/POM
Accelerated Registration

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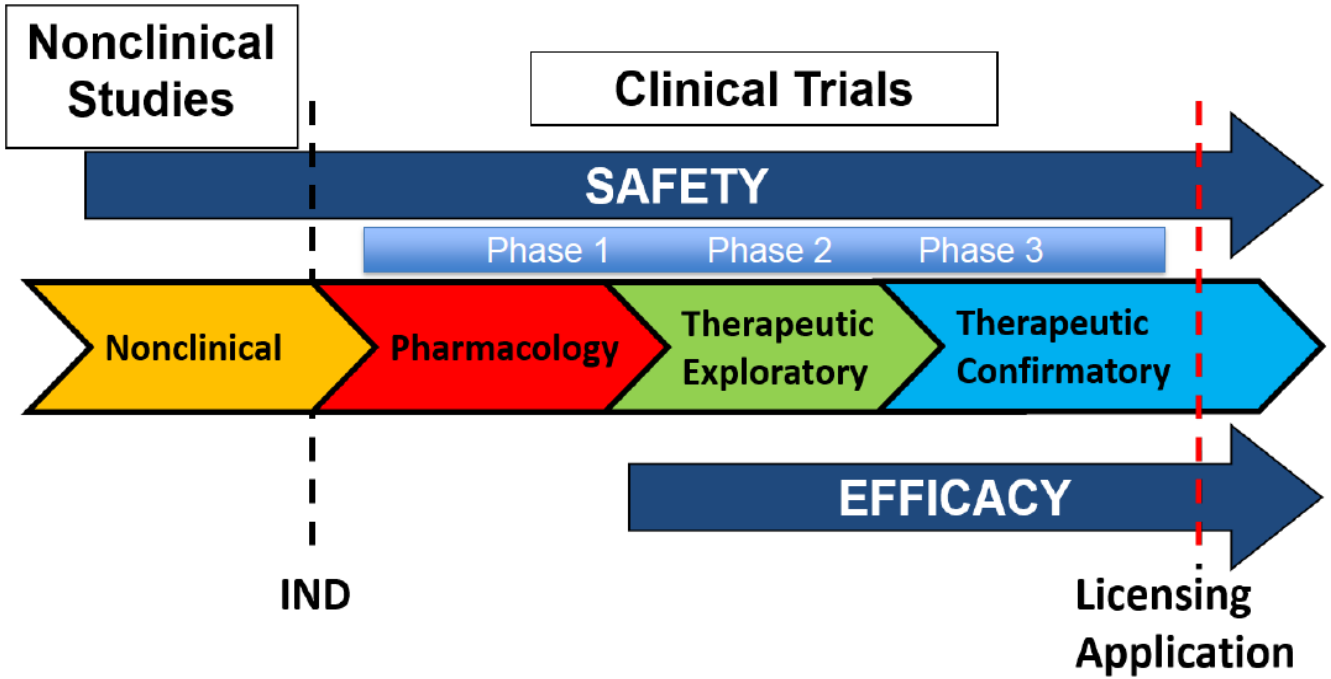
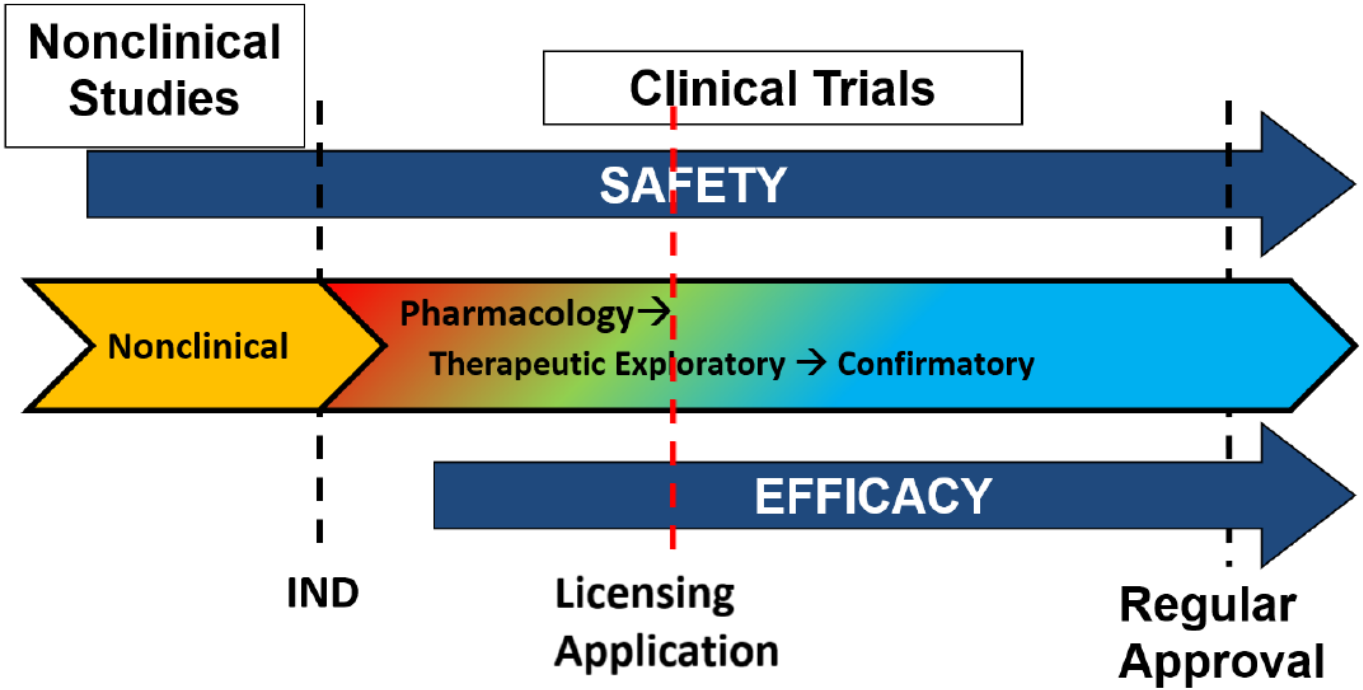
"Phased" Drug Development Paradigm



Prowell, T.M., M.R. Theoret, and R. Pazdur, *Seamless Oncology-Drug Development.* N Engl J Med, 2016. **374**(21): p. 2001-3

Seamless Oncology Drug Development Paradigm



Prowell, T.M., M.R. Theoret, and R. Pazdur, *Seamless Oncology-Drug Development*. N Engl J Med, 2016. **374**(21): p. 2001-3

Evolution of Phase 1 trials in the era of MTA, immunotherapy (IO), cell therapy..

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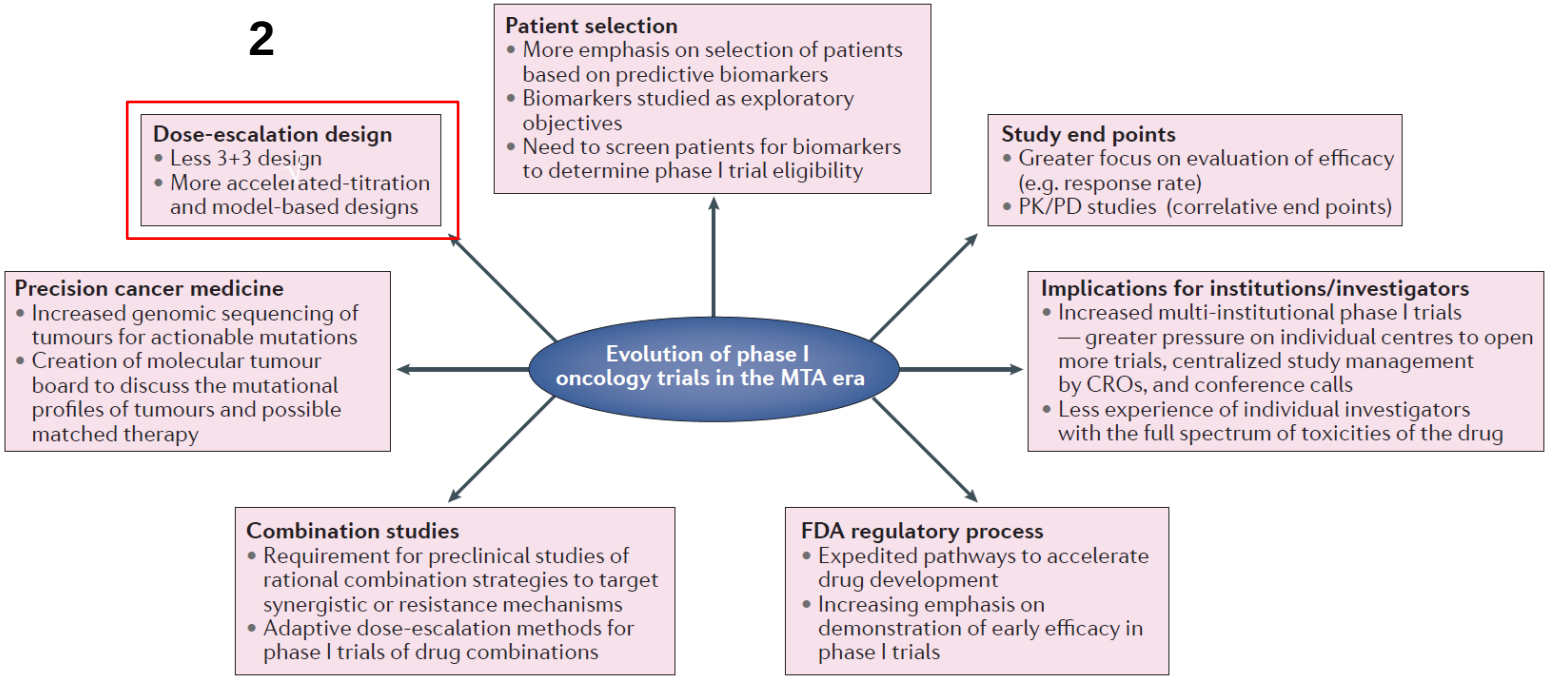

Wong et al. Nat Rev Clin Oncol. 2016 Feb;13(2):106-17

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Evolution of Phase 1 trials: dose escalation

- Monotonic relationship for toxicity and efficacy assumed for all drug modalities, but often untrue
- Cytotoxic chemotherapy generally causes DLTs shortly after drug administration
- Cumulative low-grade toxicities and delayed toxicity are not captured within the DLT-assessment window.
- MTAs/IOs/cell-therapy often show delayed/chronic toxicity
- Maximum tolerated dose (MTD), Optimal biological dose, Optimal immunological dose, Optimal cell dose.

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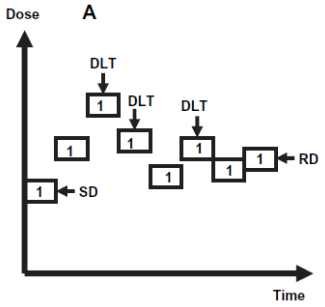
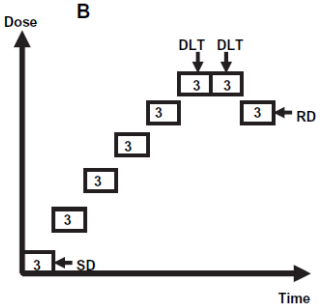
Dose escalation methodologies (All safety end point based)

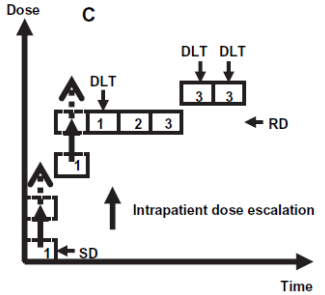
Up-and-down design

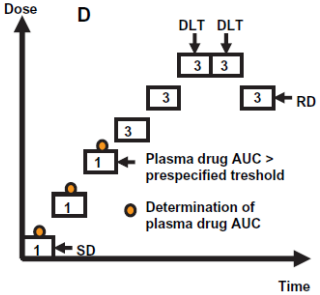




Traditional 3+3 design

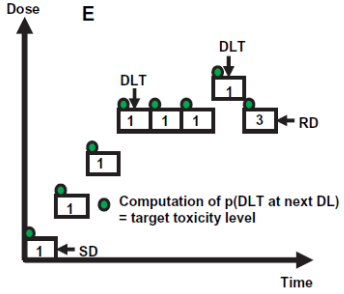
Accelerated titration design

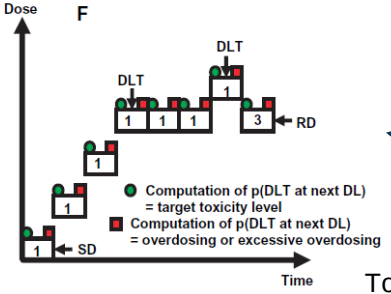




Pharmacologicall y-guided dose escalation

Continual reassessment method





Escalation with overdose control

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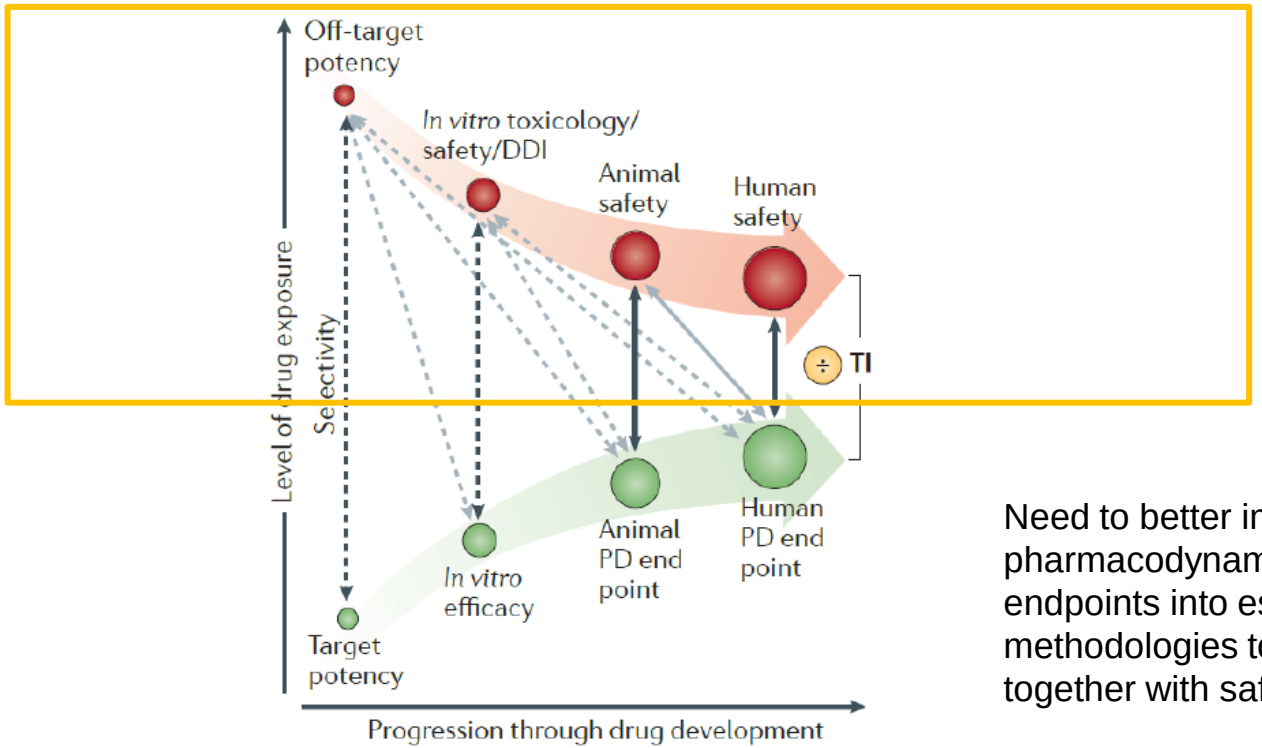
Tourneau et al. JNCI 2009 101:708 - 720

Dose escalation methodologies (All safety end points based)

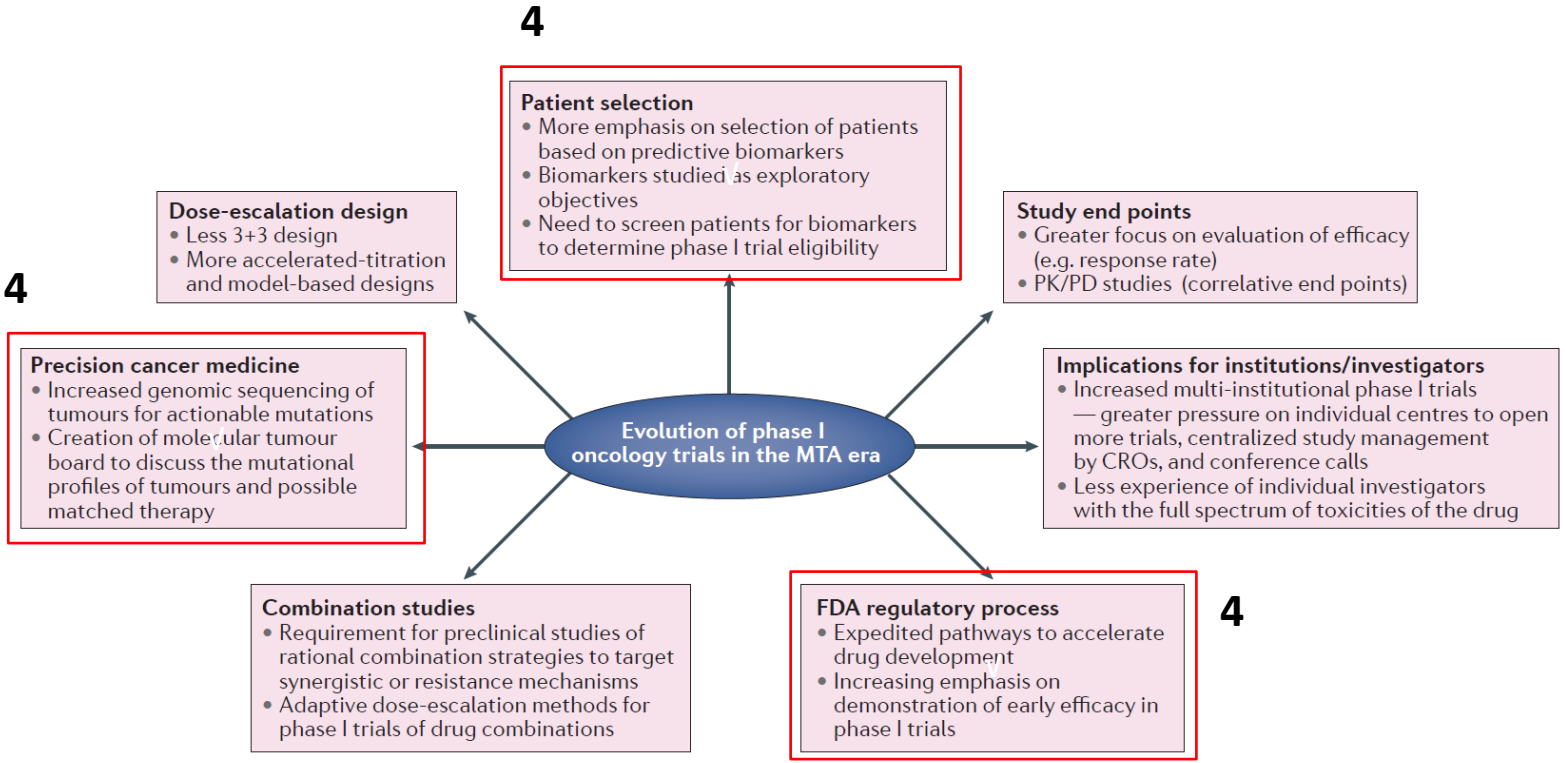


Need to better implement pharmacodynamics/efficacy endpoints into escalation methodologies to drive decisions together with safety endpoints

Nature Reviews, Drug Discovery, Vol 11, Oct 2012, 751-761

Evolution of Phase 1 trials in the era of MTA, immunotherapy (IO), cell therapy..

REVIEWS



MTA: molecular targeted agent

Wong et al. Nat Rev Clin Oncol. 2016 Feb;13(2):106-17

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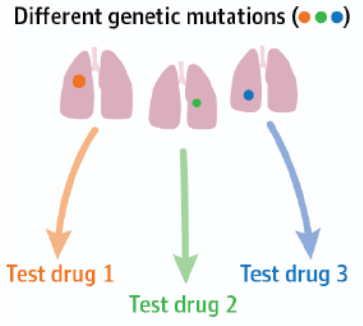
Master Protocol Trial Designs

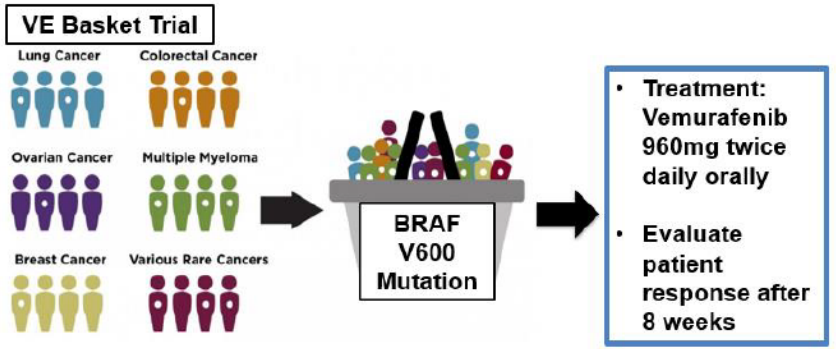
Umbrella

- One type of cancer with multiple drugs and predictive biomarkers
- Patients are matched based on biomarker analysis
- Examples
  - LUNG-MAP
  - BATTLE
  - I-SPY2



Basket

- Multiple tumor types with one drug and a predictive biomarker
- Biomarker-driven approach



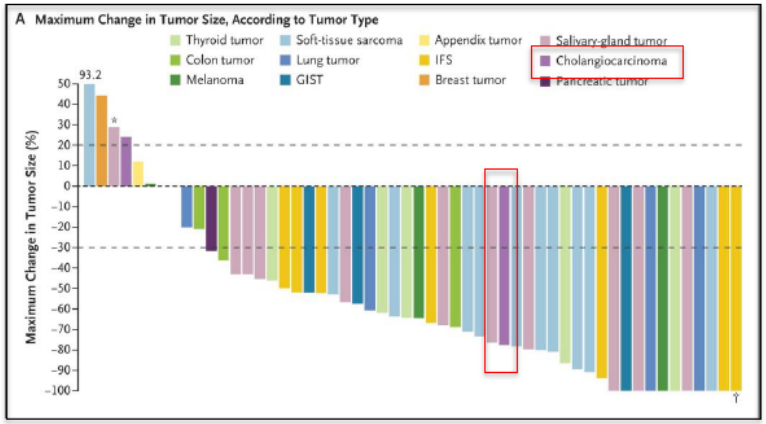
Hyman, et al. 2015. 'Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations', *New England Journal of Medicine*, 373: 726-36.

Paradigm Shift

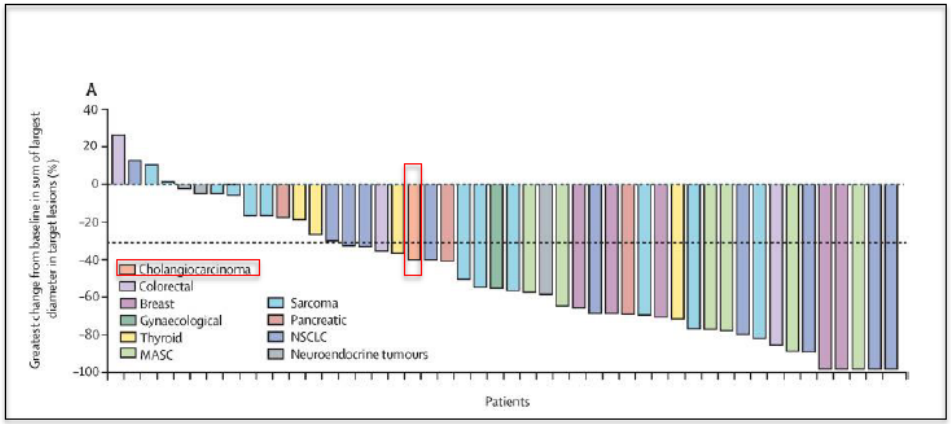
AGNOSTIC INDICATION

Prerequisite: detailed biologic understanding + clinical data showing large magnitude and consistency of effect

Why Tissue Agnostic Development?
Example: cholangiocarcinoma and NTRK



Larotrectinib NTRK+; Drilon et al., NEJM, 2018



Entrectinib NTRK+; Doebele et al., The Lancet Oncology, 2019

Conclusions

-Phase 1 oncology studies are evolving in their design and scope

-Clinical/Statistical/Operational/Regulatory aspects can still be improved; new creative solutions can speed up drug development, reduce costs and increase patients' benefit

-Phase 1/2a studies are now the critical and central stage of the development of a new drug in oncology

-Dose optimization is becoming critical for the successful development of a new oncology drug

-Enrolling patients in Phase 1 trials will become part of standard practice given the increased benefit observed in participating patients

-New platform studies and agnostic development are also changing the traditional drug development paradigms

Thank you

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