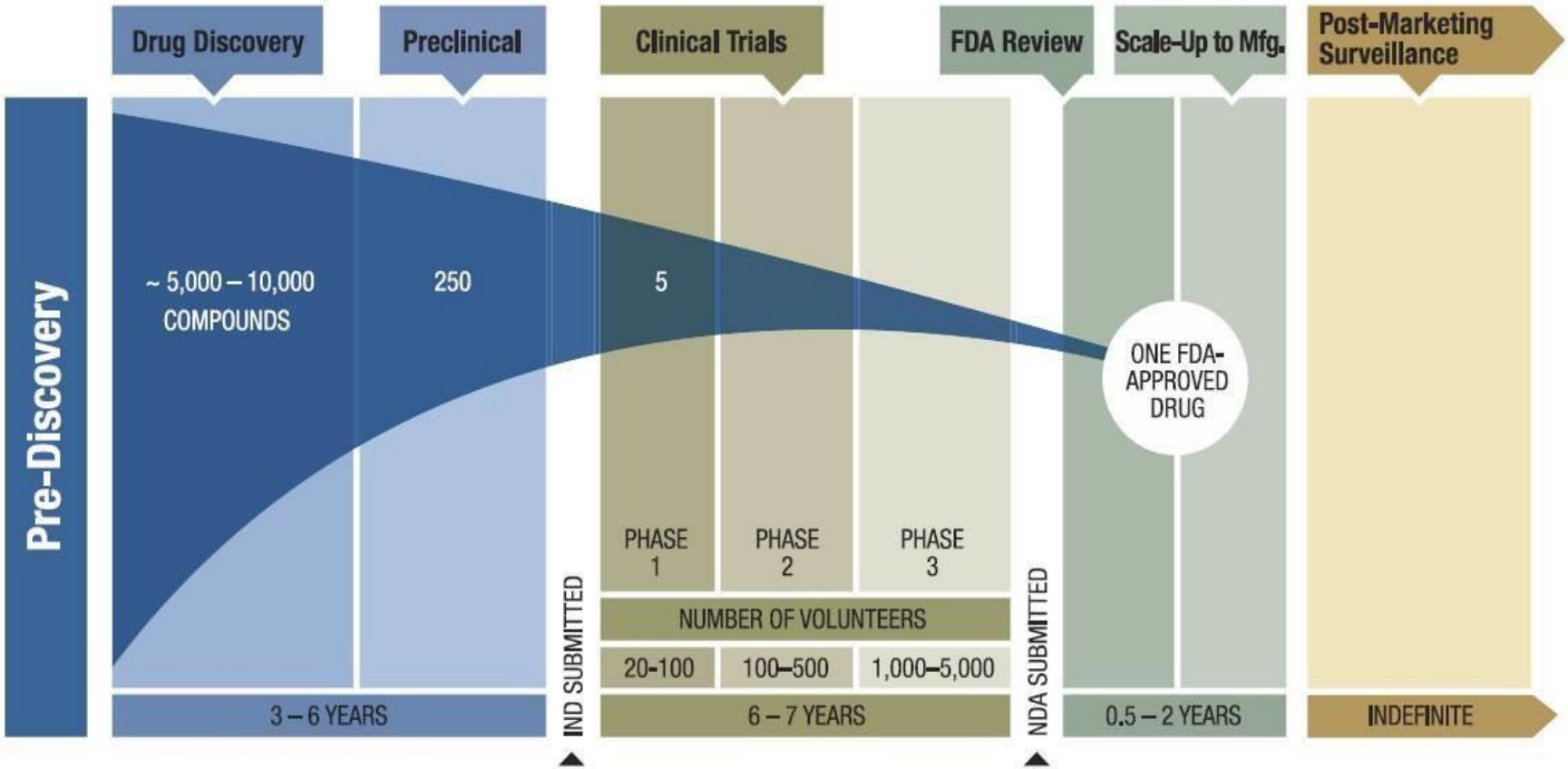
CLINICAL TRIALS IN ONCOLOGY
In the era of the Precision Medicine

Florence, 23 January 2020

GIOVANNI NAVALESI

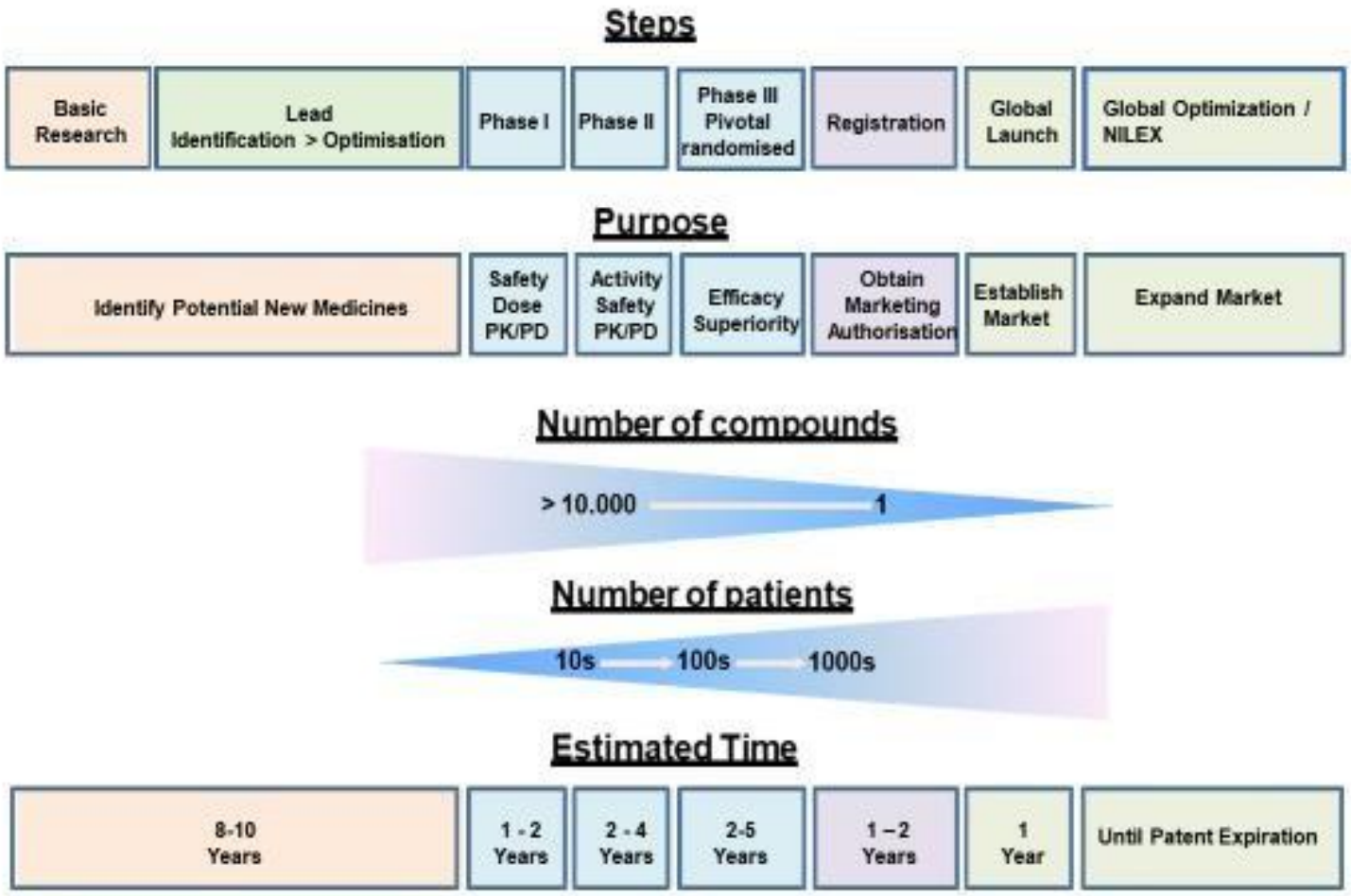
PEC PHARMA EDUCATION CENTER

Drug Discovery and Development Timeline



Graphic Courtesy of the American Association of Cancer Research 2011 Cancer Progress Report

Oncology Drug Development: The Traditional Model



J. Verweij and H.R. Hendricks, 2019

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL TRIAL ENDPOINTS

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oncology PRO®
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ENDPOINTS NEED TO MATCH THE PURPOSE OF THE TRIAL

Phase 1:	Evaluate toxicity
	Study drug disposition (pharmacokinetics, PK)
	Proof of concept that drug inhibits its target (pharmacodynamics, PD)
	Determine dose and schedule for Phase 2
Phase 2:	Estimate anti-tumour efficacy
	Further define toxicity
	Further PD studies
Phase 3:	Compare outcomes reflecting patient benefit with usual standard of care

ENDPOINTS APPROPRIATE FOR OTHER TYPES OF TRIAL

Phase 0: Trials in which a (usually) low dose of a drug is given. Appropriate endpoints are measures of drug disposition and target inhibition

Phase 4: Post-marketing studies. Appropriate endpoints are those of efficacy and toxicity under real-life conditions

Trials of local therapy: In addition to endpoints used in trials of systemic therapy, other appropriate endpoints may include:

- Local relapse-free survival
- Functional effects
- Completeness of resection

ENDPOINTS IN PHASE I AND PHASE II TRIALS

- While the primary goal of phase I trials is to evaluate toxicity and tolerance (and PK and PD) agents that show no signs of activity rarely succeed in later trials.
- The primary goal in phase II is to determine if there is sufficient evidence of *anti-tumour activity* to undertake further studies in phase III (very expensive in terms of human and €€€ resources).
- Appropriate endpoints for phase II include measures of anti-tumour activity such as Overall Response Rate (ORR) or reduction of a tumour marker (e.g. PSA response rate).
- Progression-free survival (PFS) or percent without progression at a given time are also appropriate endpoints in phase II trials, especially if they are randomised.
- Identification of biomarkers is important in early phase trials. New endpoints such as reduction in circulating tumour cells (CTCs) are under investigation

Phase I: Primary Goal(s)

Evaluate Toxicity:

- Define dose limiting toxicity (DLT)
- Define maximum tolerated dose (MTD)
- Begin development of side-effect profile

Evaluate Pharmacokinetics PKs): ADME

How the drug(s) is:

- Absorbed
- Distributed
- Metabolized
- Excreted

May provide early evidence of response, but *NOT* primary aim

Phase I: Patient Population

- 15 – 30 (< 100) subjects
- Usually many cancer types (e.g. solid tumors)
- Refractory to standard therapy
- No remaining standard therapy
- Adequate organ function
- Adequate performance status

Phase I: Standard Design

- Open label, non-randomized, dose escalation
- Low starting dose
  - 1/10th the lethal dose (LD10) in the most sensitive species tested = dose at which 10% of the animals die
  - Unlikely to cause serious toxicity
  - Pediatric dose starts at 80% of adult MTD
- 3-6 patients per cohort
- Increase dose gradually
  - Most common scheme is a Modified Fibonacci

Classic Modified Fibonacci Dose Escalation Scheme

% Increase Above Preceding Dose:

Level 1: Starting dose

Level 2: 100% increase from Level 1

Level 3: 67% increase from Level 2

Level 4: 50% increase from Level 3

Level 5: 40% increase from Level 4

Levels 6+: 33% increase from Level 5+

Phase II: Primary Goals

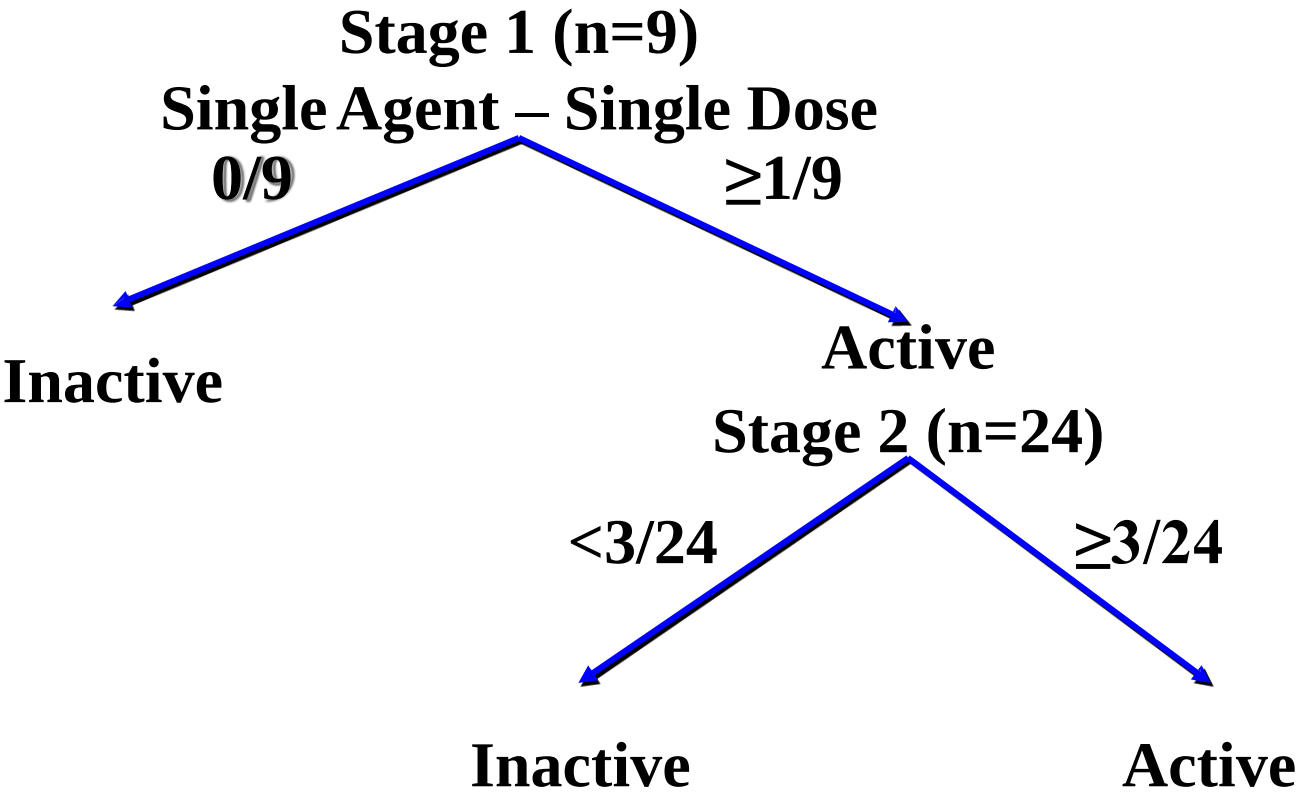
Evaluate activity

Further safety (adverse events) evaluation at the MTD

Phase II: Patient Population

- ~100 subjects (100-300)
- More homogenous population that is deemed likely to respond based on:
  - phase I data
  - pre-clinical models, and/or
  - mechanisms of action
- Subject needs to have measurable disease
- May limit number of prior treatments

Phase II: Standard Design



Two-stage design with early stopping rule for efficacy or futility

Phase II: Endpoints

- Response (see response assessment module for more details)
  - Complete Response (CR)
  - Partial Response (PR)
  - Stable Disease (SD)
  - Progressive Disease (PD)
- Additional safety data

Phase III: Primary Goals

Efficacy compared to standard therapy

- Activity demonstrated in Phase II study

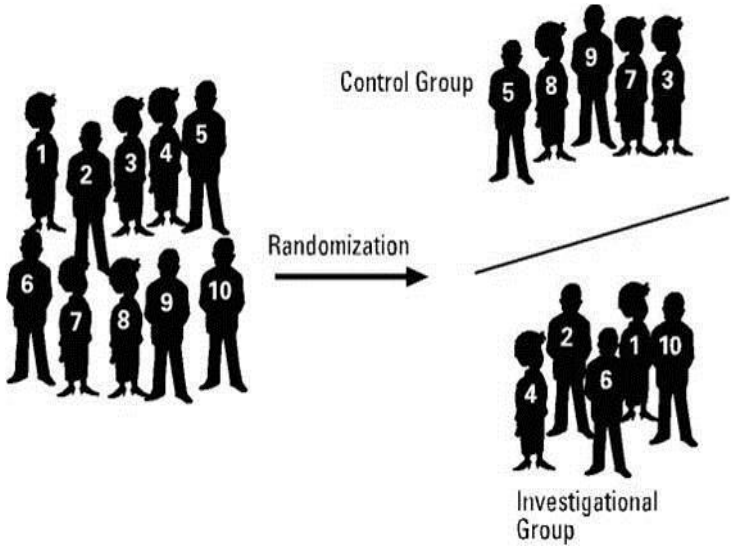
Further evaluation of safety

Phase III: Patient Population

- Hundreds to thousands of subjects
- Single cancer type
- May be front-line therapy
- Well-defined eligibility criteria
- Internal control group (e.g., standard treatment, placebo)
- Multi-institutional participation necessary to reach targeted accrual goals

Phase III: Standard Design

- Randomized assignment of patients to treatment arms
- Equal distribution of known important prognostic factors to each arm (stratification)



ENDPOINTS IN PHASE III TRIALS

- The goal of Phase 3 trials is to compare outcomes reflecting patient benefit with the usual standard of care.
- There are essentially only 2 ways in which patients may benefit from treatment:
  - They either live longer or they live better.
- Thus the most appropriate endpoints of phase III trials are:
  - Overall Survival (OS)
  - Quality of Life (QoL)
- Any other endpoint is a surrogate endpoint, and should be shown to predict OS or QoL.

SURROGATE ENDPOINTS IN PHASE III TRIALS

- While OS is a preferred endpoint and not subject to bias, the survival time for patients with many types of cancer is (fortunately) quite long. This is especially true for trials of adjuvant therapy.
- Disease-Free Survival (DFS), also known as Relapse-Free Survival (RFS), is often used as a primary endpoint in phase III trials of adjuvant therapy.
- Progression-Free Survival (PFS) is used commonly as a primary endpoint in phase III trials evaluating treatment of metastatic cancer.
  - Since the size of a trial is determined by the number of "events", and recurrence or progression of cancer usually occurs before death, trials with DFS or PFS as the primary endpoint can be evaluated earlier, and require a smaller sample.
  - Some investigators also prefer these endpoints because they are not influenced by subsequent therapies.

CRITERIA FOR ESTABLISHING "SURROGACY"

- Surrogacy of an endpoint such as PFS for OS requires that a patient with longer PFS will have longer OS. It is not sufficient that PFS be correlated with OS.
- A valid surrogate for OS should satisfy the Prentice criteria:
  - The treatment has an effect on survival time.
  - The treatment has an effect on the surrogate.
  - The surrogate is associated with survival time.
  - The treatment effect on survival is captured by the surrogate.
- It is rare that endpoints such as DFS or PFS have been shown to be true surrogates for OS

Prentice RL, Stat Med 1989;8 431–440
Heller G, Ann Oncol 2015;26 (10):2012-16

Traditional divisions of treatments by types of cancer

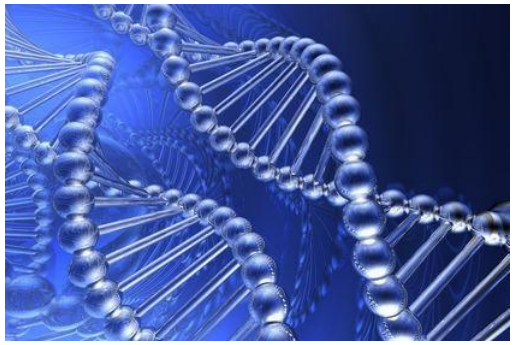
- Sites: Breast, Lung, Gastrointestinal, Genitourinary, Melanoma, Leukemia, Lymphoma, Myeloma, Sarcoma
- Traditional trials in sub-sites, histologies, early stage, advanced stages relapsed disease
- But increasingly disease is characterized molecularly into much finer divisions

Problems with Current Trial Design

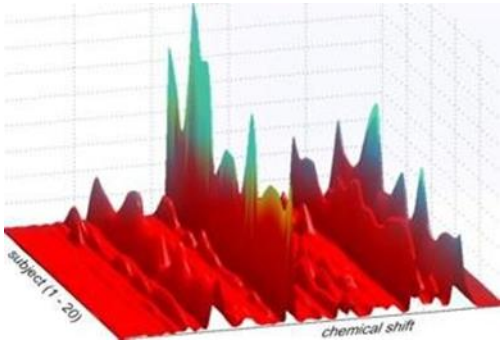
- Classical phase I,II, and III models require enormous resources
- Time to bring a new oncology drug to market 8-12 years
- Cost to bring a new drug to market can exceed $1 billion
- 70% of oncology drugs fail in phase II
- 59% of oncology drugs fail in phase III
- Have focused on histology-dependent strategies
- Limited collaboration between sponsors, academia, and funding sources
- Traditional models not designed to address “niche” agents with very small populations expected to benefit

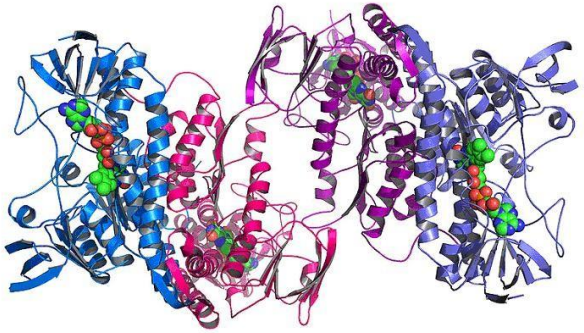
Kaitin, KI, Dimasi JA. Pharmaceutical Innovation in the 21st century: new drug approvals in the first decade, 2000-2009. Clin Pharmacol Ther 2011; 89: 183-188.
KolaI, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004 Aug; 3(8): 711-715.

A Revolution in Cancer Therapy



Genomics

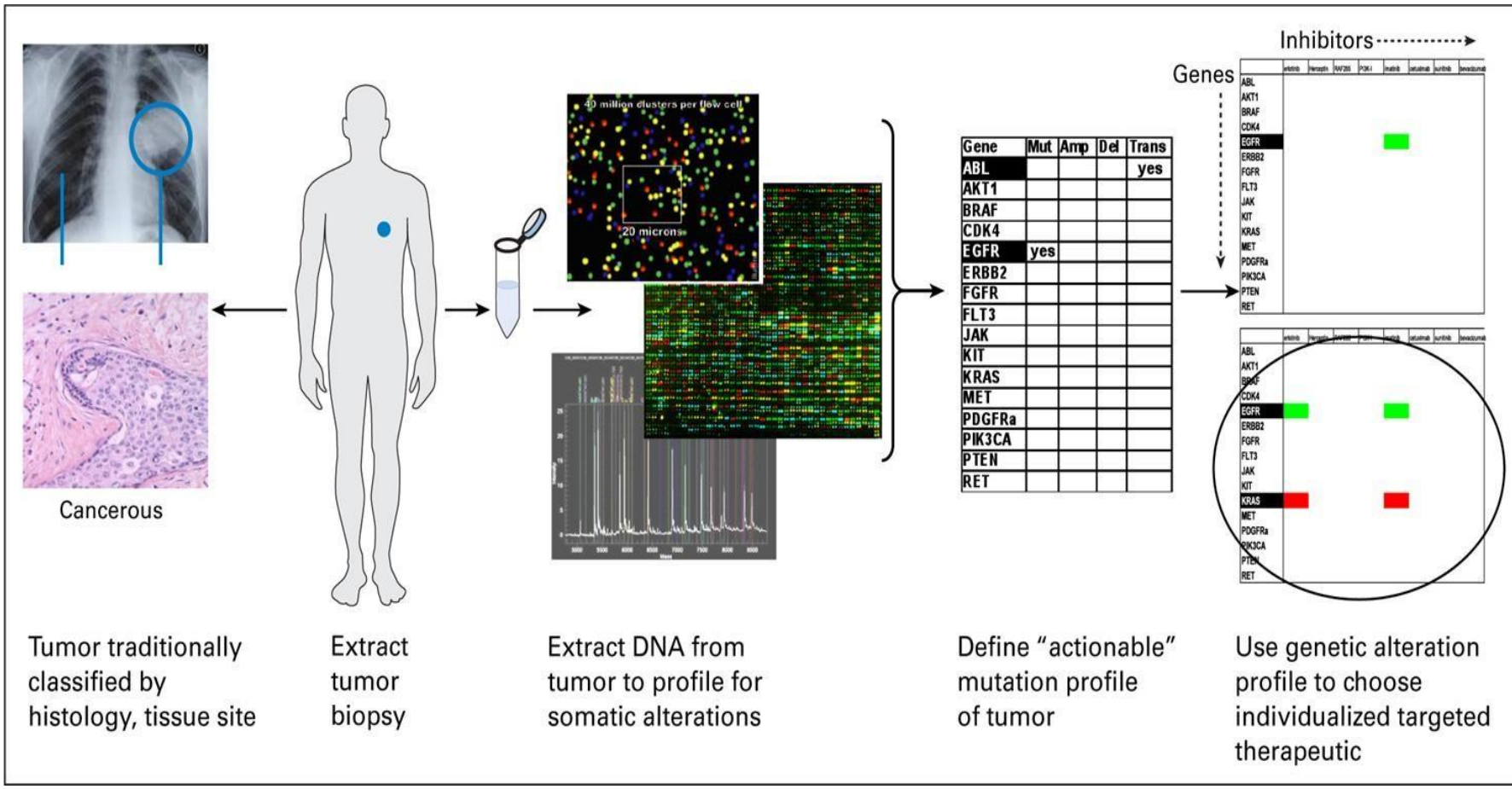




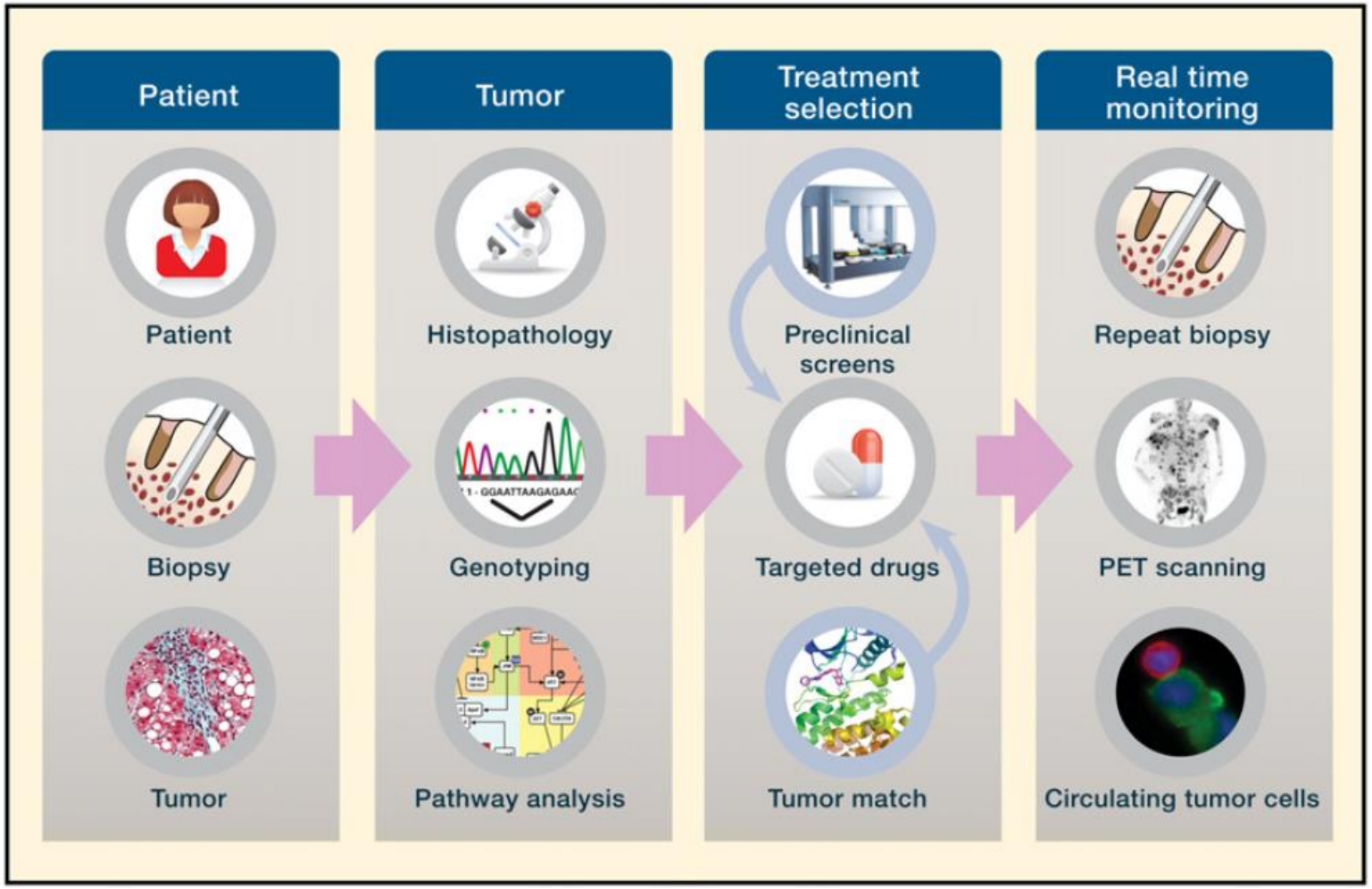
Proteomics

Immuno-oncology

THE PROMISE OF PRECISION MEDICINE



A New Paradigm in Cancer Treatment



Haber, Gray, Baselga Cell 2011

Regulatory impulse

- FDA responsibilites:
  - "advancing the public health by helping to *speed* innovations that make medicines *more effective, safer*, and more *affordable*"
    - Better drugs, sooner, at lower cost…

http://www.fda.gov/AboutFDA/WhatWeDo/default.htm

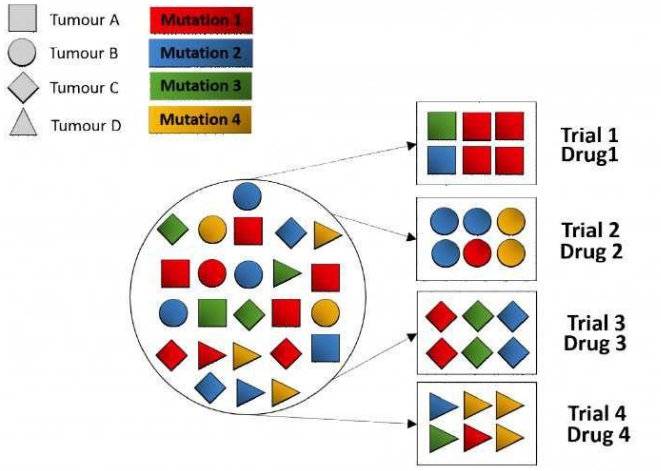
Three waves of early studies designs

Historical evolution of Early clinical trials designs: waves and challenges

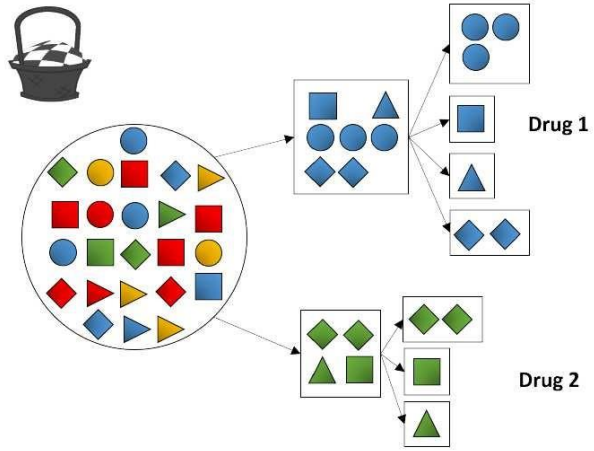
- 1/ Classical designs: the era of *cytotoxic* drugs
- 2/ Precision Medicine designs: the wave of *targeted* drugs
- 3/ Seamless designs: the *immunotherapy* tsunami.

Paradigm of Precision Medicine studies

Traditional histology-determined treatment allocation



Histology-agnostic enrollment of marker-defined cohorts



Benner, 2016

New Trial Designs

Methodologies

1. Biomarker guided design
    1. Basket trials
    2. Umbrella trials
2. Adaptive Design

Major Goals

1. Shorten time to get drugs to the patients who need them
2. Reduce costs
3. Increase the number of trial participants getting the best treatment

Basket trials

A basket trial is a histology-independent design where each sub-trial enrols multiple tumour types ("the basket") with one common genetic mutation. The hypothesis is that response to the targeted therapy is determined by the molecular variant and (largely) independent of tumour histology. The prerequisites are that the drug sufficiently inhibits the target and the tumour depends on the target.

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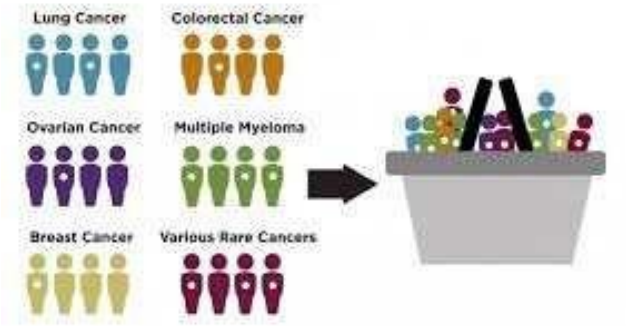
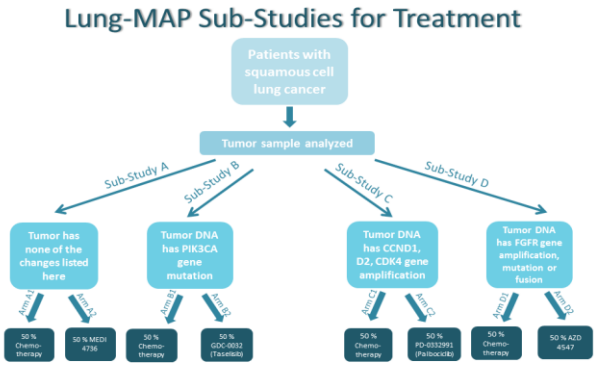
Basket/Umbrella

Basket

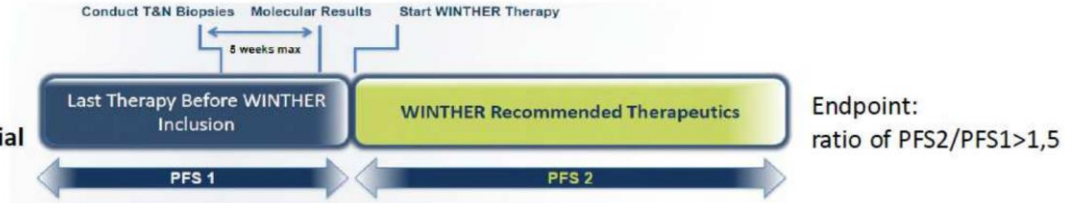


Umbrella

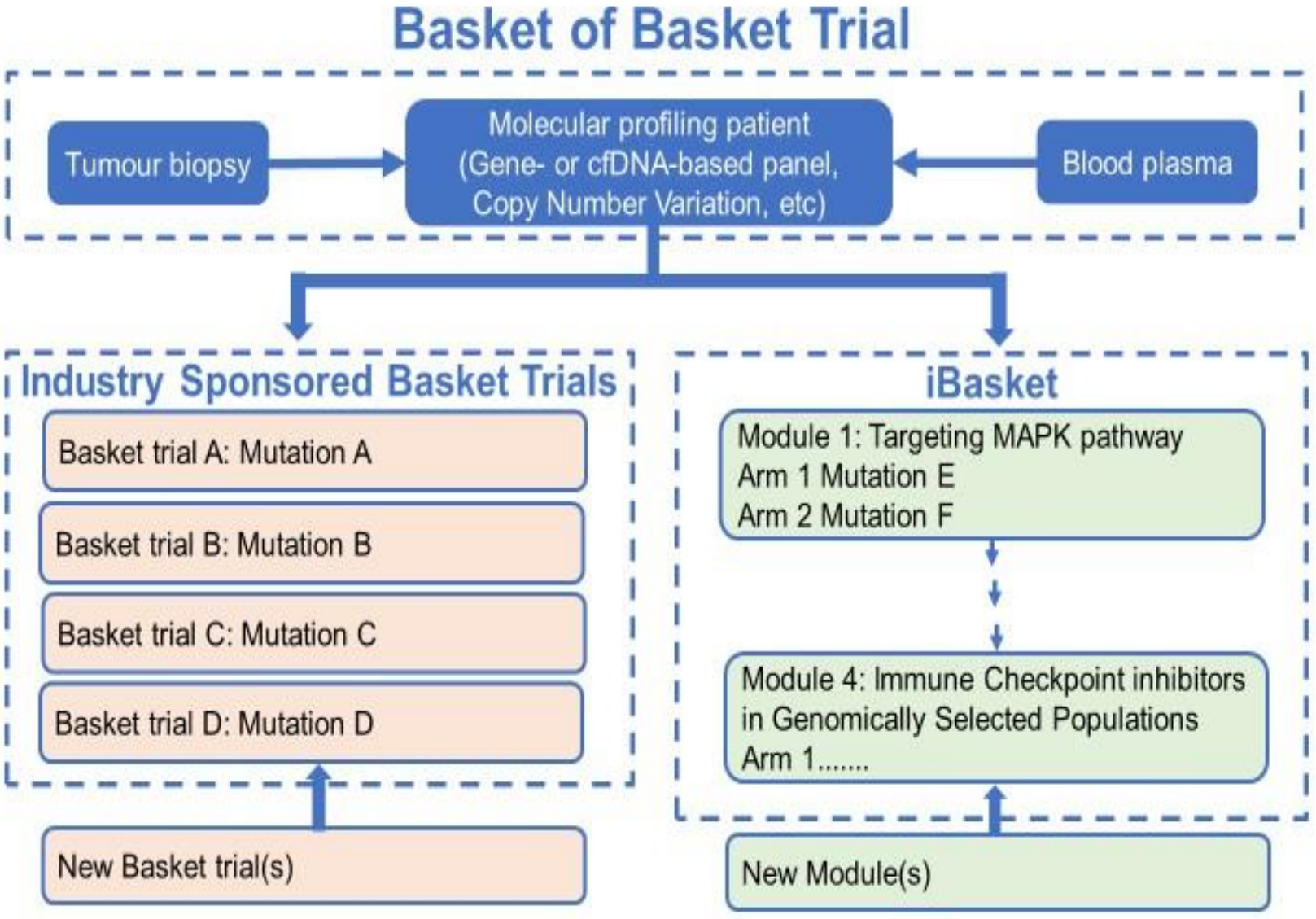


”N of 1”

Example of Winther Trial



Endpoint:
ratio of PFS2/PFS1>1,5



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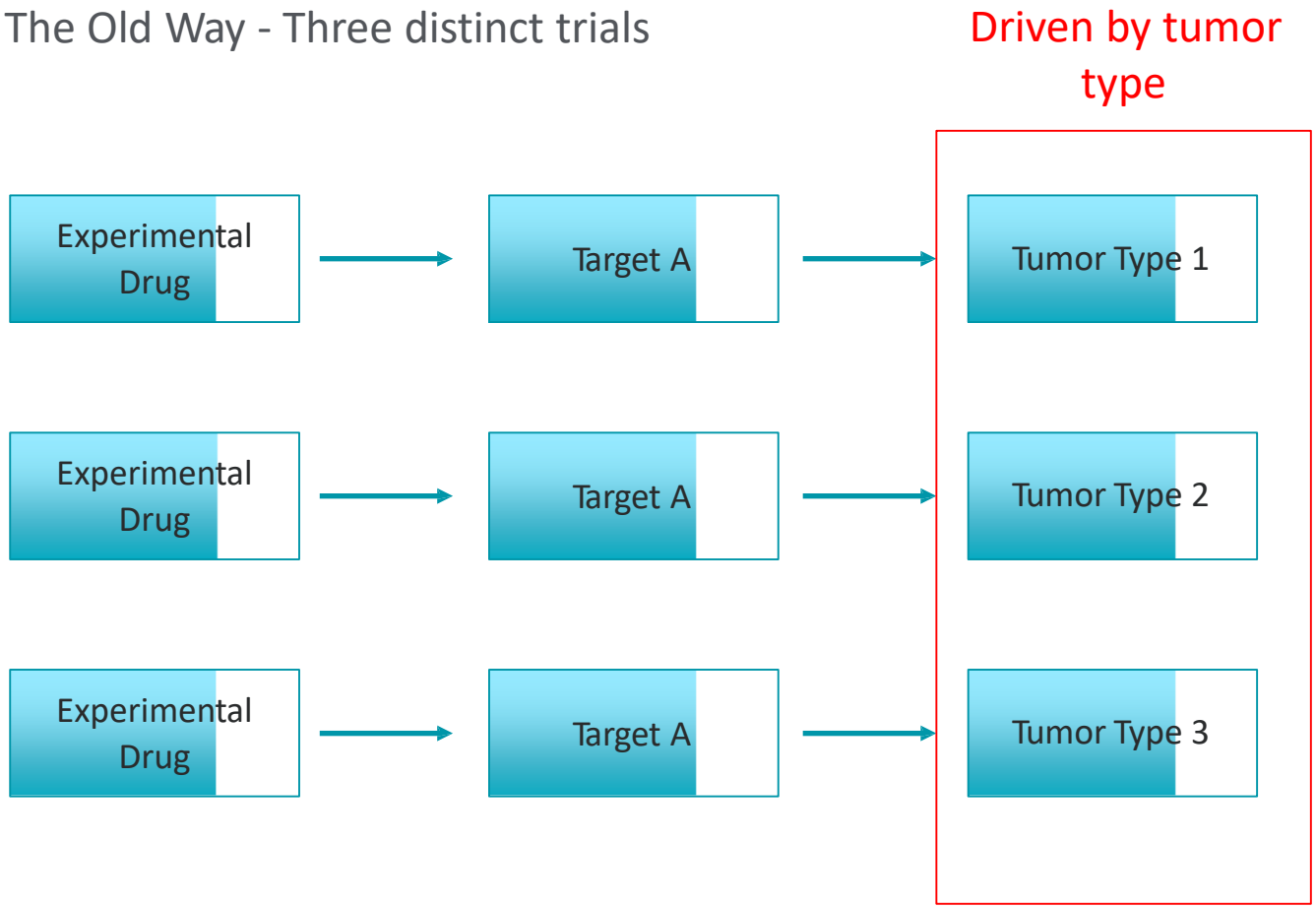
Classical Trials

One Molecular Abnormality Targeted Across Multiple Tumor Types

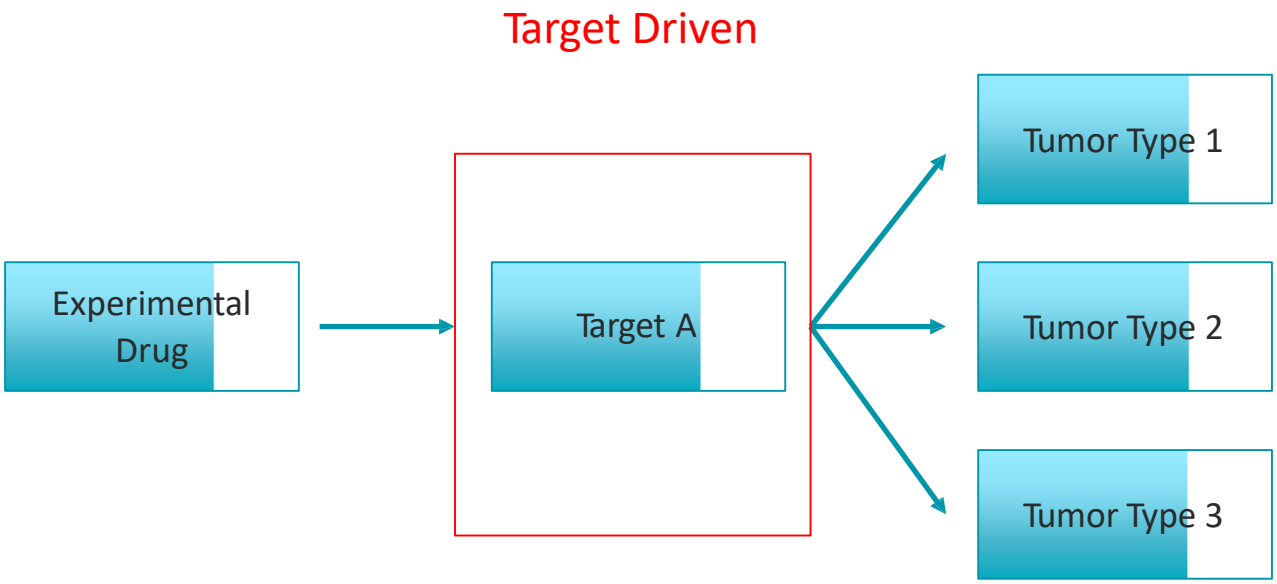
The Old Way - Three distinct trials



Basket Trials

One Molecular Abnormality Targeted Across Multiple Tumor Types

Simultaneous execution of multiple studies



Redig, A. and Pasi, JA. Basket Trials and the Evolution of Clinical Trial Design in an Era of Genomic Medicine. Journal of Clinical Oncology, Vol. 33, 2015

Umbrella trials

An umbrella trial evaluates the efficacy of different targeted agents each against a different genetic mutations (sub-trials) within a single histology ("the umbrella").

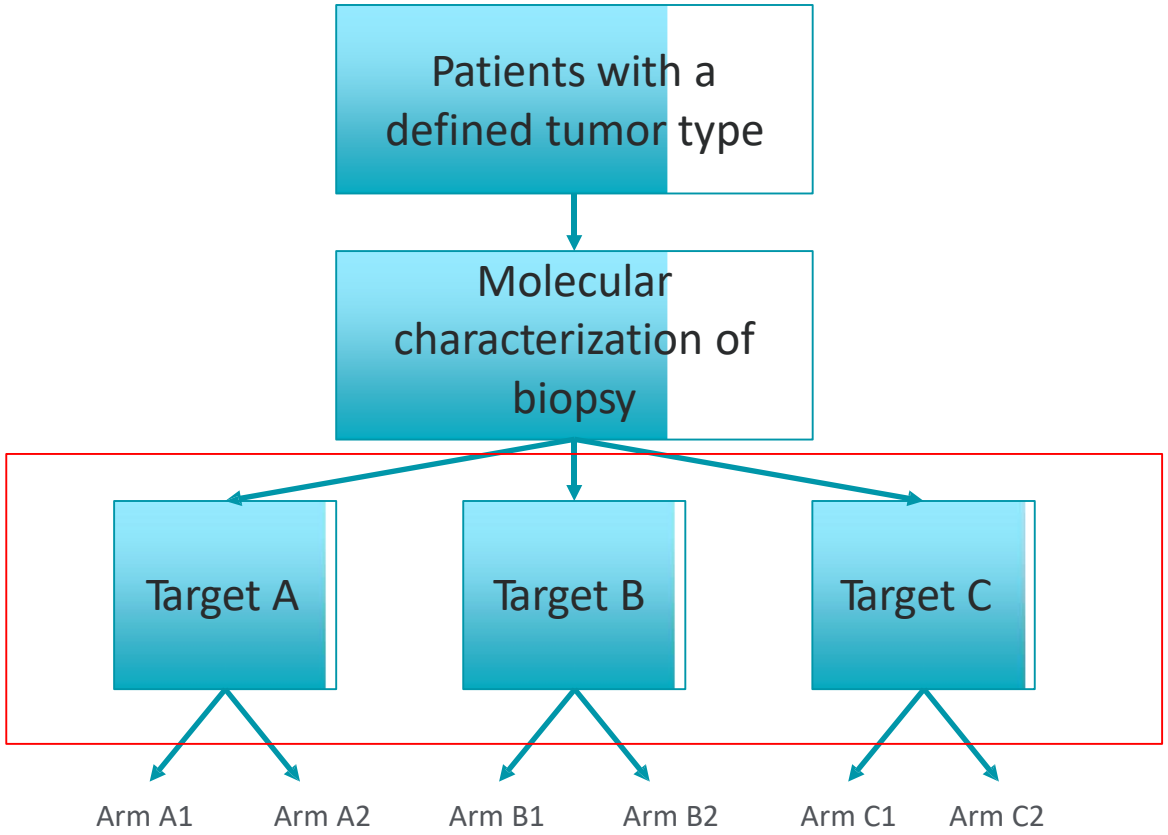
A response is

assumed to be (primarily) determined by the histological context.

J. Verweij and H.R. Hendricks, 2019

Umbrella Studies

One tumor type, multiple molecular targets



Histology
&
Target Driven

Sleijfer, S et al. Designing Transformative Clinical Trials in the Cancer Genome Era. J Clin Oncol 31: 1834-1841.

Adaptive Trial Designs

Key Features

1. All changes are pre-planned
2. Allows the trial to “learn” from early results
3. Can increase the proportion of patients getting the better treatment
4. May shorten the time it takes to complete the trial
5. Can be very complex to manage

FDA Approves XXX (Immunotherapy) for Microsatellite Instability-High and Mismatch Repair Deficient Cancers

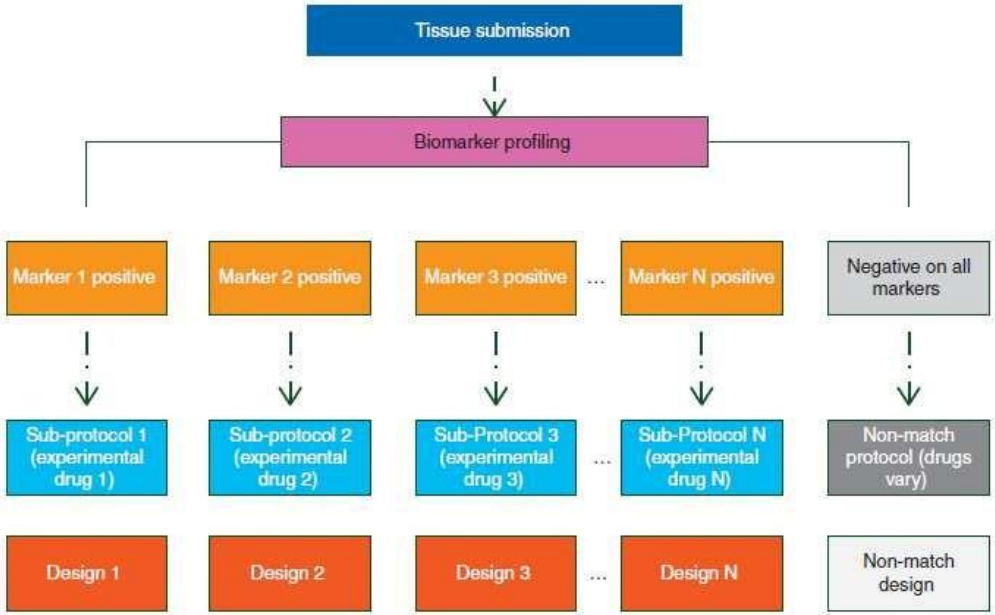
The FDA has granted an accelerated approval to XXX for **the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors** that have progressed after prior treatment and who have no satisfactory alternative treatment options, as well as for patients with MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan.

- "**This is an important first for the cancer community**," Richard Pazdur, MD, acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of
- Excellence, said in a statement.
  "Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now **approved a drug based on a tumor's biomarker without regard to the tumor's original location."**

Seamless Phase II-III trials

- Minimize overall trial time (no stop between phases)
- Flexibility to study crucial aspects
  - dose finding
  - subroup selection
- All enrolled patients are considered in the final analyses

Concept of "Master Protocol"



Renfro, Ann Oncol 2016

Challenges of seamless studies

- *Competitive/challenging slots* (extramural): many arms, few slots, many sites
- *New endpoints* in Early Phase: costs, PROs, efficacy…
- Re-building of *Early Phase programs*
  - Sophisticated low-volume "three-star Michelin" program plus very efficient high-volume "McDonalds franchise" program in same restaurant!
  - Different tumor type populations
    - Knowledge and expertise needed
    - Synergy with late phase programs
  - Ph1 Programs models re-visited

SEAMLESS ONCOLOGY-DRUG DEVELOPMENT

"WE BELIEVE THAT THE DESIRE TO PROVIDE EARLIER ACCESS TO HIGHLY EFFECTIVE DRUGS SHOULD ENCOURAGE FURTHER USE OF SEAMLESS EXPANSION-COHORT TRIALS"

"WE CANNOT ABANDON OUR COMMITMENT TO WELL- DESIGNED, WELL-CONDUCTED CLINICAL TRIALS"

T. M. PROWELL, M. R. THEORET, R. PAZDUR NEJM, 2016

Name of Drug	Indications	Date
NEW APPROVALS		
Osimertinib (Tagrisso)	Metastatic EGFR T790M mutation-positive NSCLC, as detected by FDA-approved test, progressing during or after EGFR TKI therapy	November 2015
Daratumumab (Darzalex)	Multiple myeloma after three or more prior lines of therapy, including PI and immunomodulatory agent, or disease double refractory to PI and immunomodulatory agent	November 2015
Ixazomib (Ninlaro)	In combination with lenalidomide and dexamethasone for multiple myeloma after one or more prior therapy	November 2015
Necitumumab (Portrazza)	In combination with gemcitabine and cisplatin for first-line treatment of metastatic squamous NSCLC	November 2015
Alectinib (Alecensa capsules)	ALK-positive metastatic NSCLC progressing with or intolerant to crizotinib	December 2015
Venetoclax (Venclexta tablets)	CLL with 17p deletion, as detected by FDA-approved test, after one or more prior therapy	April 2016
Cabozantinib (Cabometyx)	Advanced RCC after prior antiangiogenic therapy	April 2016
Atezolizumab (Tecentriq)	Locally advanced or metastatic urothelial carcinoma progressing during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	May 2016
NEW USES		
Trametinib (Mekinist) and dabrafenib (Tafinlar)	In combination for unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by FDA-approved test	November 2015
Nivolumab (Opdivo)	Advanced RCC after prior antiangiogenic therapy	November 2015
Ofatumumab (Arzerra injection)	Extended treatment for patients in complete or partial response after two or more lines of therapy for recurrent or progressive CLL	January 2016
Eribulin (Halaven injection)	Unresectable or metastatic liposarcoma after prior anthracycline-containing regimen	January 2016
Palbociclib (Ibrance capsules)	In combination with fulvestrant for hormone receptor–positive, HER2-negative advanced or metastatic breast cancer progressing after endocrine therapy	February 2016
Obinutuzumab (Gazyva injection)	In combination with bendamustine followed by obinutuzumab monotherapy for treatment of FL relapsing after or refractory to rituximab-containing regimen	February 2016
Everolimus (Afinitor)	Progressive, well-differentiated, nonfunctional NET of gastrointestinal or lung origin (unresectable, locally advanced, or metastatic disease)	February 2016
Crizotinib (Xalkori)	Metastatic NSCLC with ROS1-positive tumors	March 2016
Lenvatinib (Lenvima)	In combination with everolimus for advanced RCC after one prior antiangiogenic therapy	May 2016
Nivolumab (Opdivo)	Classic HL relapsing or progressing after autologous HSCT and post-transplantation brentuximab vedotin (Adcetris)	May 2016
Liquid biopsy test (cobas)	Detection of exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR gene to identify patients with metastatic NSCLC eligible for treatment with erlotinib (Tarceva)	June 2016
Pembrolizumab (Keytruda)	Recurrent or metastatic HNSCC progressing during or after platinum-containing chemotherapy	August 2016
Atezolizumab (Tecentriq)	Metastatic NSCLC progressing during or after platinum-containing chemotherapy	October 2016


Thank You