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Phase I and early clinical trials

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Postgraduate course in Medical Oncology 15th of May

OUTLINE

- **Basics in early drug development**
- New drugs and new cancer types definitions
- Evolving methodology for early drug development and phase 1 trials in oncology
- Challenges and Perspectives

New drug development steps

	Discovery Preclinical testing	Clinical trials Phases			
		I	II	III	IV
Years	6.5	**1.5**	**2**	**3.5**	
Test population	Laboratory and animal studies	**Healthy or patient volunteers**	**patient volunteers**		
Purpose	Assess safety, biological activity and formulation	**Determining safety and dosage**	**Evaluate effectiveness Look for side effects**	**Confirm effectiveness Monitor adverse reactions from long-term use**	Pharmaco-vigilance Pharmaco-epidemiology
				Registration	

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Major Endpoints in Phase I trials

- Dose Limiting Toxicity
- Maximum Tolerated Dose
- Recommended Phase II Dose

Dose Limiting Toxicity – DLT

- Defined as unacceptable toxicity related to the study drug
- Usually assessed after cycle 1
- Described in a consensual manner according to the different versions of the NCI-CTCAE
  - Grade 4 neutropenia lasting more than 7 days
  - Febrile neutropenia Grade 4
  - Thrombocytopenia Grade 3 and thrombocytopenia + bleeding
  - Grade 3 non haematological toxicity (except nausea and vomiting)

Maximum Tolerated Dose (MTD)

- Corresponds to the dose at which a certain percentage of patients have DLT (usually 33%)
- Determined from the toxicities observed during the first cycle of treatment for each patient included
- Important definition in view of not recommending an infra-therapeutic dose for phase 2 trials

Recommended Phase 2 dose (RP2D)

- Corresponds to the most effective dose with an acceptable toxicity profile
- Often defined as the dose level below MTD
- Not always very precise from the start and often requiring readjustments during phase 2 trials

Pharmacokinetics & Pharmacodynamics

- Pharmacokinetics:
  - Refers to how the body acts on the drug
  - Involves the study of drug absorption, distribution, metabolism
  - Clearance, half-life

- Pharmacodynamics:
  - Refers to how the drug acts on the body
  - Drug action
  - Drug effect including off/on target toxicities
  - Drug response
  - Relationship between dose and response

Starting Dose level

- Choice of a safe starting dose for phase I trials of cytotoxic agents is based on an extrapolation of the results of animal toxicity studies taking into account several parameters:

- Eg:
  - The no observed adverse effect level (NOAEL)
  - Lethal dose in 10% of mice (0.10xLD10)
  - Toxic Dose Low (TDL = lowest dose that produces side effects and that is such that twice that dose is not lethal) in dog or monkey

Dose-finding in oncology : traditional 3+3 design

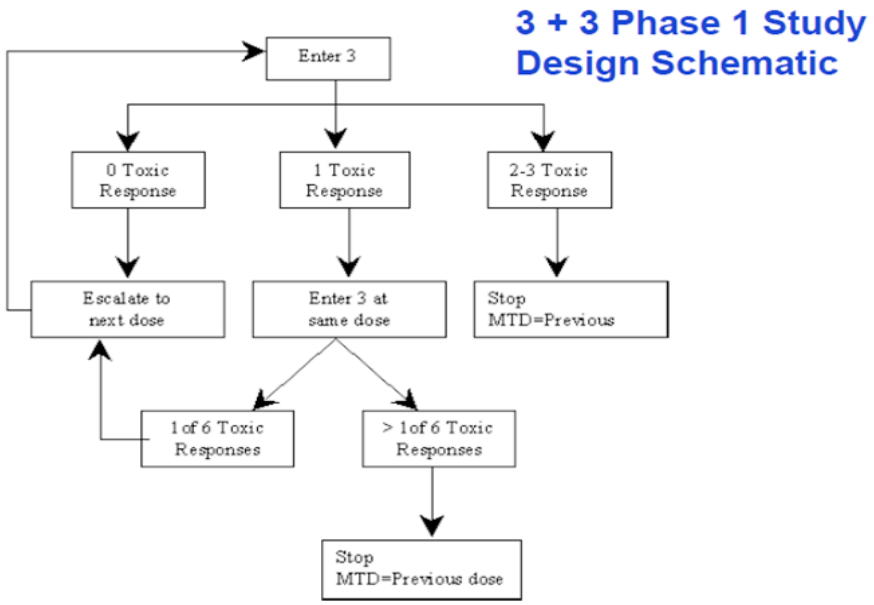
The most widely used design in oncology

Patients are assigned in groups of 3/DL
If only 3 patients on the current dose then:

- *no DLT -> 3 on next higher dose*
- *one DLT -> add 3 on the same dose*
- *two or more DLTs -> MTD is exceeded*

If 6 patients on the same dose, then:

- If at *most one DLT-> 3 on next higher dose*
- *If two or more DLTs -> MTD exceeded*



The estimated MTD is the highest dose level with observed toxicity rate less than 0.33.

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Choice of administration route

- Depends on the mechanism of action of the agent studied
- Depends on pre-clinical data
- Important for the toxicity profile
- Important for dose-intensity
- Importance of the sequence in combinations studies (synergy, antagonism)

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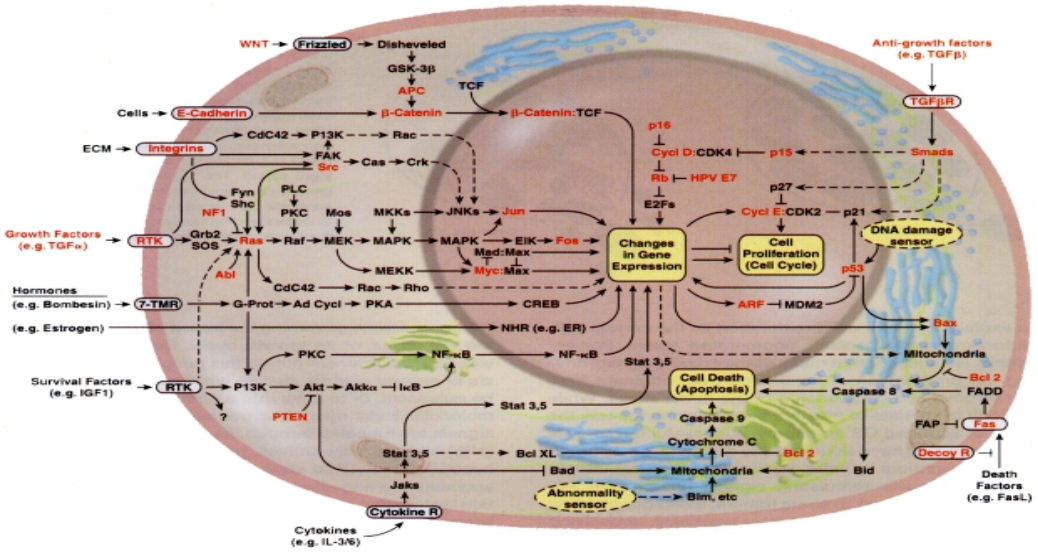
The molecular and immune biology of cancer cells is better understood



Hanahan et Weinberg, Cell, 2000

Hanahan et Weinberg, 2011

From empirical oncology to molecular and immunological therapeutic approaches

A wealth of novel therapeutic strategies based on molecular understanding

- Oncogenic drivers “de-addiction”
  - Inhibition of critical signaling pathways
  - Specific cytotoxicity

- **New targets**
  - Signaling pathways, cell cycle, DNA repair, Angiogenesis, Epigenetic, Apoptosis, Invasion, Metabolism

- **New agents**
  - TKIs, Mab, ADC ..

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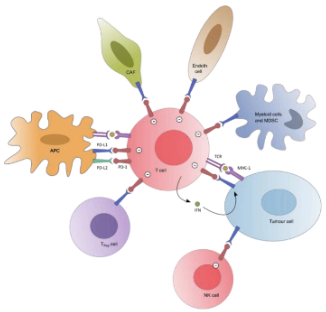
A wealth of novel therapeutic strategies based immune biology understanding



- CP inhibitors

- CP agonists

- Immunomodulators (IDOi, A2A antagonists, ..)

- Adoptive cell transfer : CAR T and others

- Vaccines

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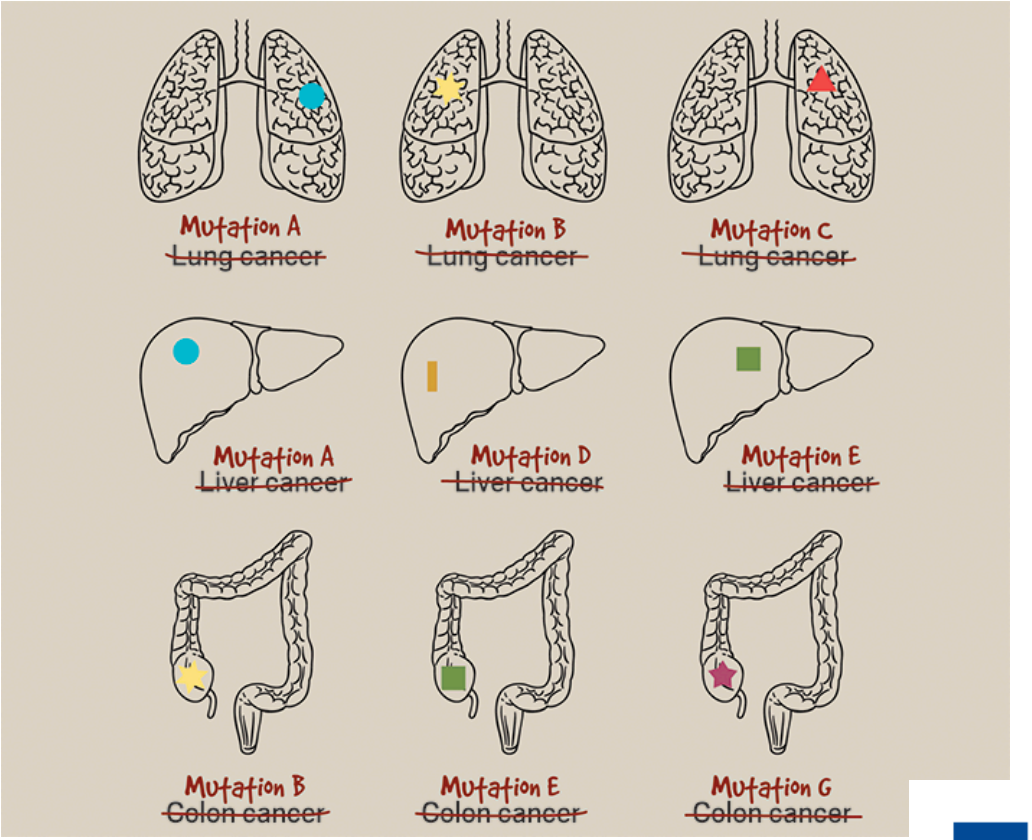
More and More « tumor-agnostic » treatment strategies

Treat patients based on cancer genetics and molecular features ..

without regards to the cancer type



Credit: Yang H. Ku/C&EN/Shutterstock

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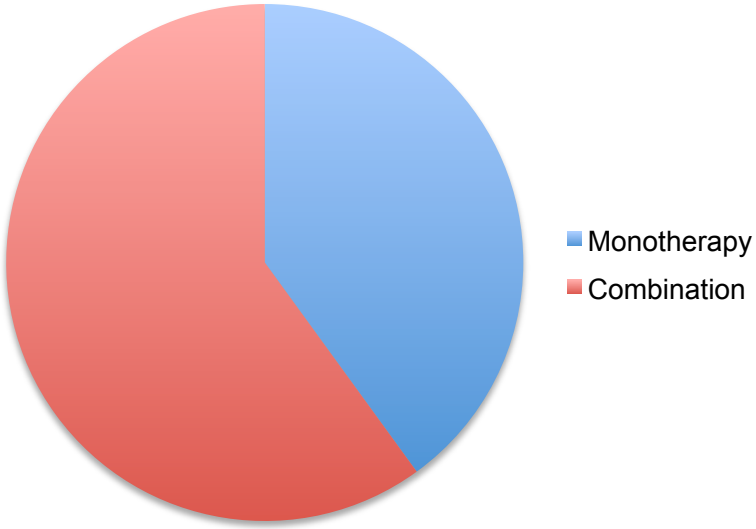
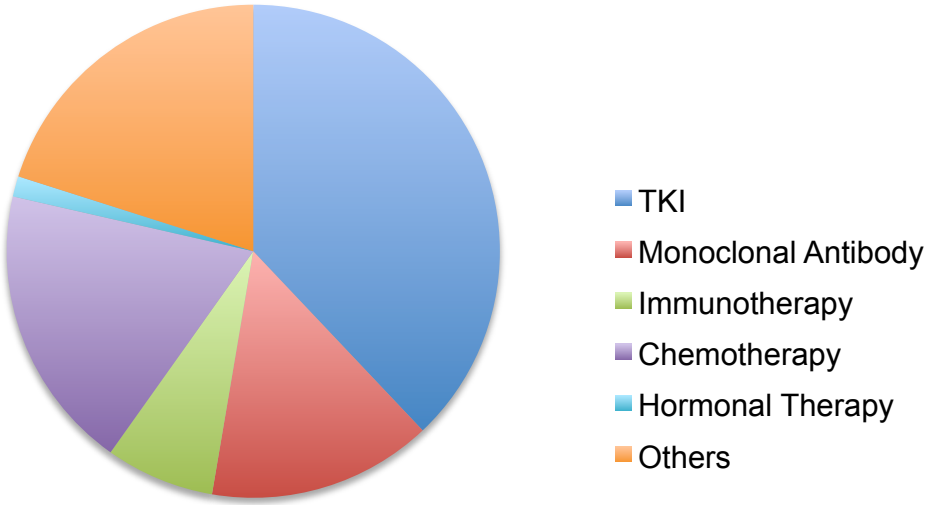
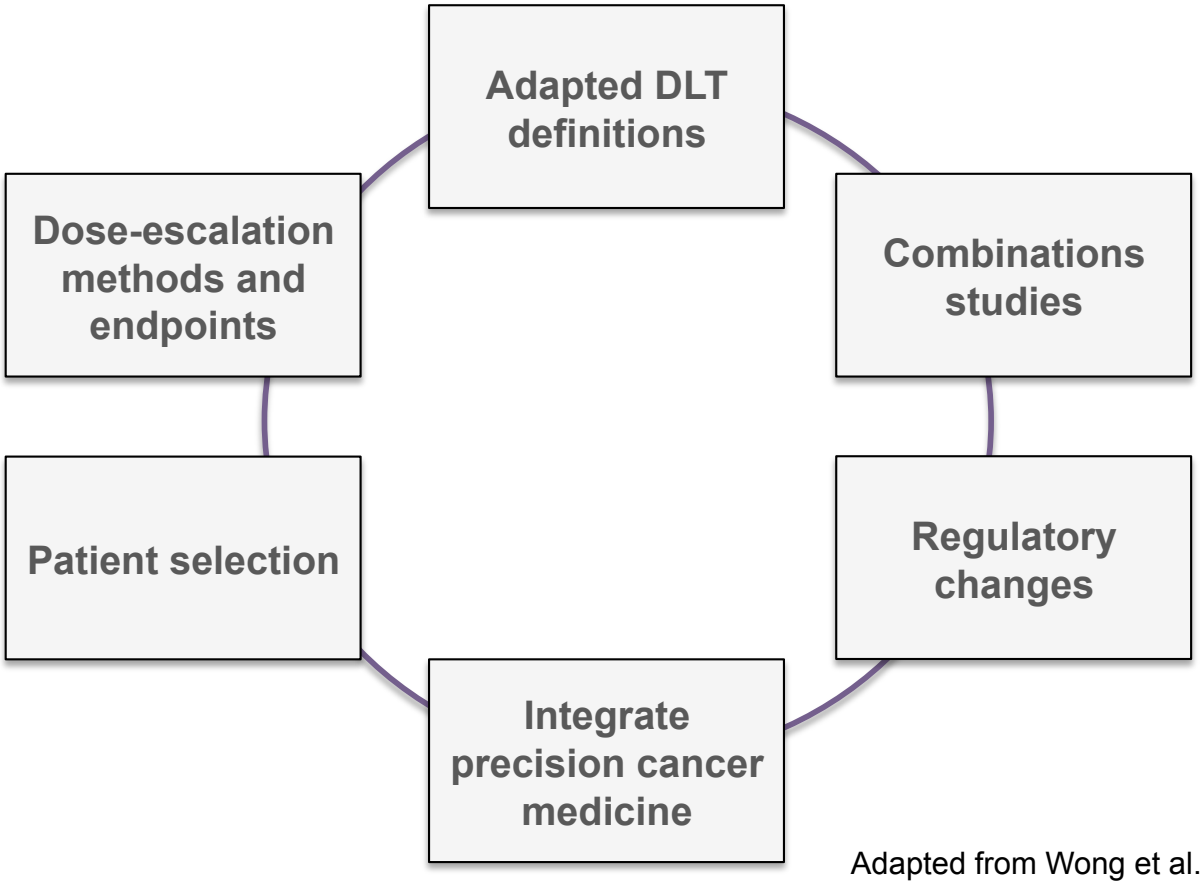
Phase 1 published from 01/2014 to 06/2015





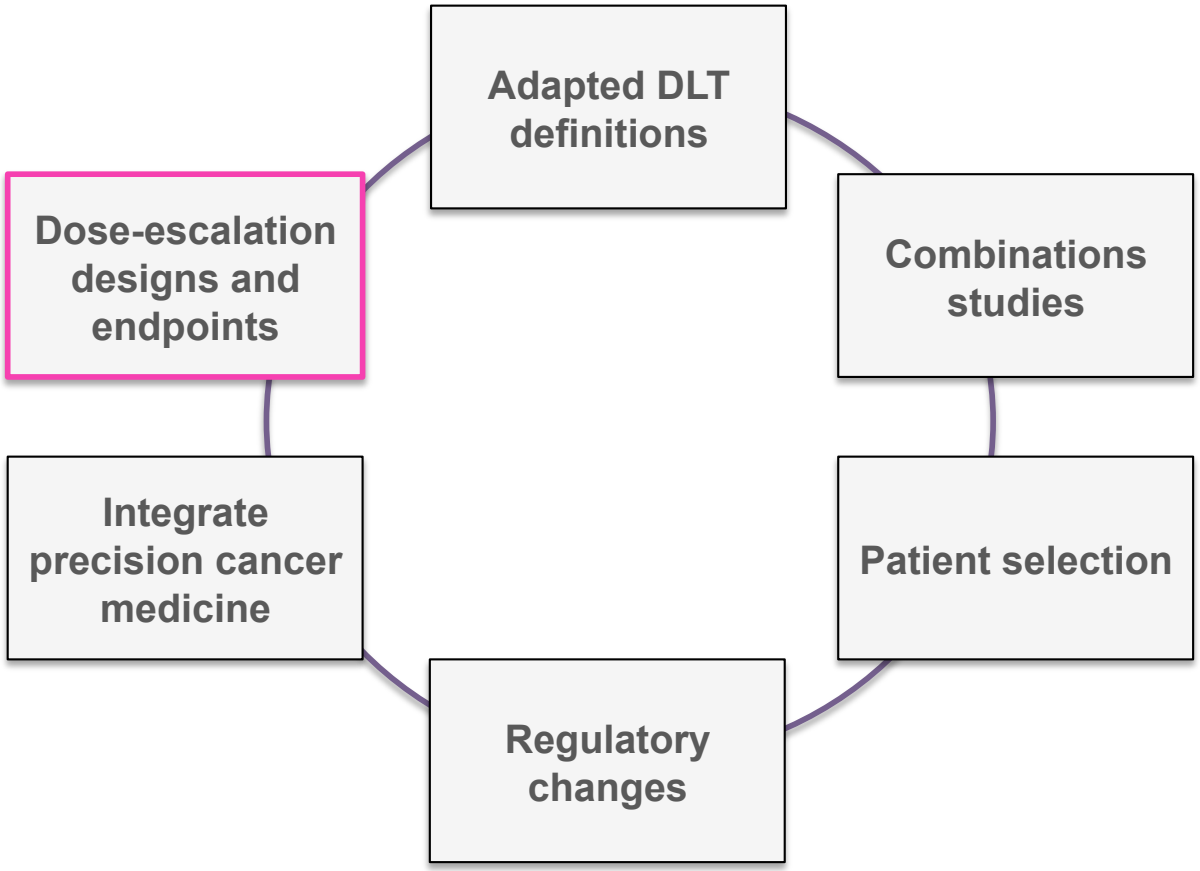
Italiano A et al, NEJM 2018

Key areas of phase I trials in oncology that have evolved to adapt to novel oncology treatments and increase the efficiency of drug development



Adapted from Wong et al. Nature Reviews

Considerations for the evolution of phase I oncology trials



Adapted from Wong et al. Nature Reviews 2016

Evolving landscape of early phases from cytotoxics to IO agents

	Cytotoxic chemotherapy	Molecular-targeted agents	IO agents
Patients number	30-50 unselected pts	30-200 ''molecularly'' selected pts	100-1000 ''immunologically'' selected pts
Setting	Late settings	Late and earlier settings	
MTD	MTD reached	MTD unconstantly reached	MTD rarely reached
Design	3+3	3 + 3 with large expansion cohorts	Accelerated titration/Adaptive designs/ Multiple expansion cohorts
Endpoints	Safety	Safety and activity	Safety and activity

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Mandatory biopsies ++++ for PD biomarkers, DE purposes

Adapted from Postel Vinay et al. Annals of Oncol. 2016

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New dose escalation methods for phase I cancer clinical trials.

- Accelerate drug development
- Limited number of patients treated at a suboptimal dose
- Integrate drug mechanism of action and target activation to find the optimal RP2D

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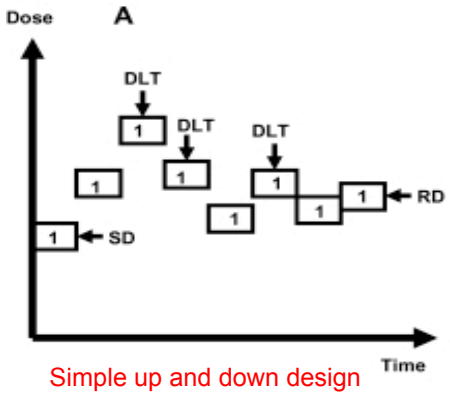
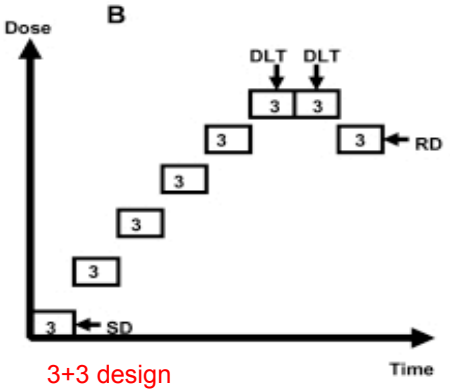
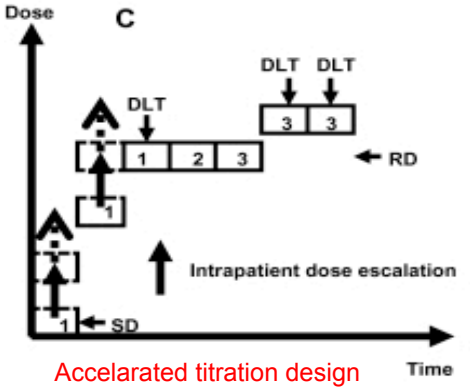
Methods for dose escalation in phase 1 trials



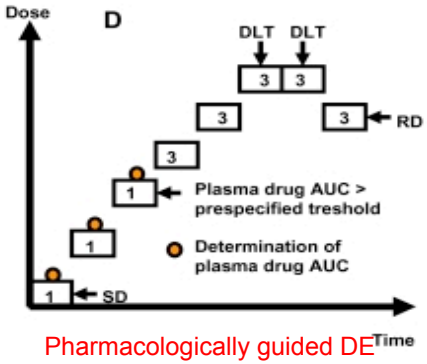
Simple up and down design



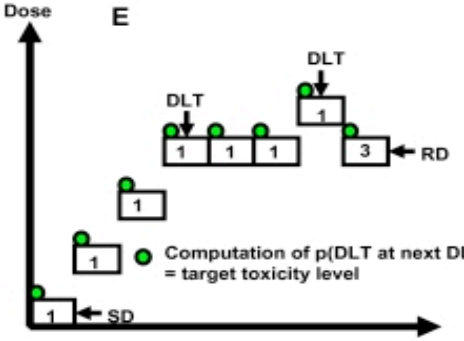
3+3 design



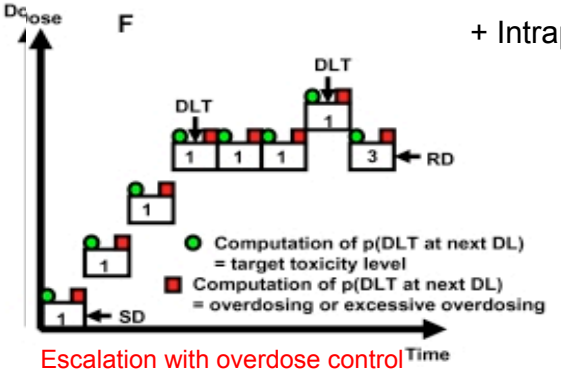
Accelarated titration design



Pharmacologically guided DE



Modified continual reassessment method



Escalation with overdose control

+ Intrapatient DE

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Le Tourneau C J Natl Cancer Inst. 2009

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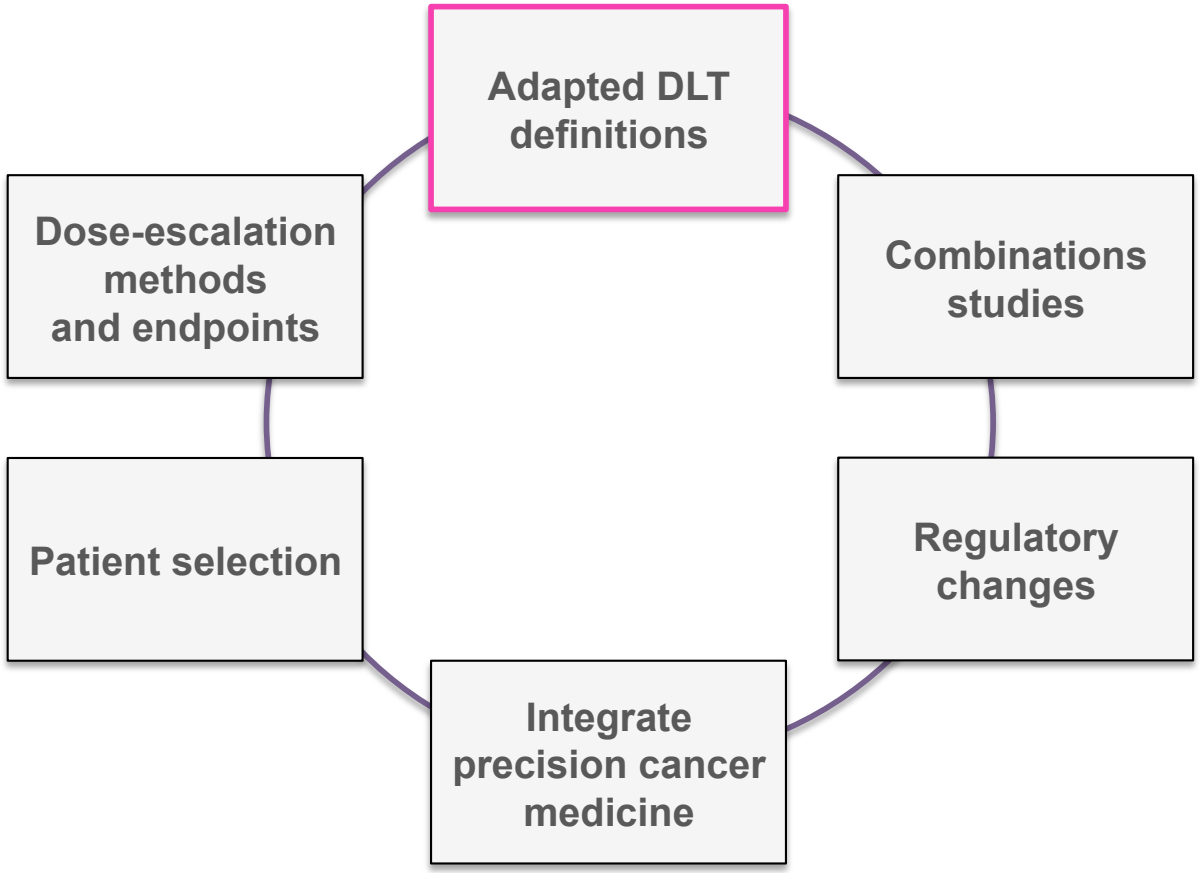
Considerations for the evolution of phase I oncology trials



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Adapted from Wong et al. Nature Reviews 2016

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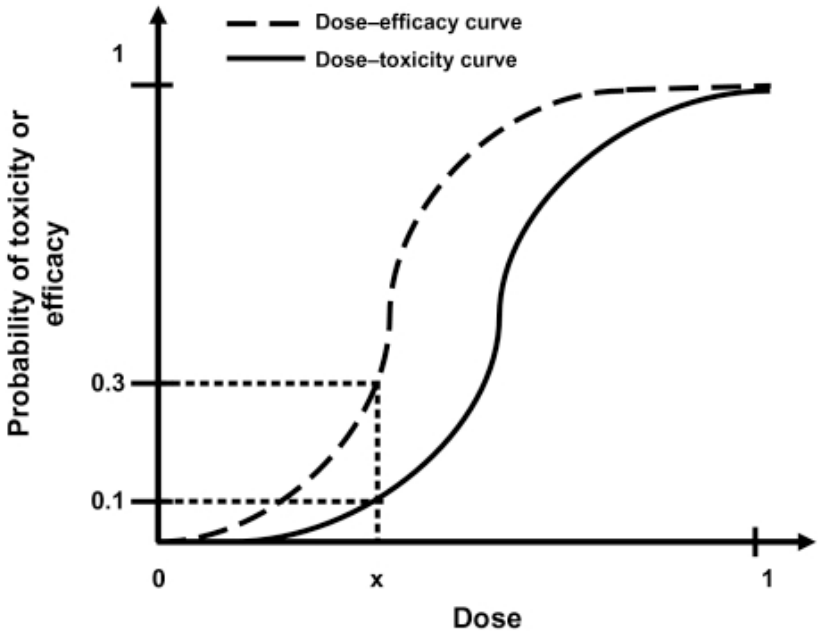
Typical dose–toxicity and dose–efficacy curves for cytotoxic agents

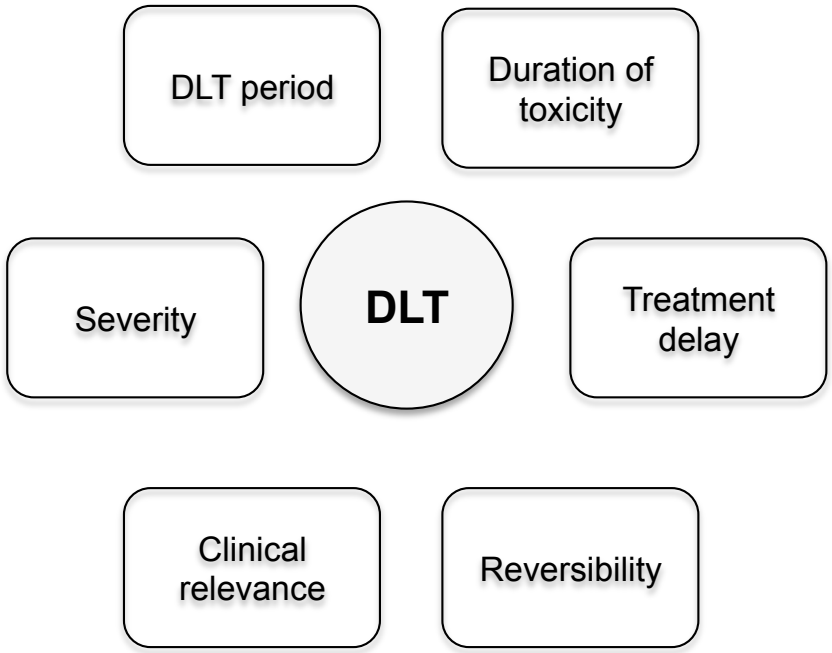


- Hypothesis : Toxicity and efficacy increase when the dose is increasing
- MTD considered as the optimal dose
- **Still true in the era of MTA/IO ??**

Le Tourneau C J Natl Cancer Inst. 2009

Adapted DLT definitions

DLT: Occurrence of severe toxicities during the first cycle of systemic cancer therapy: a trigger for dose-escalation



<u>new drugs = new toxicities</u>

<u>(including long term toxicities)</u>

- Better definition of the induced toxicity in relation to the study drug
- Extended DLT period
- Consider the clinical importance of each grade and toxicity type
- Use of expansion cohorts

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Adapted from Paoletti X, Eur J Cancer. 2014

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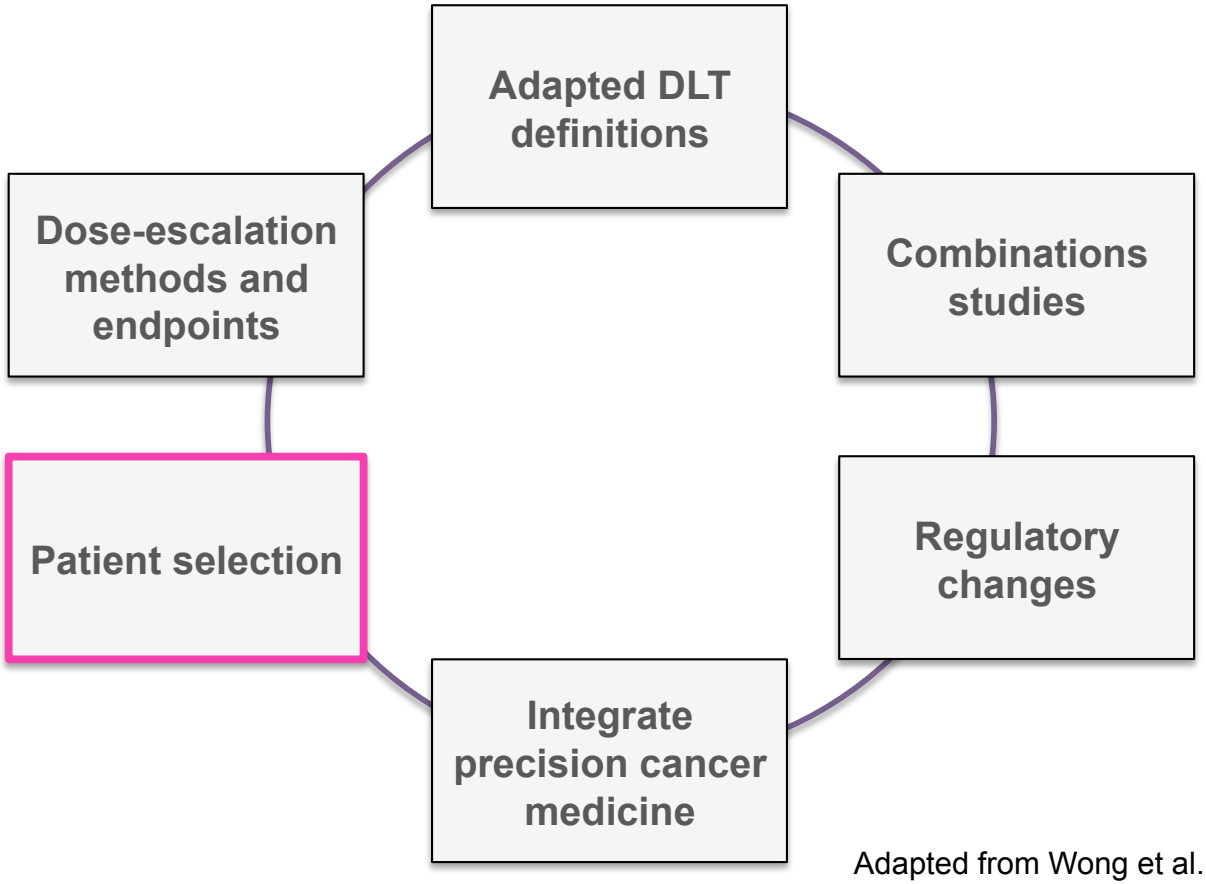

Adapted from Wong et al. Nature Reviews

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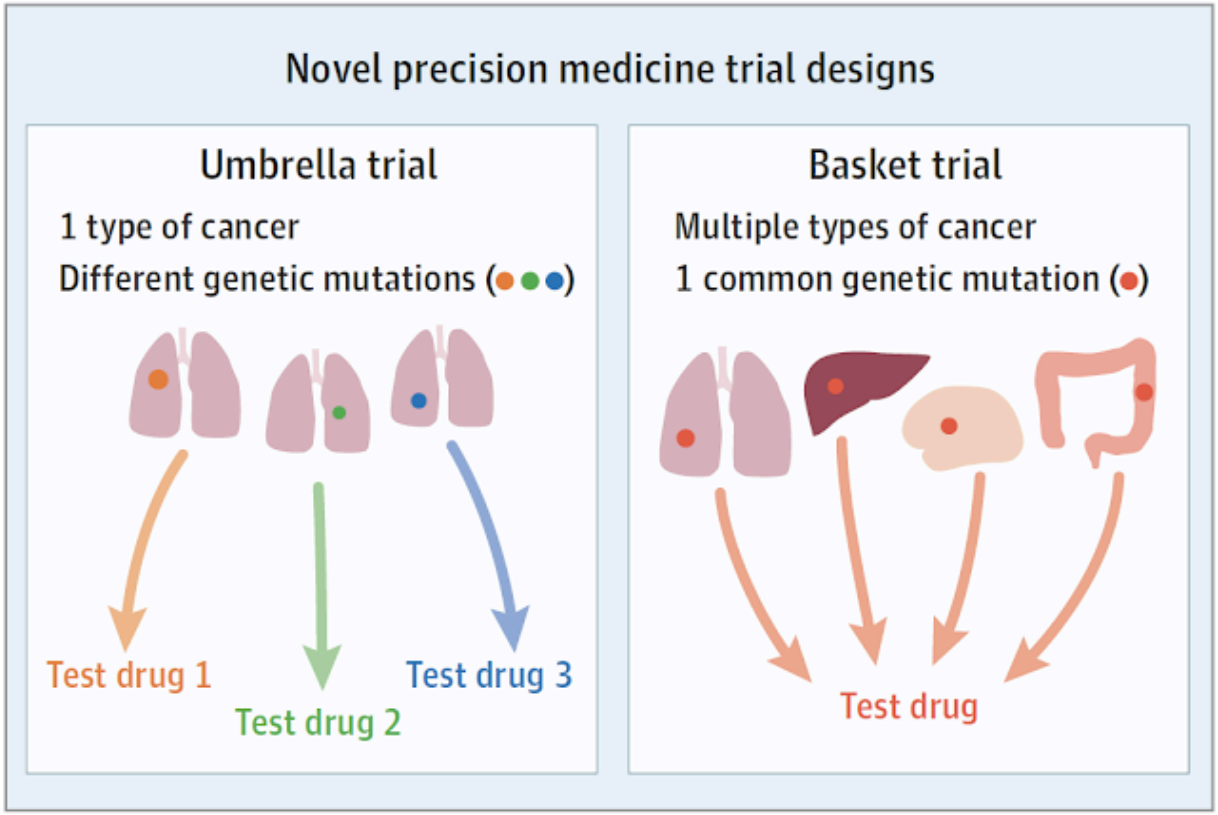
SELECTED DESIGNS IN DRUG DEVELOPMENT BASED ON MOLECULAR BIOLOGY OR ON STRATEGY

Genotype driven	Basket trials	Test the effect of one drug on single mutation in a variety of cancer types
	Umbrella trials	Test the impact of different drugs in different mutations in a single type of cancer
New designs	Adaptive trial	Allows the modification of some parameters of the trial as data accrue, e.g. sample size reassessment, stop for early efficacy/ futility, drop an arm **A platform trial** is a type of adaptive trial designed to evaluate multiple treatments efficiently.

Can be used for large phase 1 trials, phase 2

Biomarker selection & New study designs



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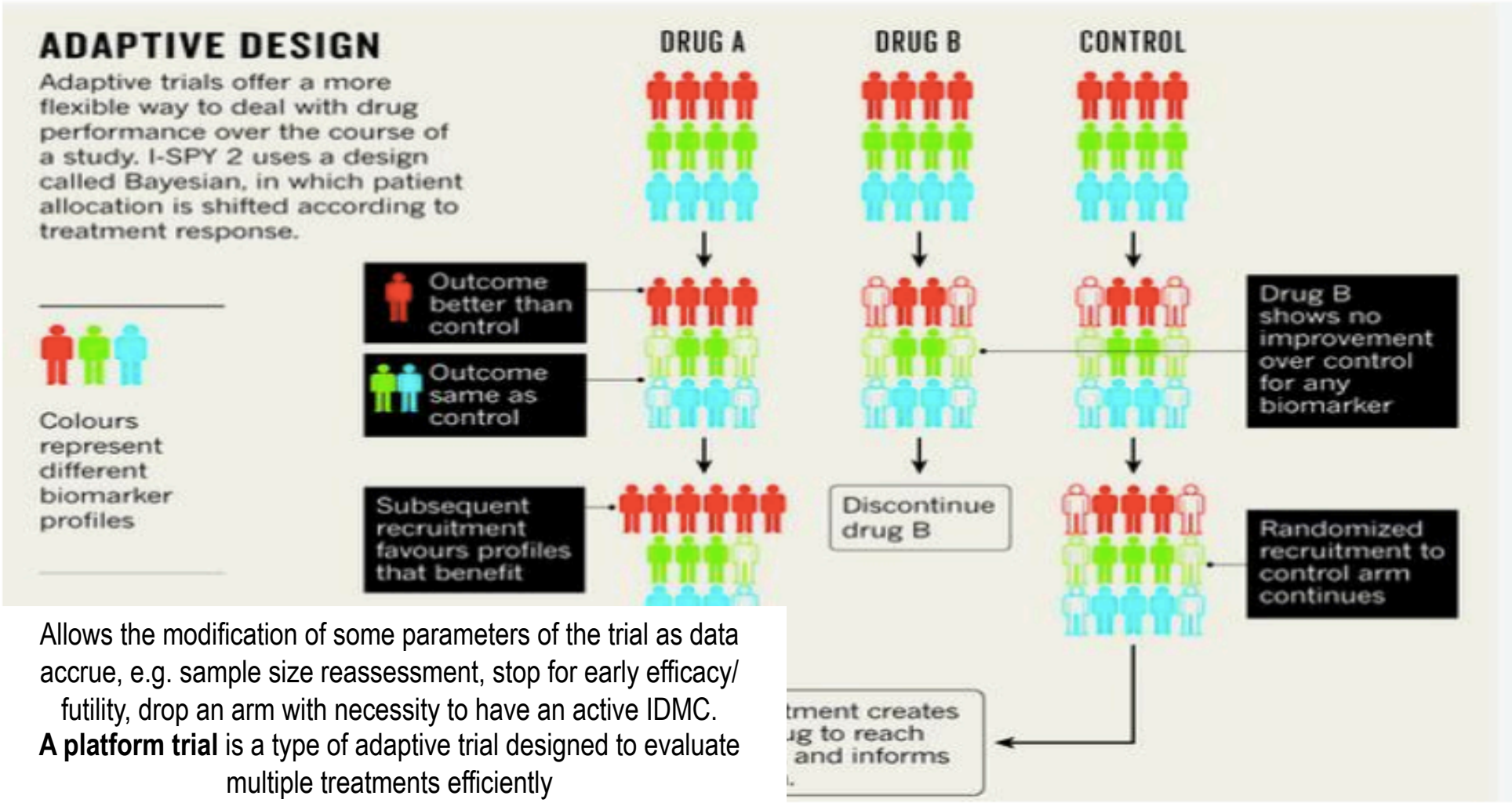

Allows the modification of some parameters of the trial as data accrue, e.g. sample size reassessment, stop for early efficacy/ futility, drop an arm with necessity to have an active IDMC.

A platform trial is a type of adaptive trial designed to evaluate multiple treatments efficiently

Encouraging trends in modern Phase 1 oncology trials

224 trials between 01/2014-06/2015

ORR : 19.8%

Factors significantly associated with an RR:

- Trials investigating a single tumor type
- Presence of a tumor biology eligibility criterion
- Combination of treatments
- Presence of an expansion cohort

Table 1. Characteristics of the Trials.*

Variable	No. of Trials (%) (N = 224)
Trial sponsorship	
Academic	106 (47.0)
Industry	118 (53.0)
No. of patients	
0–25	131 (58.5)
26–50	68 (30.4)
>50	25 (11.0)
Initial human trial	
Yes	84 (37.5)
No	140 (62.5)
Expansion cohort	
Yes	64 (28.6)
No	160 (71.4)
Focus of drug efficacy	
Specific histologic characteristics	103 (46.0)
Miscellaneous histologic characteristics	121 (54.0)
Treatment	
Tyrosine kinase inhibitor	85 (38.0)
Monoclonal antibody	33 (15.0)
Immunotherapy	16 (7.0)
Chemotherapy	42 (19.0)
Hormonal therapy	3 (1.0)
Other†	45 (20.0)
Form of therapy	
Monotherapy	90 (40.0)
Combination therapy	134 (60.0)
Tumor biology eligibility criterion	
Yes	30 (13.0)
No	194 (87.0)

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Italiano et al. NEJM 2018

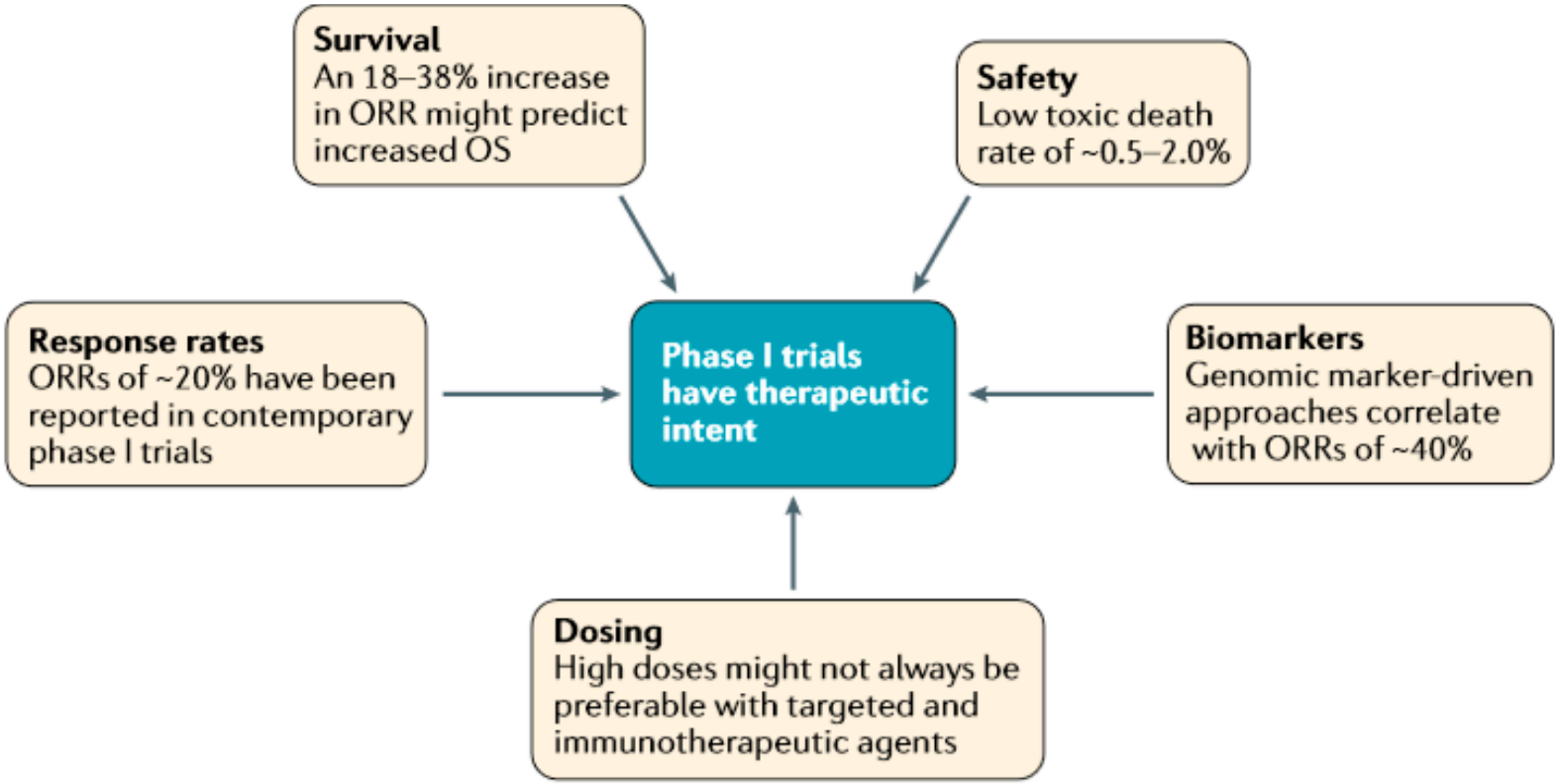
Response rates in selected oncology phase 1 trials

Series	Period covered	Trials included (*n*)	Patients (*n*)	Agents tested (*n*)	ORR	Grade 5 AEs at least possibly related to drug
Estey et al. (1986)	1974–1982	187	NR	54	4.2%	NR
Decoster et al. (1990)	1972–1987	211	6,639	87	4.5%	0.5%
Horstmann et al. (2005)	1991–2002	460	11,935	NR	10.6%	0.49%;
Roberts et al. (2004)	1991–2002	213	6,474	149	3.8%	0.54%
Schwaederle et al. (2016)	2011–2013	Biomarker-driven trials of targeted agents: 57	Biomarker-driven trials: 2,655	NR	31.1% (42% in the case of genomic biomarkers)	1.9%
		Non-biomarker-driven trials of targeted agents: *n* = 177	Non-biomarker-driven trials: *n* = 10,548		5.1%	NR
		Non-biomarker-driven trials of cytotoxic agents: *n* = 116			Non-biomarker-driven trials of cytotoxic agents: 4.7%	Non-biomarker-driven trials of cytotoxic agents: 2.2%
Waligora et al. (2018)	2004–2015	170	4,604	NR	10.29%	2.09%
Chakiba et al. (2018)	2014–2015	224	NR	224	19.8%	NR

AE, adverse event; NR, not reported; ORR, overall response rate

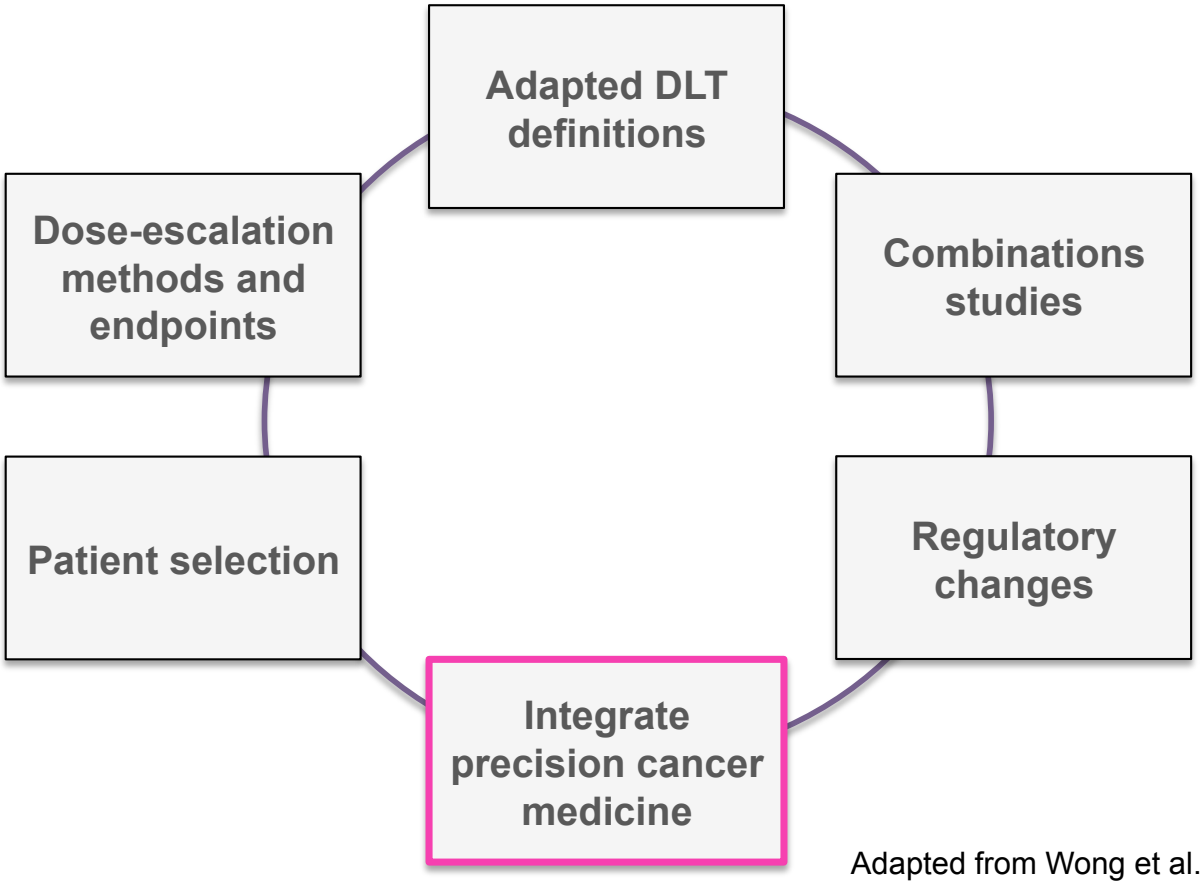
Adashek JJ et al; Nat Rev Clin Oncol. 2019 Dec

Phase 1 trials are more and more considered a valid therapeutic option for cancer patients



Adashek JJ et al; Nat Rev Clin Oncol. 2019 Dec

Considerations for the evolution of phase I oncology trials



Adapted from Wong et al. Nature Reviews

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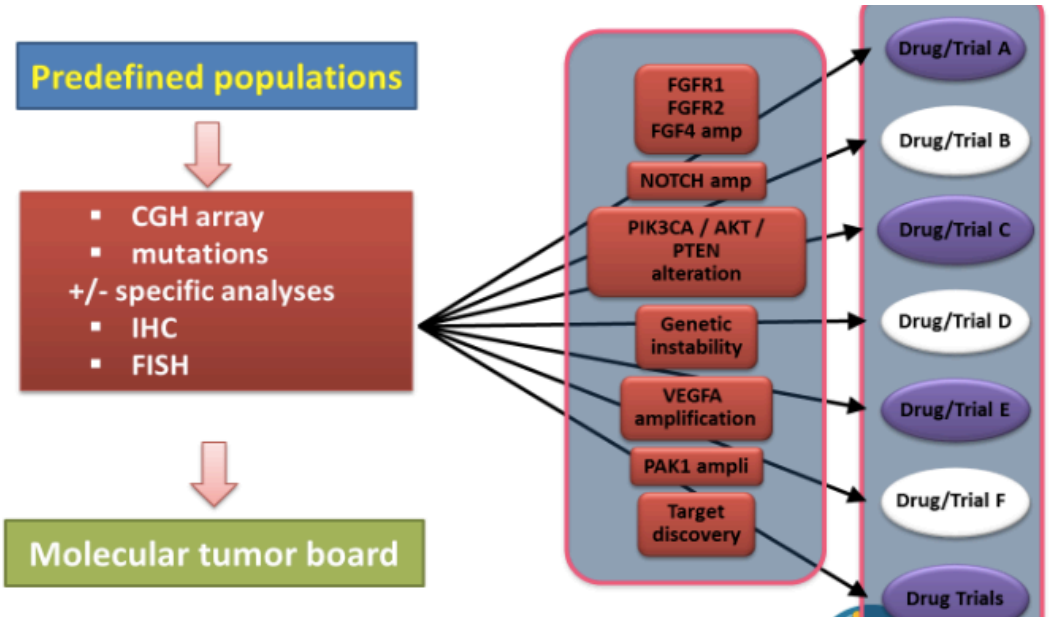
Integrate Precision medicine and « working together »



A collaboration between Belgian universities and their network hospitals

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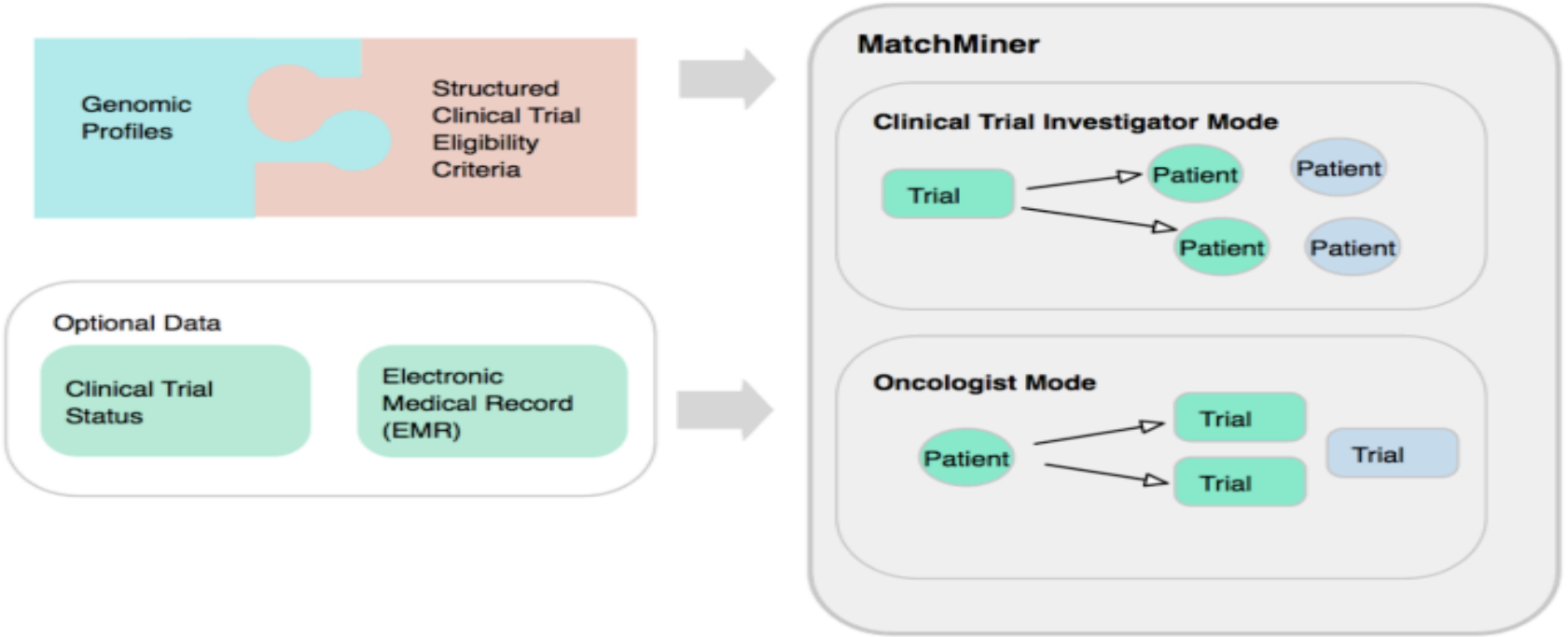
BSMO

MatchMiner

Developed at Dana Farber Cancer Institute

Open source computational platform for **matching** patient-specific genomic profiles to **precision cancer medicine clinical trials.**



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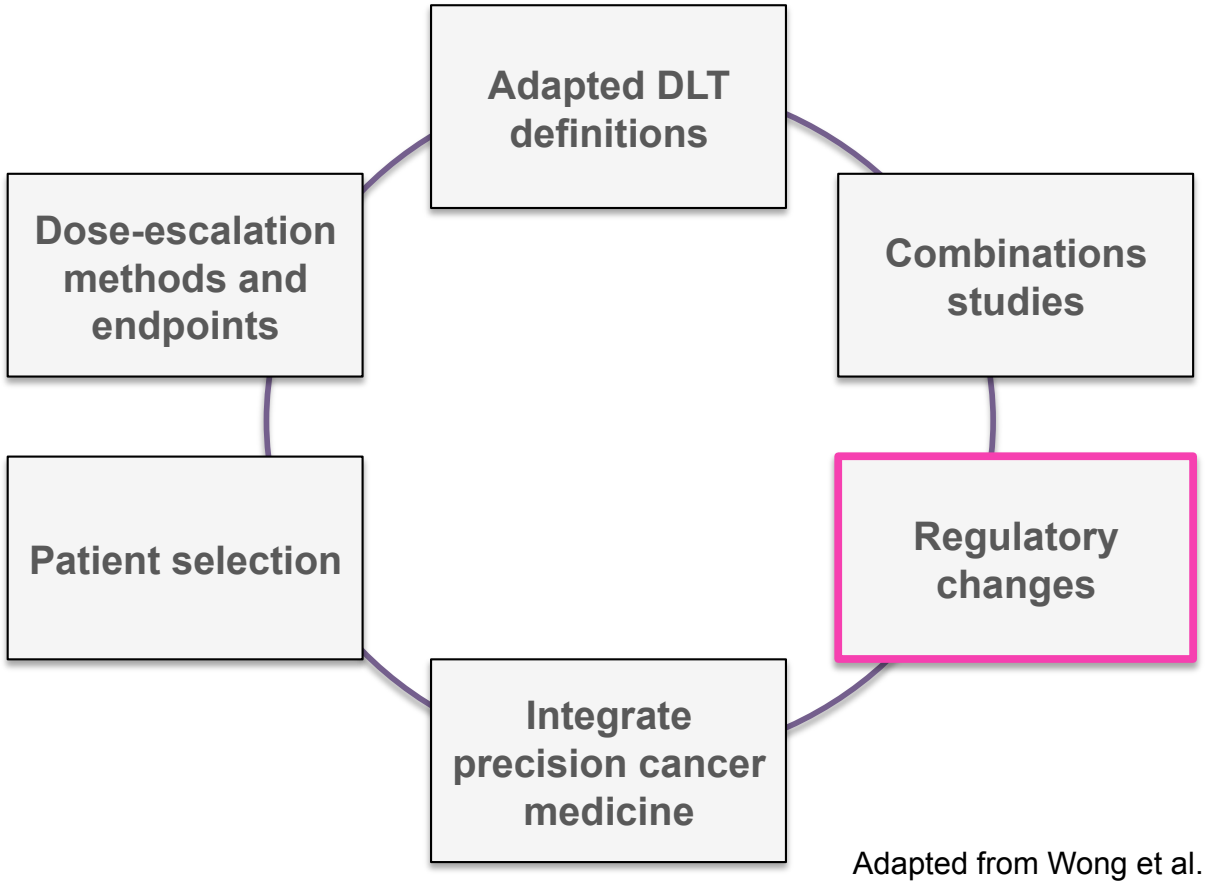

Adapted from Wong et al. Nature Reviews

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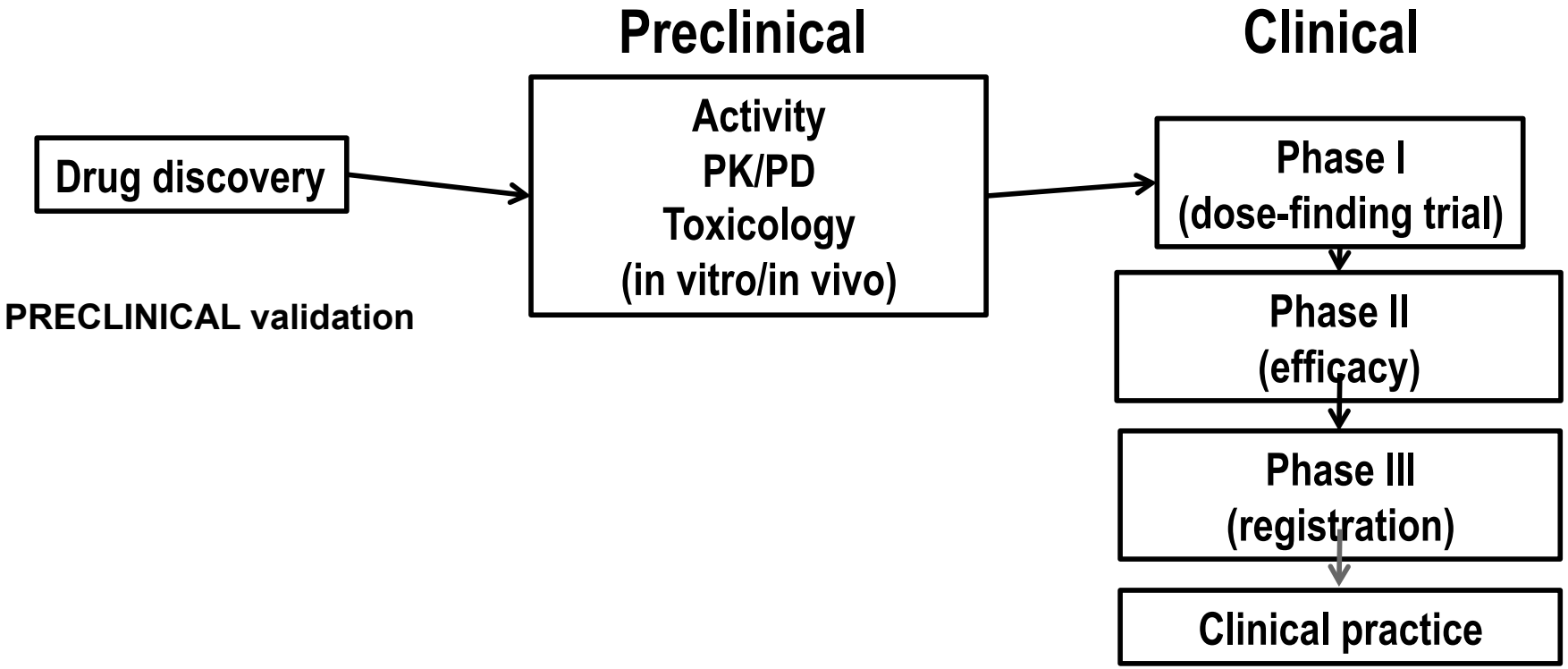
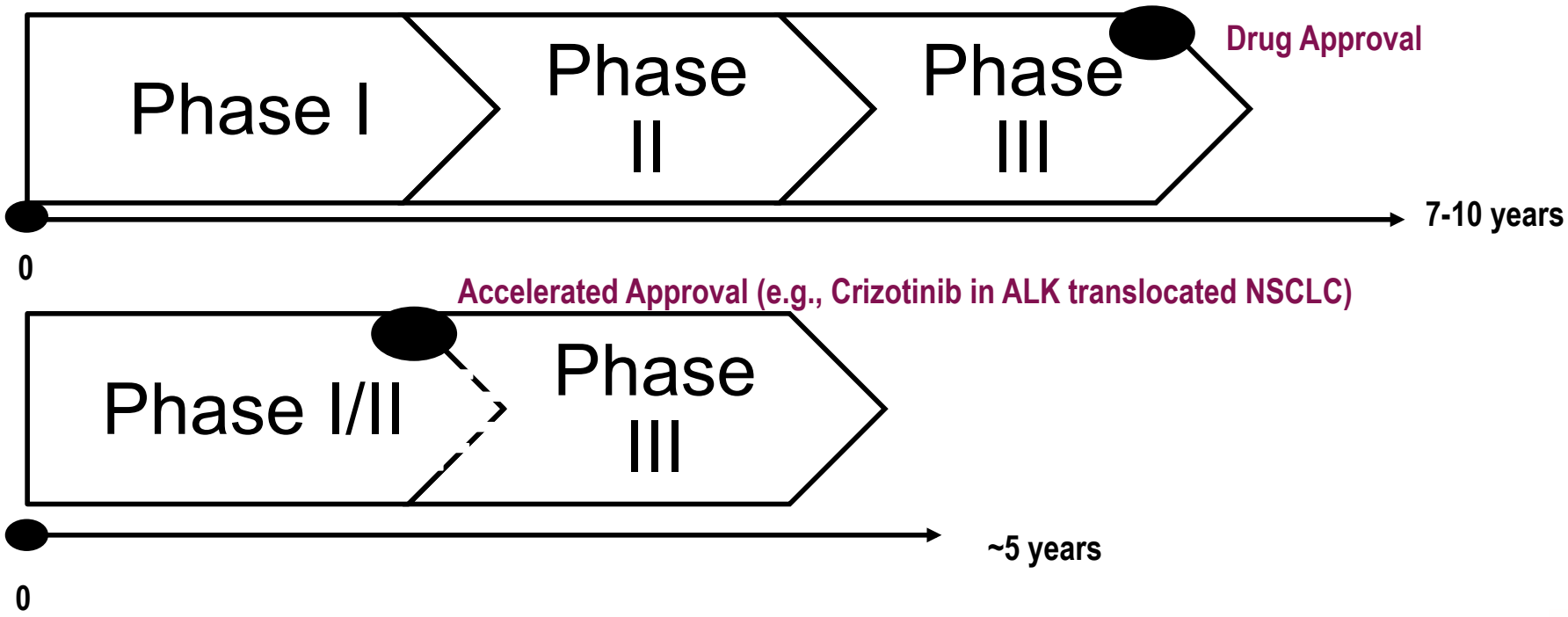
Classical approach of drug development



Recent developments in the clinical research methodology and regulatory changes



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Adapted from Postel Vinay et al. Annals of Oncol. 201

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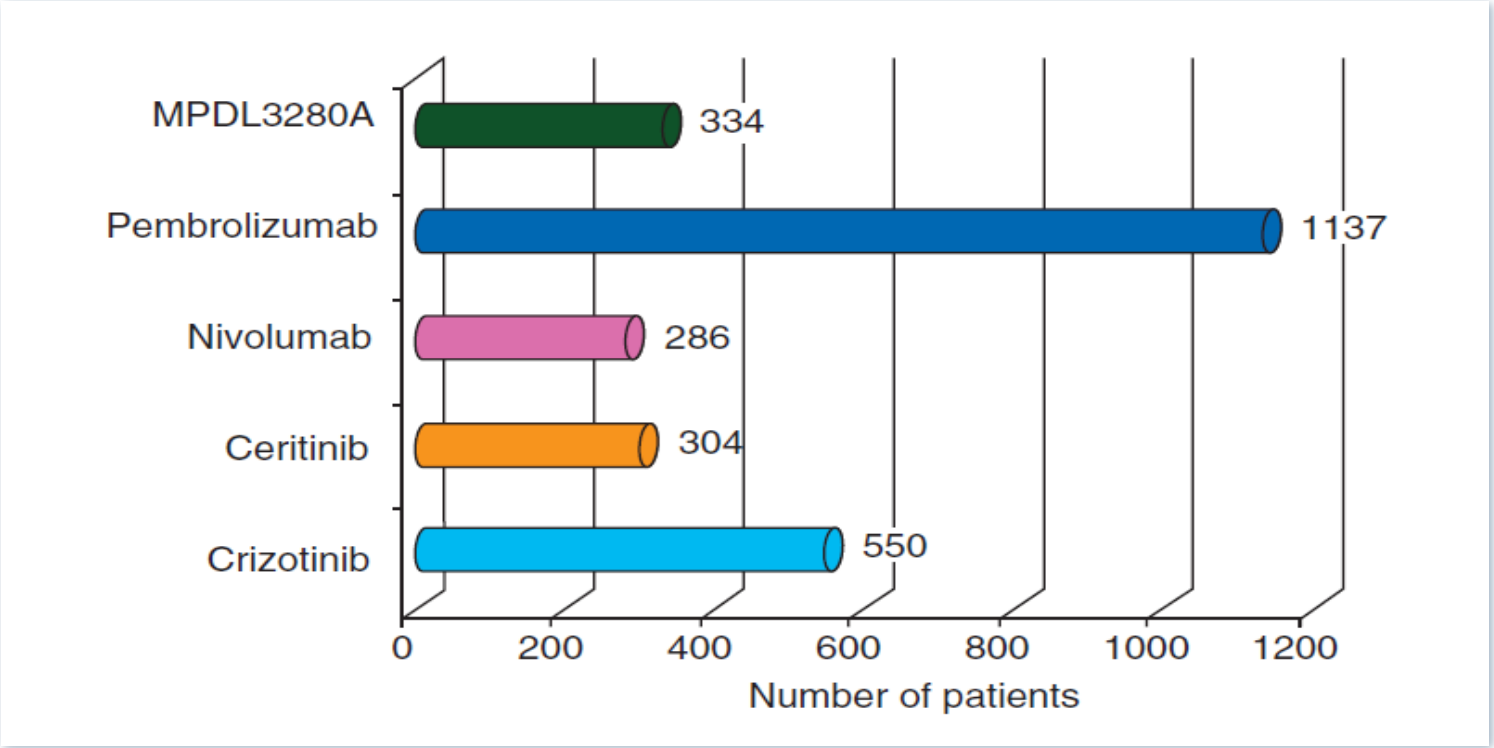
Number of patients enrolled in recent phase I trials having led to conditional approval or breakthrough designations



Postel-Vinay S et al, Annals of Oncology 2016

Tumor-Agnostic treatment strategies for cancer
Example of TRK fusions

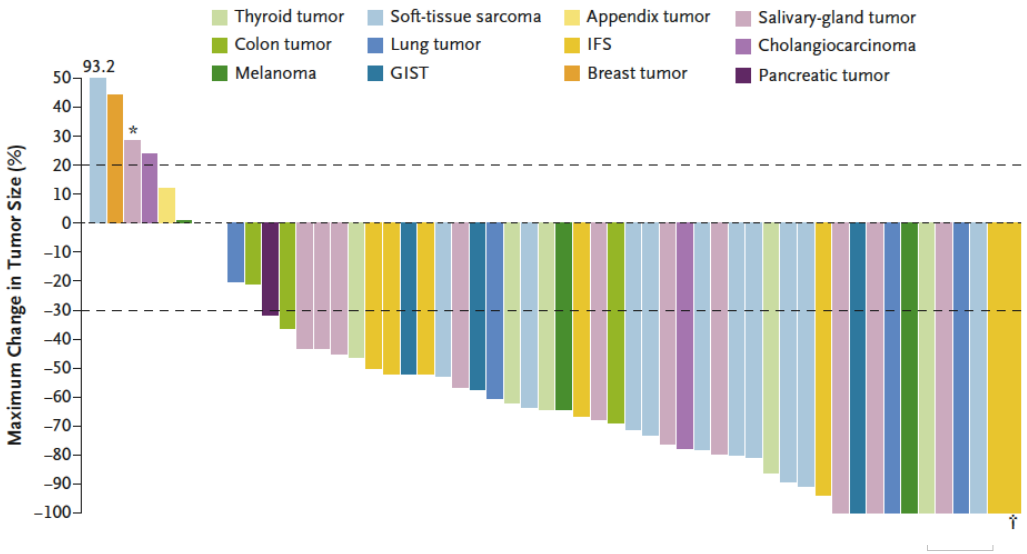
- Can be harbored by **1%** of all cancers
- Targeted treatments are very potent

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

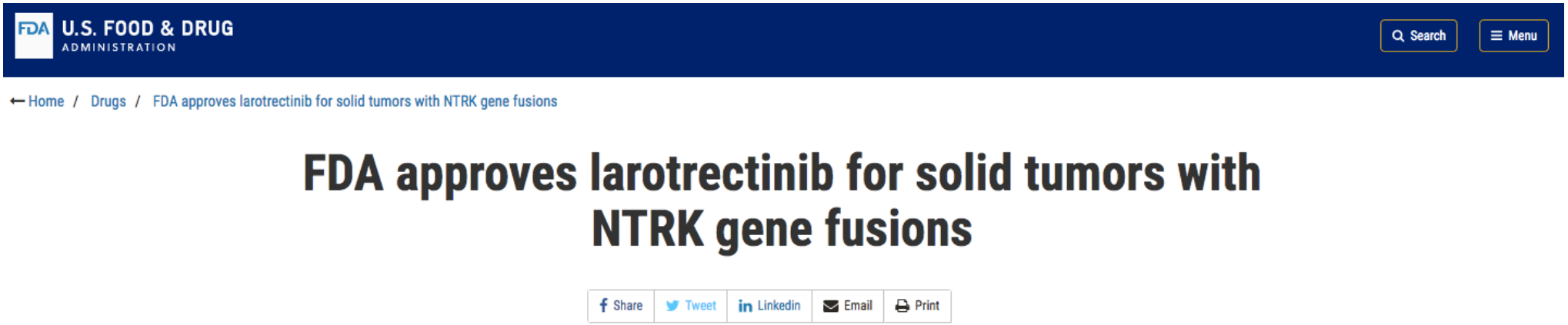
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman



Tumor-Agnostic treatment for cancer

Example of TRK fusions



Novembre 2018

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- **Challenges and Perspectives**

Challenges in “target-oriented” clinical research

1. Tumor heterogeneity and **accumulation of rare genomic alterations**:
   - Need for data sharing and molecular tumor boards to better orient patients

2. **Limited access** to targeted-oriented clinical trials for cancer patients:
   - High attrition rate
   - Ethical issues.

3. Drug development is even more challenging that the molecular aberration targeted is rare :
   -High number of patients to screen for 1 patient to be included in one clinical trial

4. Patients sometimes have **to travel even outside their home country and far from family** to access those specific clinical trials targeting a molecular abnormality.

Challenges for therapeutic development of IO agents

- Optimal dose and schedule selection

- Optimal sequence/rechallenge

.> Maximize benefit for patients and minimize economic burden

- Identify resistant/sensitive disease to immunological approaches

.> Biomarkers (immunoscore, Immunomics, …)

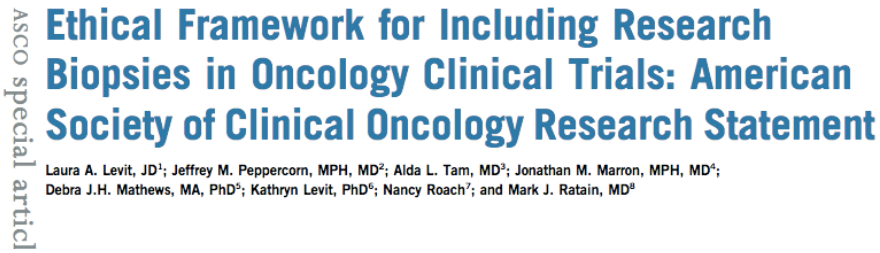
- New patterns/definitions of tumor assessment and disease progression

- Combinations issues

- Competitives trials and redundancy ++

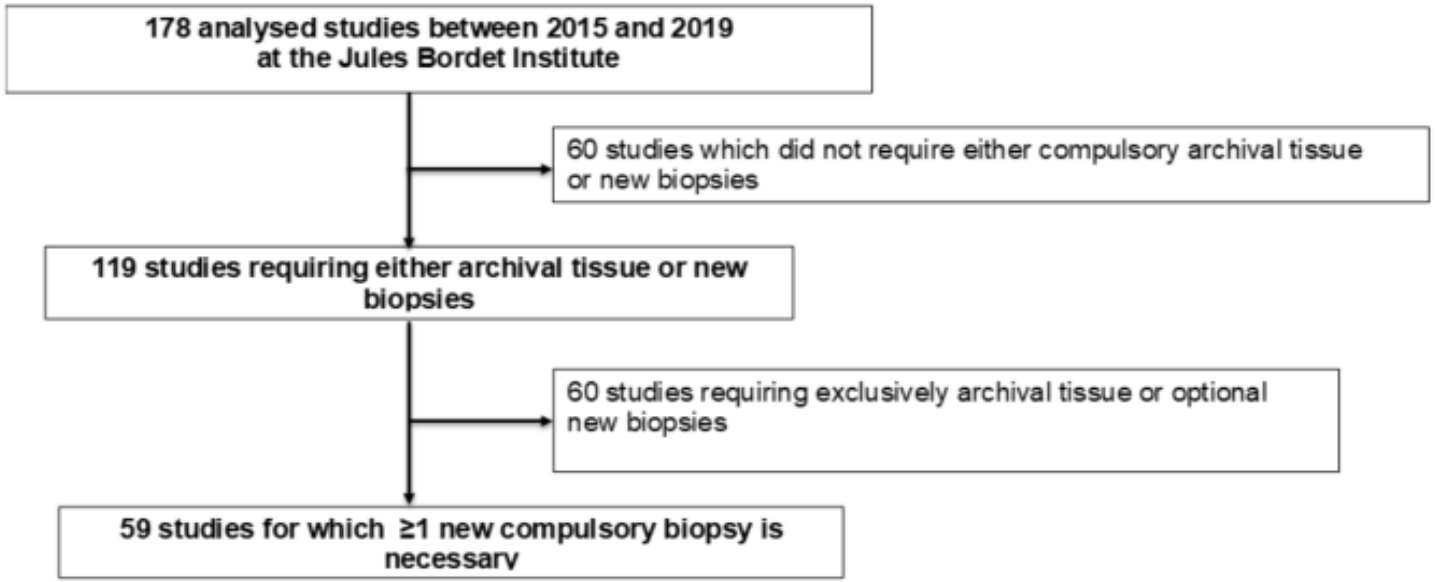
Global ethical considerations

- High attrition rate in EDD
- Benefit/risk ratio (currently evolving)
- « Mandatory biopsies » that do not have the potential to directly benefit participants



Levit LA, J Clin Oncol. 2019 Sep

Adherence to the ASCO recommendations for research biopsies and archival tissue requirements in commercial and academic clinical trials conducted at IJB



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Olympios et al, under submission
Collet et al, ESMO 2020

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Biopsy in clinical trials

No new necessary biopsy – 33%
required tissue – 67%

Type of biopsy and biomarkers characteristics among studies requiring tissue

	Studies requiring tissue (n=119)	Studies requiring new compulsory biopsy (n=59)
Archival tissue		
Compulsory	57 (48%)	13 (22%)
Optional	62 (52%)	46 (78%)
New compulsory biopsy		
No	60 (51%)	0 (0%)
1	34 (29%)	34 (58%)
2	23 (19%)	23 (39%)
>3	2 (1%)	2 (3%)
Timing of new compulsory biopsy		
At screening	/	43 (73%)
Per treatment	/	33 (56%)
At progression	/	7 (12%)
Type of biomarkers		
Integral : necessary for inclusion	35 (29%)	14 (24%)
Integral : necessary for primary objective	17 (15%)	5 (8%)
Non integral : necessary for secondary objective	5 (4%)	4 (7%)
Non integral : necessary for exploratory objective	62 (52%)	36 (61%)
Utility		
Expected utility : necessary for inclusion or primary objective	63 (53%)	36 (61%)
Potential utility	12 (10%)	8 (14%)
Unknown utility	44 (37%)	15 (25%)
Participants risk		
Low risk	4 (3%)	4 (7%)
High or moderate risk	11 (9%)	7 (12%)
Unprecised	104 (88%)	48 (81%)
Adherence with ASCO Ethical Framework	80 (67%)	23 (39%)

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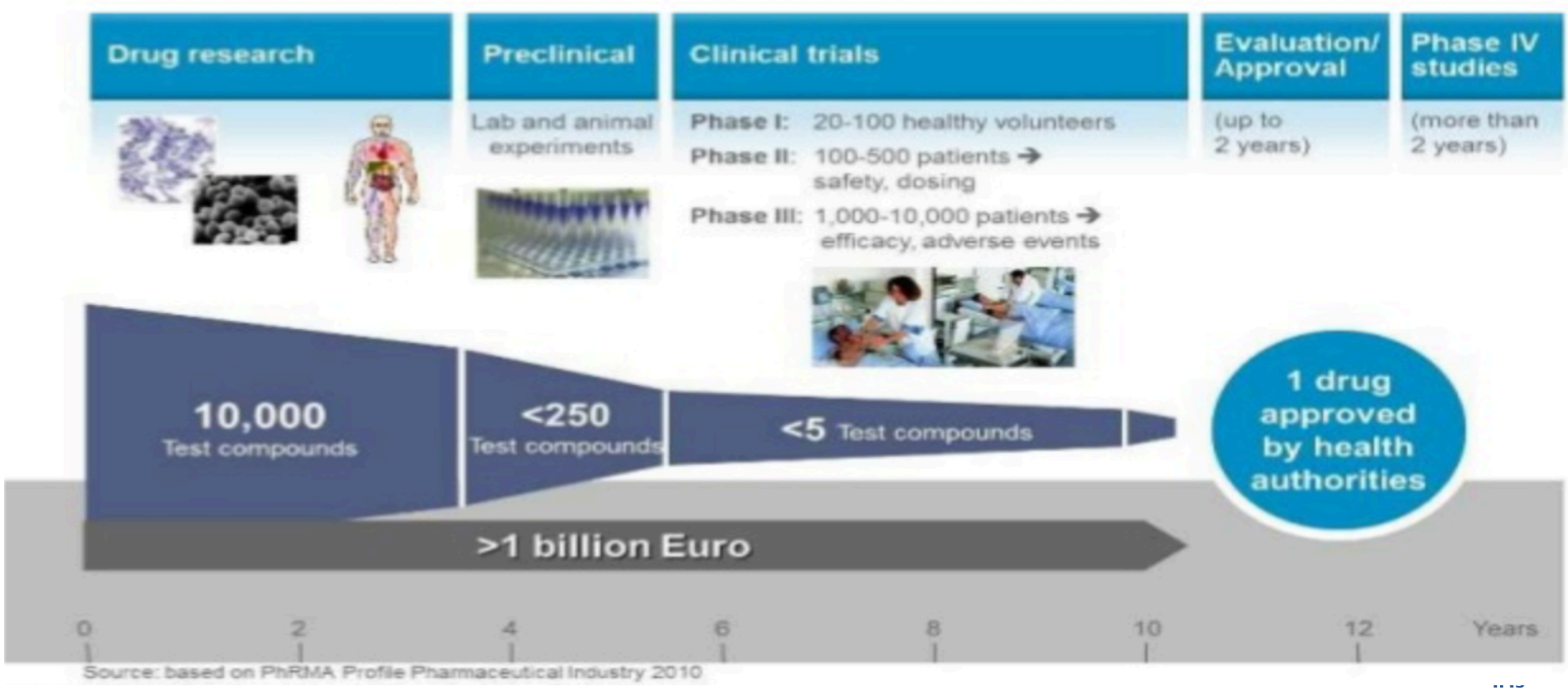
High cost and attrition rate



Aknowledgements

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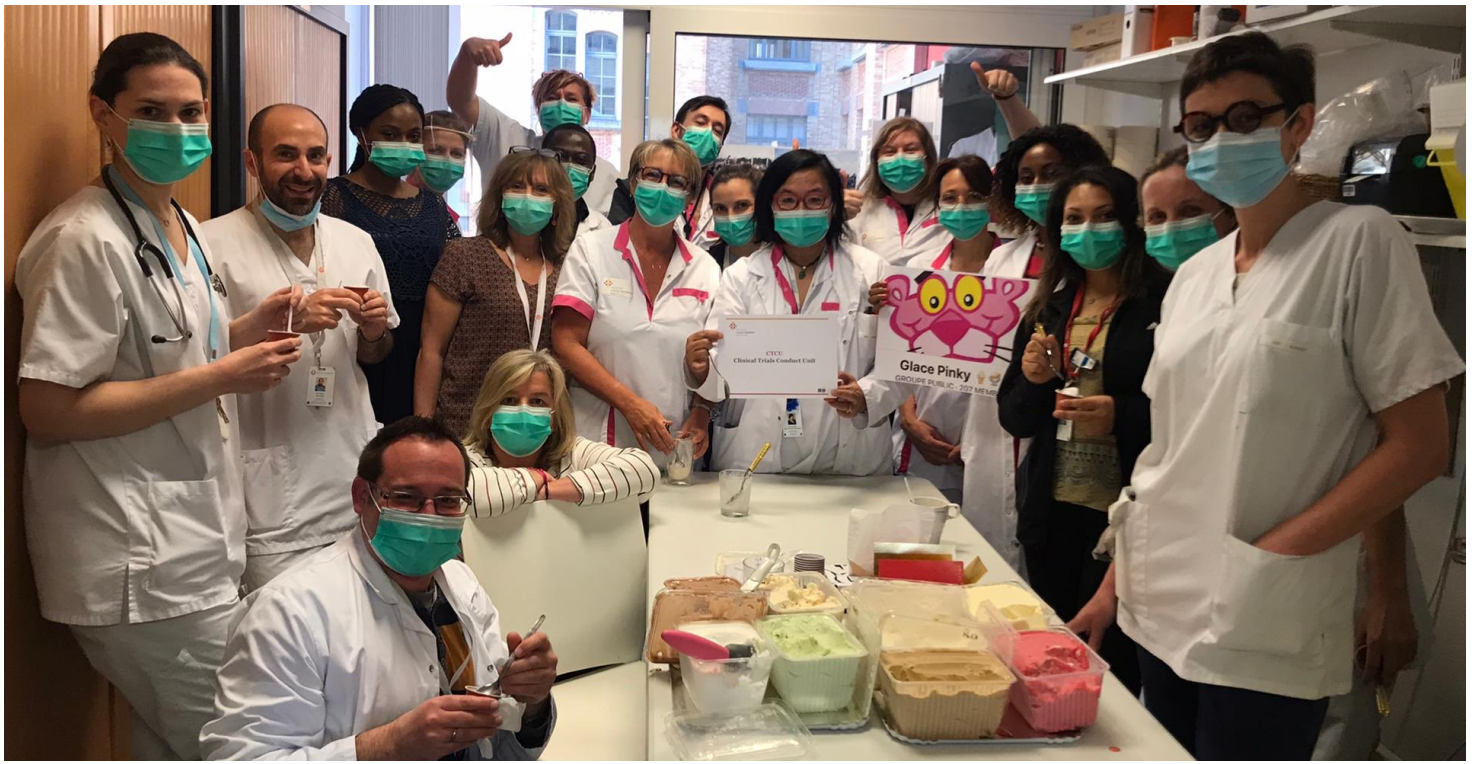
CTCU team



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