INSTITUT
JULES BORDET
INSTITUUT

Phase I trials in patients: new approaches and designs in Oncology

Session 5: How to be prepared

Nuria Kotecki, MD
Clinical Trial Conduct Unit
Institut Jules Bordet, Brussels Belgium
Executive officer – Oncodistinct network

Eufemed, 17th May 2019

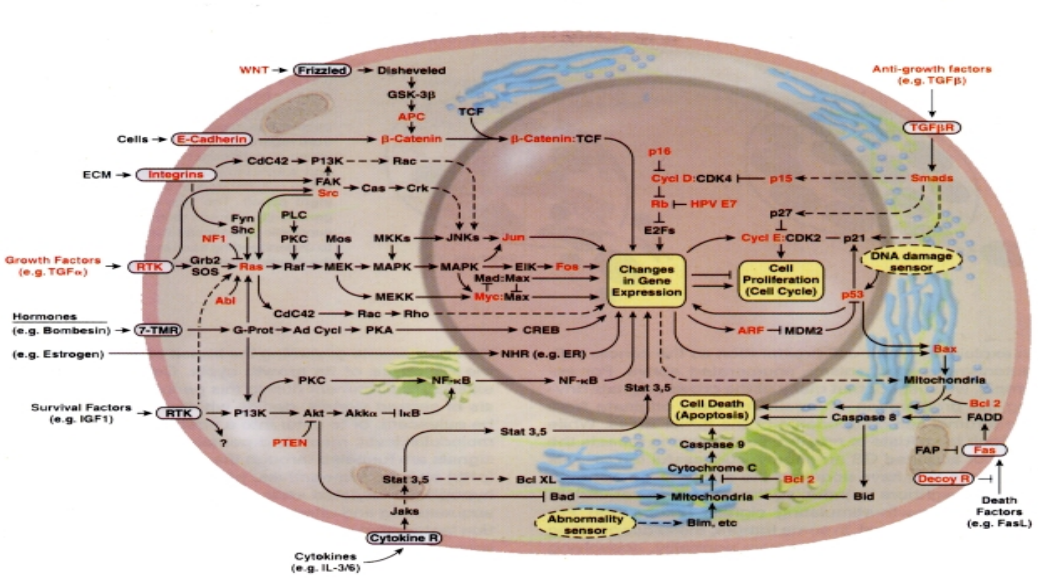
OUTLINE

- Evolving landscape in oncology: New drugs and new cancer types definitions
- Current status for new drug development and phase 1 trials in oncology
- Challenges for clinical research in oncology
- What do we need in drug development methodology ?

OUTLINE

- **Evolving landscape in oncology: New drugs and new cancer types definitions**
- Current status for new drug development and phase 1 trials in oncology
- Challenges for clinical research in oncology
- What do we need in drug development methodology ?

The molecular and immune biology of cancer cells is better understood



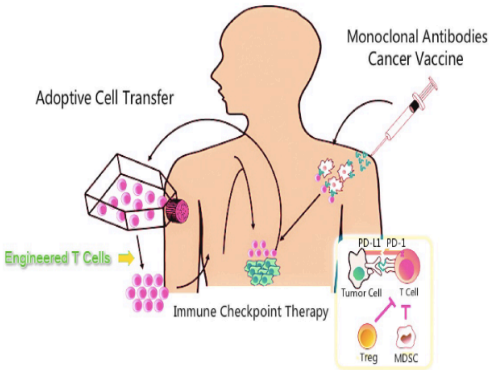
Hanahan et Weinberg, Cell, 2000

Hanahan et Weinberg, 2011

INSTITUT
JULES BORDET
INSTITUUT

ULB iris

Evolving therapeutic concepts in oncology based on molecular/immune biology understanding



Chemotherapy

↓

Molecular-targeted agents

↓

Immunotherapy

Combinations

Monoclonal antibodies

Parp inhibitors

ADC

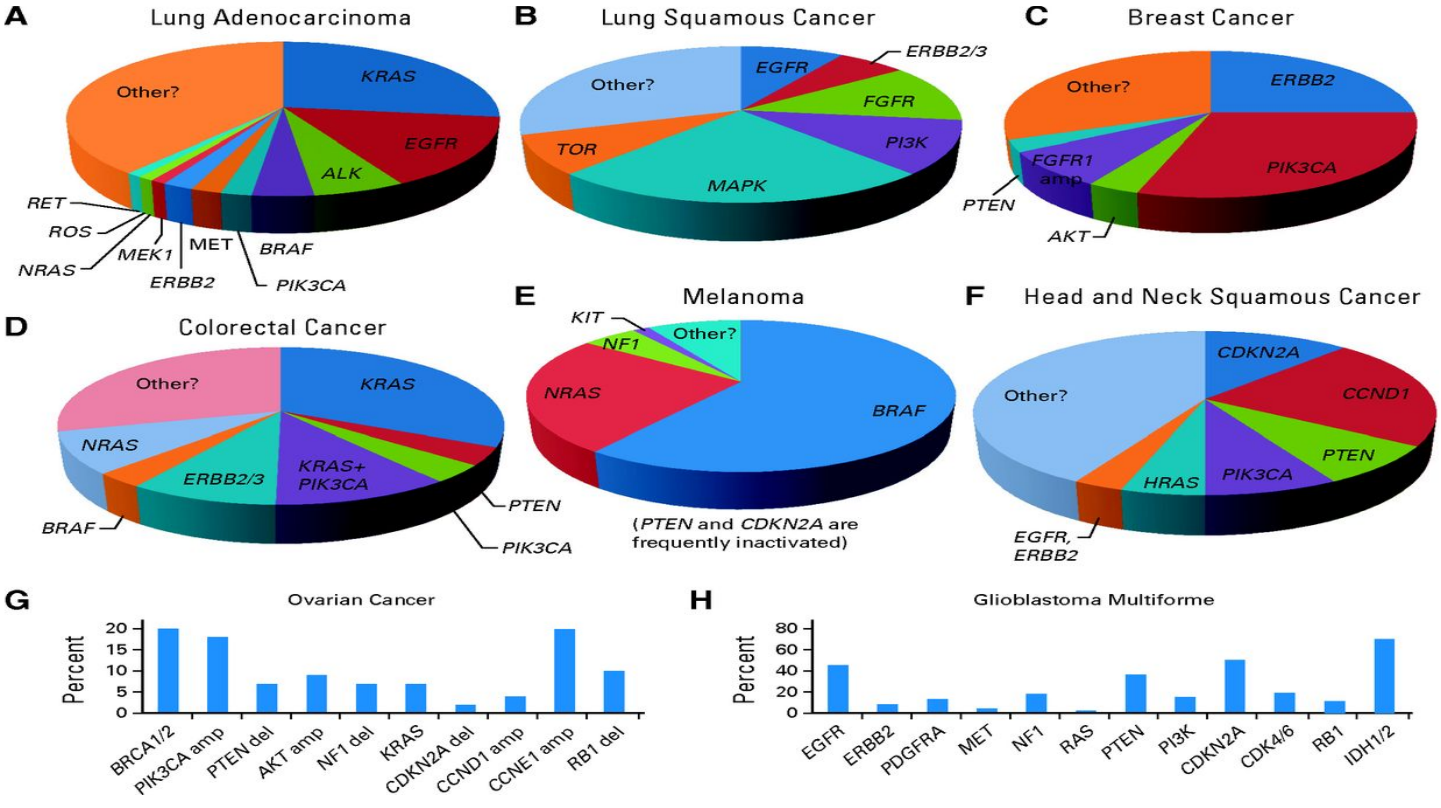
TKIs

Epigenetic modulators

cdk inhibitors

From empirical oncology to molecular and immunological therapeutic approaches

Common cancers are now rare

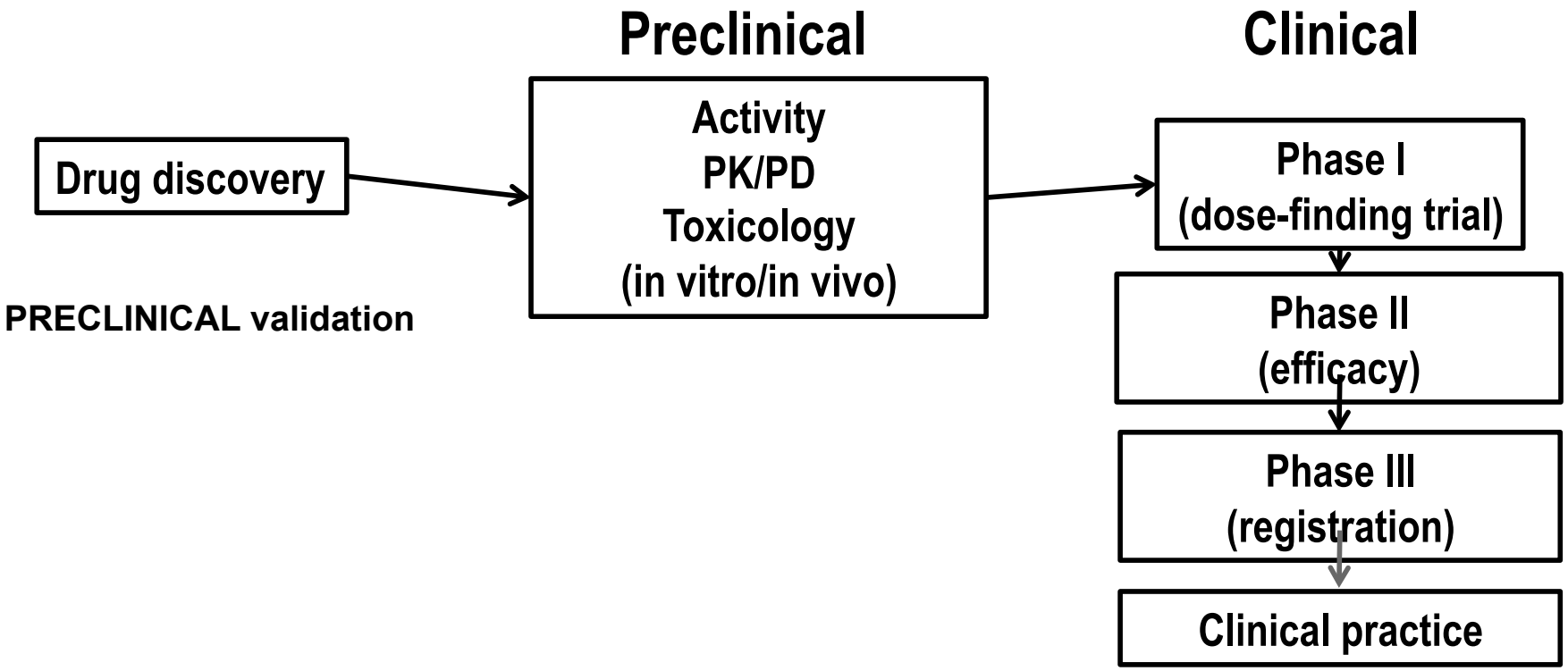


Garraway LA, J Clin Oncol 2013;31:1806-1814

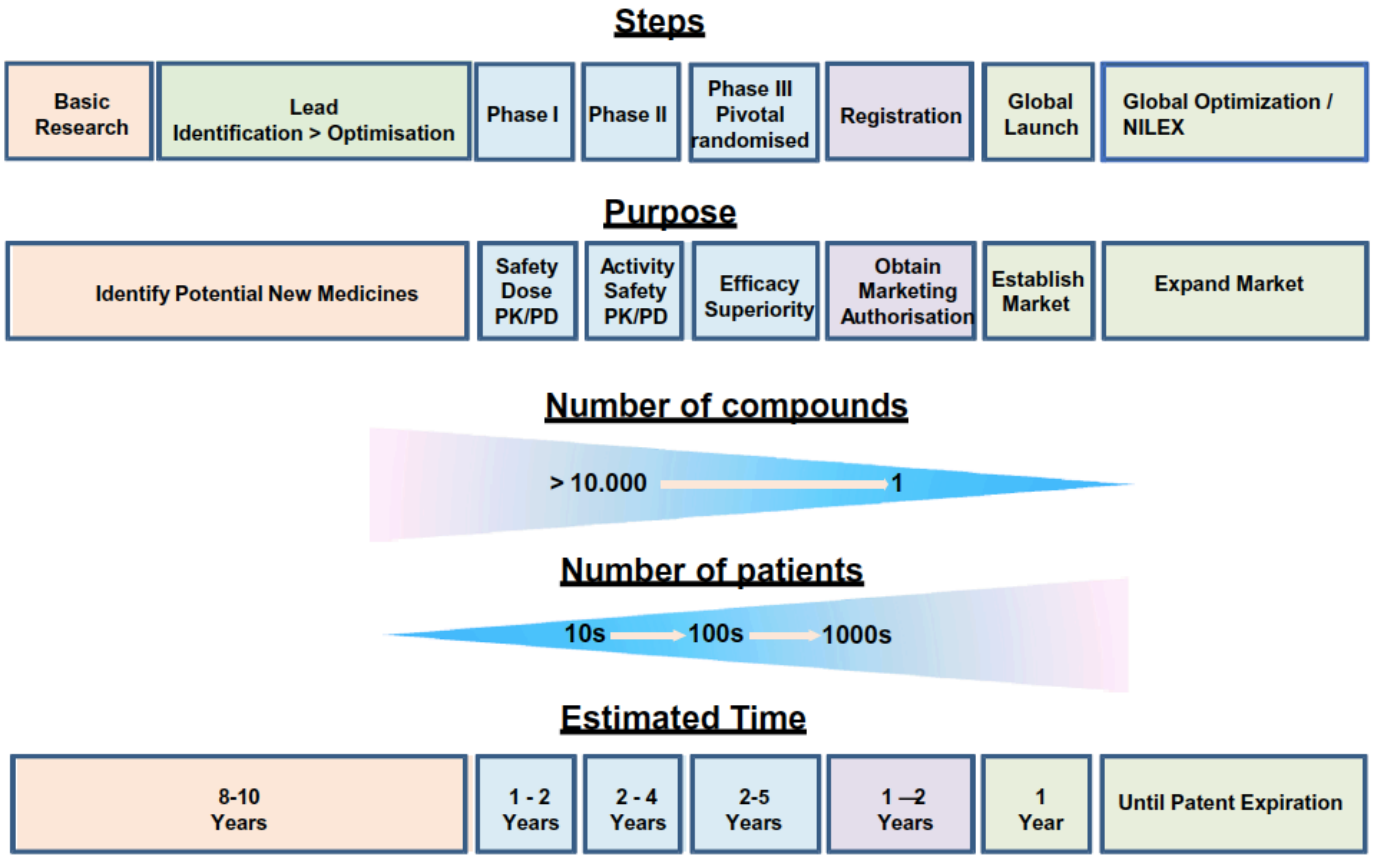
OUTLINE

- Evolving landscape in oncology: New drugs and new cancer types definitions
- **Current status for new drug development and phase 1 trials in oncology**
- Challenges for clinical research in oncology
- What do we need in drug development methodology ?

Classical approach of drug development



Classical approach of drug development

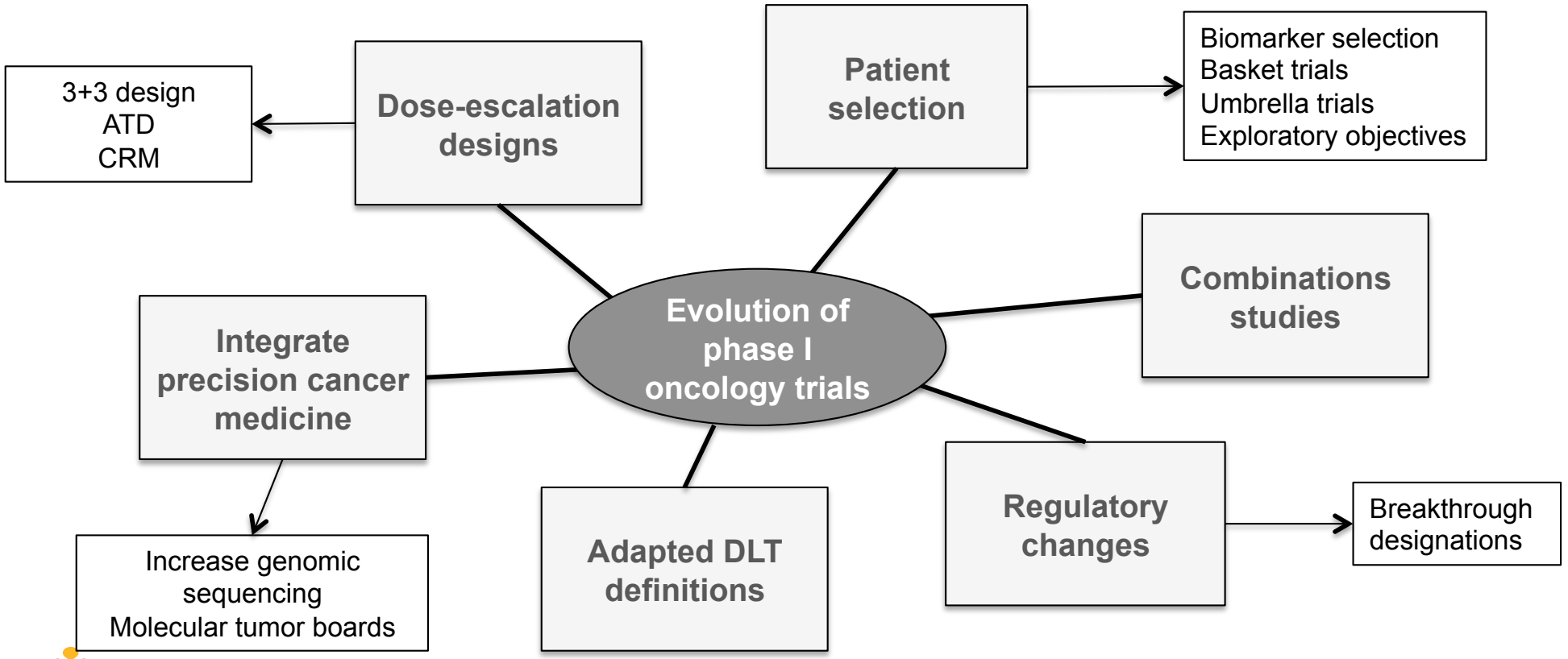


J. Verweij, et al. Cancer treatment Rev, 2019

Major endpoints in phase 1 trials

- **Dose Limiting Toxicity:** Occurrence of severe toxicities during the first cycle of systemic cancer therapy.
- **Maximum Tolerated Dose:** The highest dose of a drug or treatment that does not cause unacceptable side effects
- **Recommended Phase II Dose**

Considerations for the evolution of phase I oncology trials

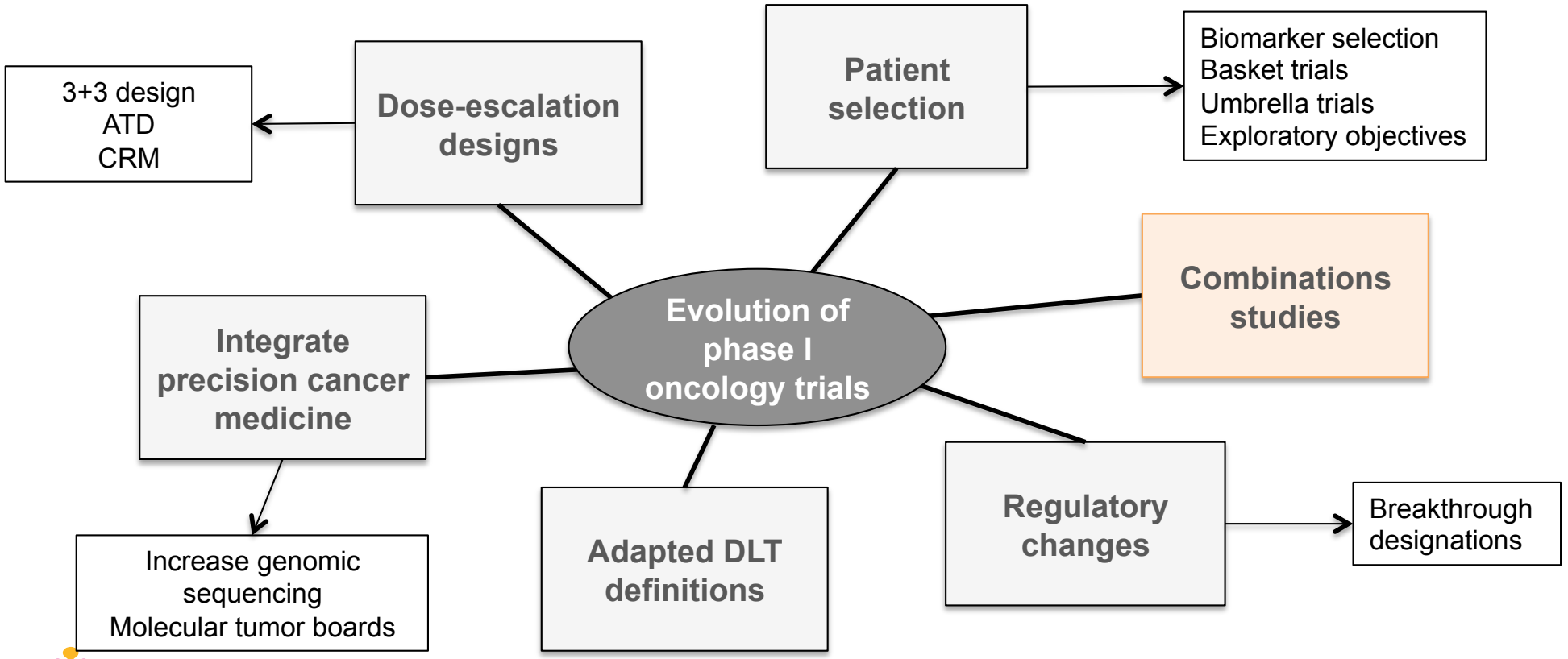


INSTITUT JULES BORDET INSTITUUT

Adapted from Wong et al. Nature Reviews 2016

ULB iris

Considerations for the evolution of phase I oncology trials



INSTITUT JULES BORDET INSTITUUT

Adapted from Wong et al. Nature Reviews 2016

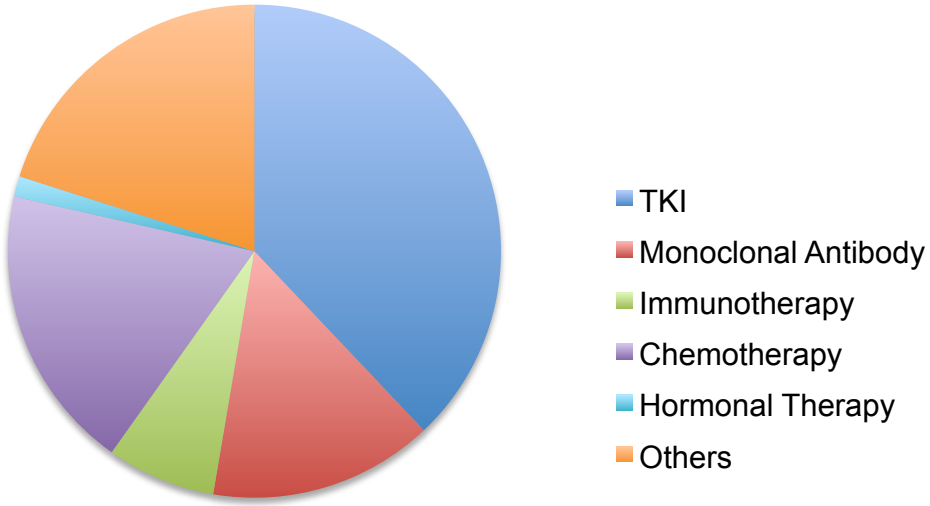
ULB iris

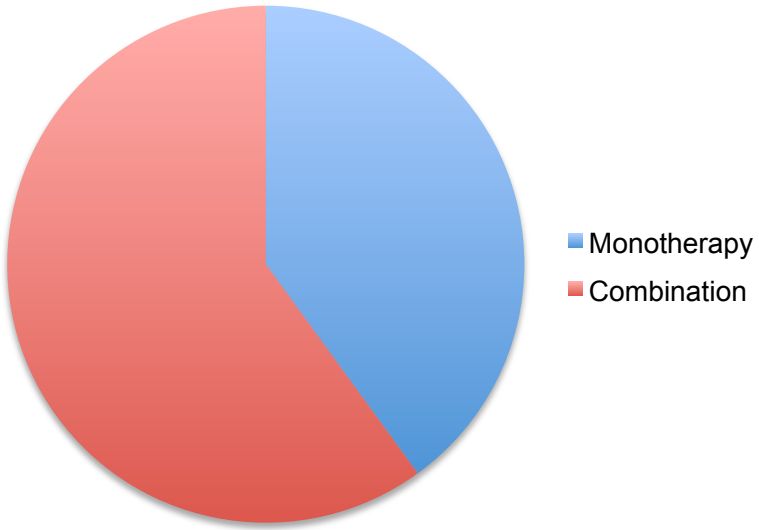
Phase 1 published from 01/2014 to 06/2015

The NEW ENGLAND JOURNAL of MEDICINE

Variable	No. of Trials (%) (N=224)
Trial sponsorship	
Academic	106 (47.0)
Industry	118 (53.0)

Expansion cohort	
Yes	64 (28.6)
No	160 (71.4)



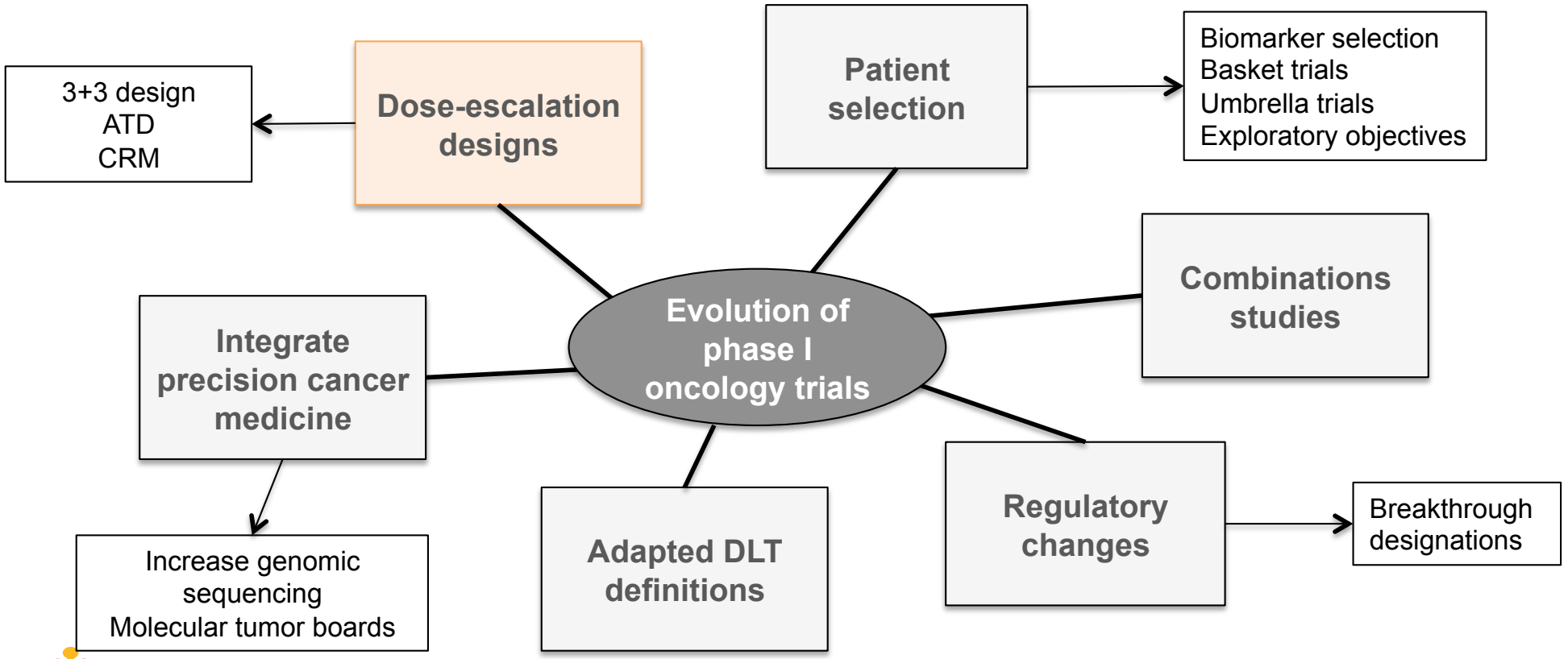


INSTITUT JULES BORDET INSTITUUT

Italiano A et al, NEJM 2018

ULB iris

Considerations for the evolution of phase I oncology trials



INSTITUT JULES BORDET INSTITUUT

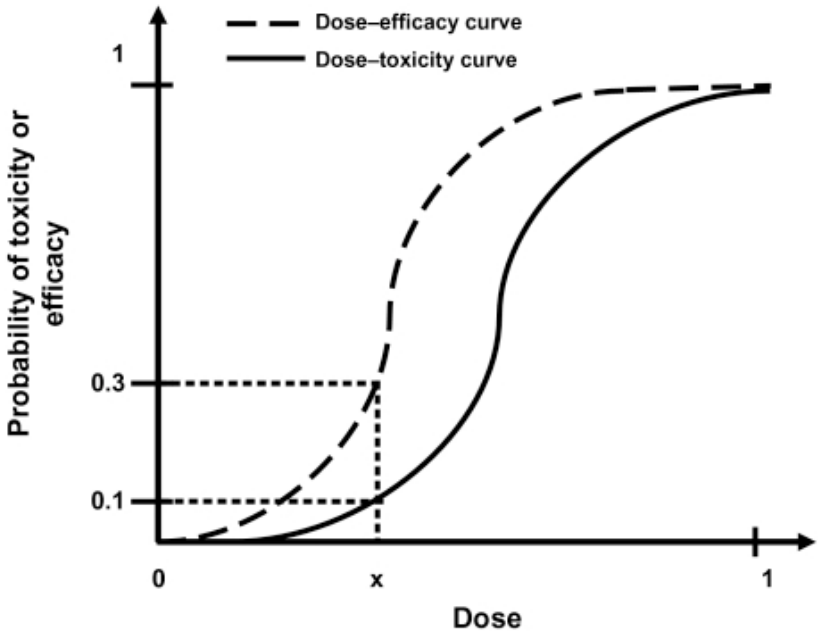
Adapted from Wong et al. Nature Reviews 2016

ULB iris

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

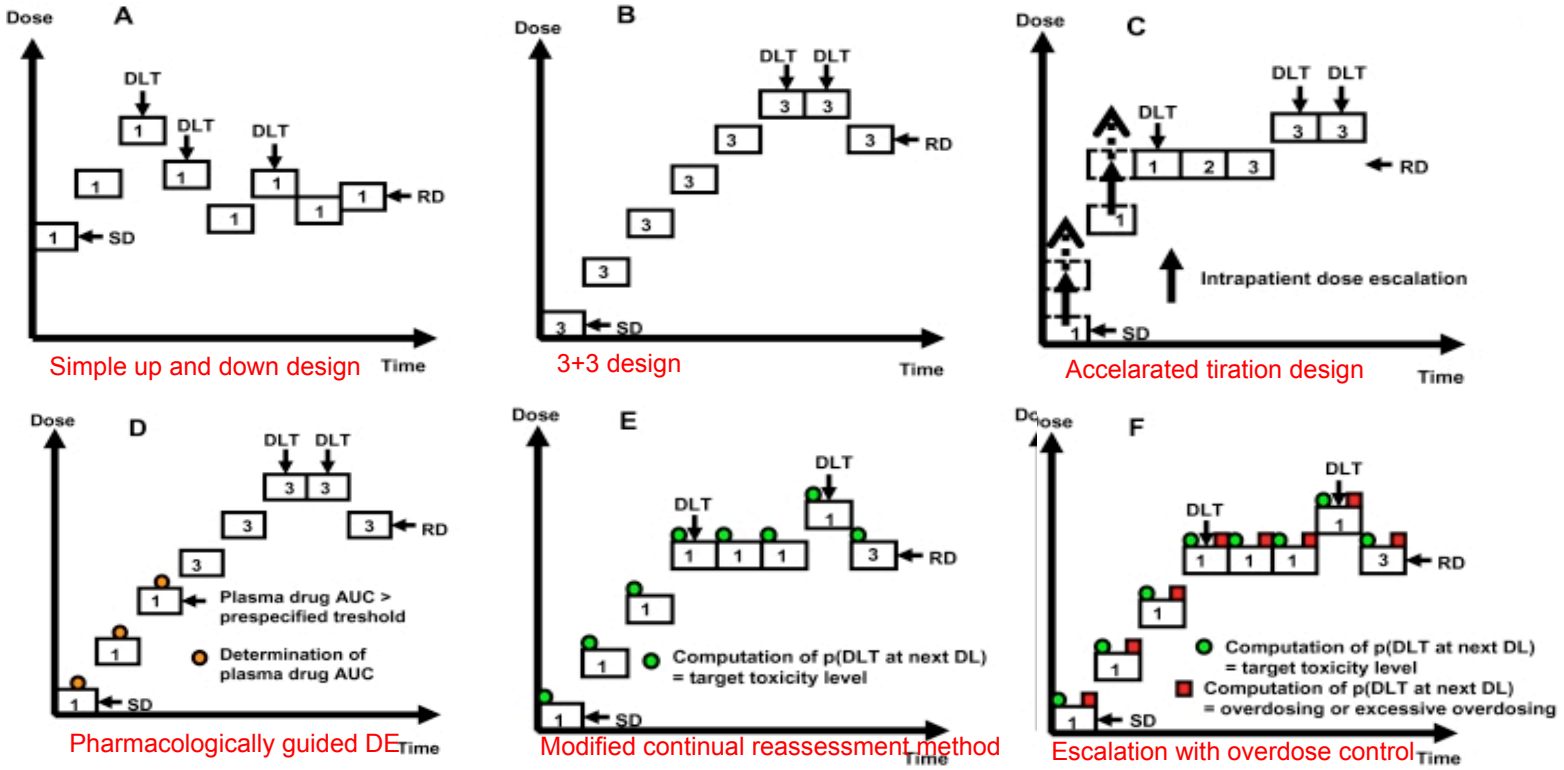
Typical dose–toxicity and dose–efficacy curves for cytotoxic agents



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

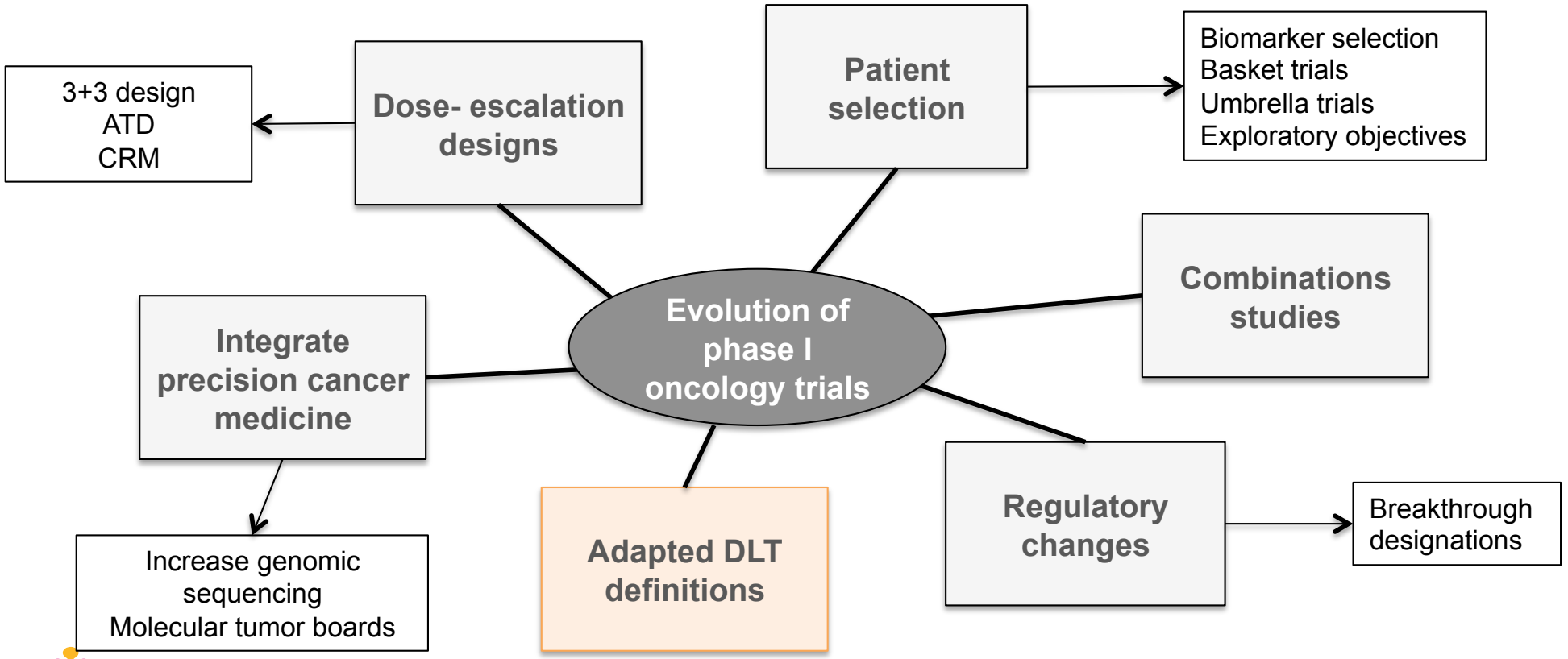
Le Tourneau C J Natl Cancer Inst. 2009

Dose escalation methods for phase I cancer clinical trials.



Le Tourneau C J Natl Cancer Inst. 2009

Considerations for the evolution of phase I oncology trials



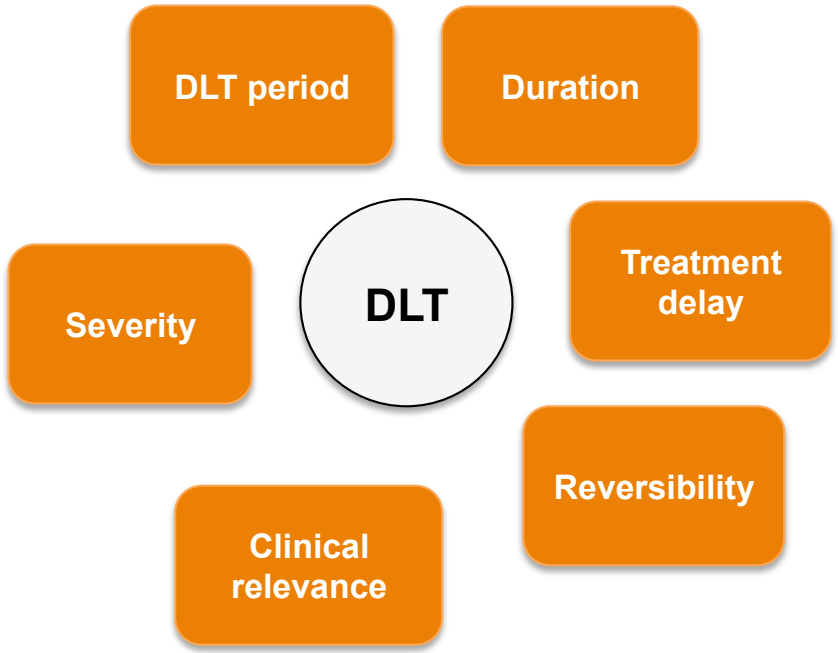
INSTITUT JULES BORDET INSTITUUT

Adapted from Wong et al. Nature Reviews 2016

ULB iris

Adapted DLT definitions

- **New toxicities** (including long term toxicities):
- Extended DLT period
- Better definition of the induced toxicity in relation to the study drug
- Use of expansion cohorts
- Consider the clinical importance of each grade and toxicity type

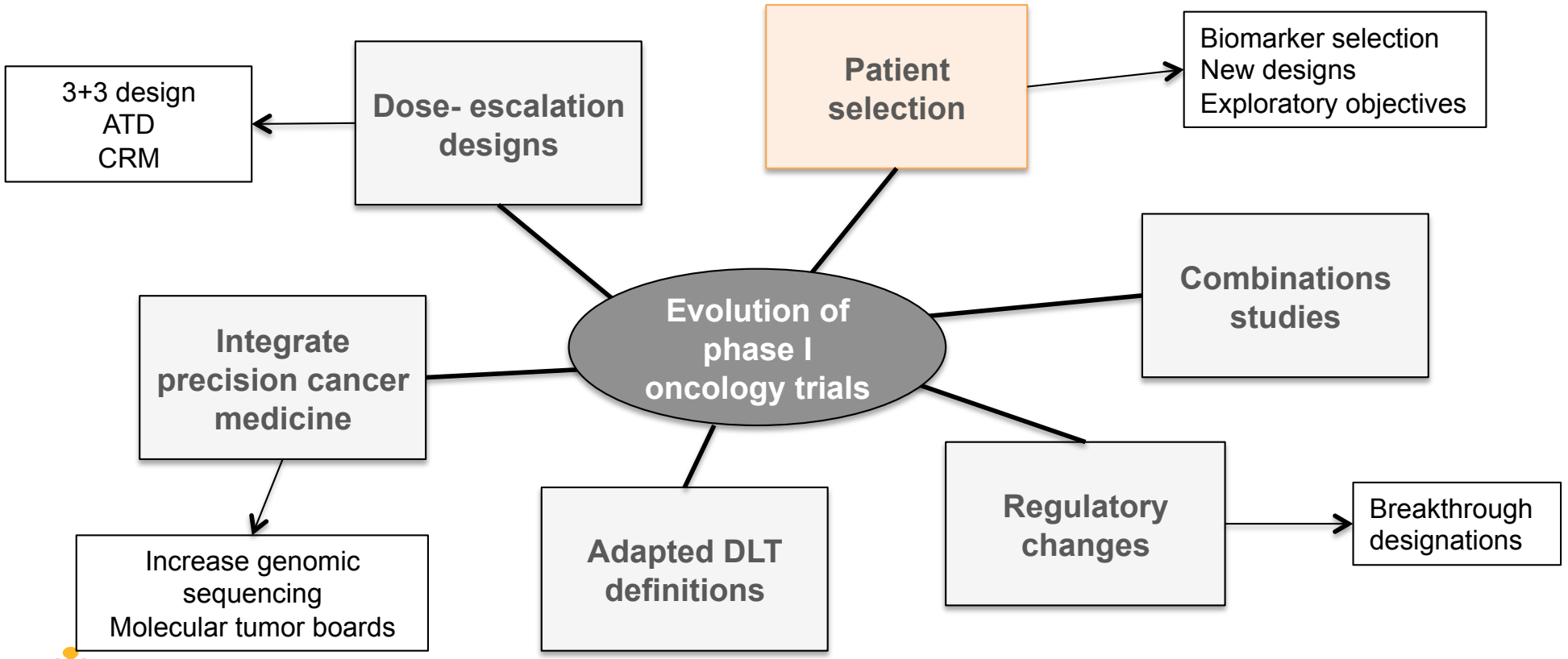


INSTITUT JULES BORDET INSTITUUT

Adapted from Paoletti X, Eur J Cancer. 2014

ULB iris

Considerations for the evolution of phase I oncology trials



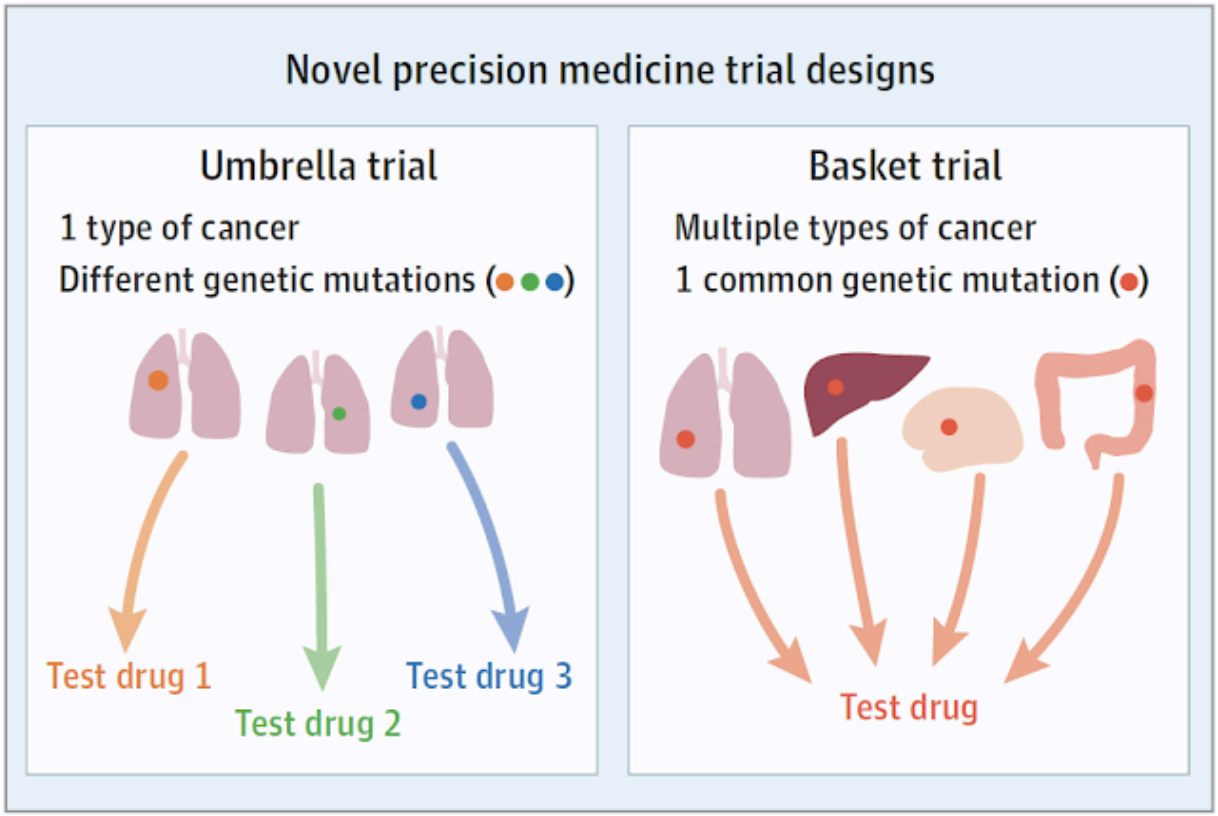
INSTITUT JULES BORDET INSTITUUT

Adapted from Wong et al. Nature Reviews 2016

ULB iris

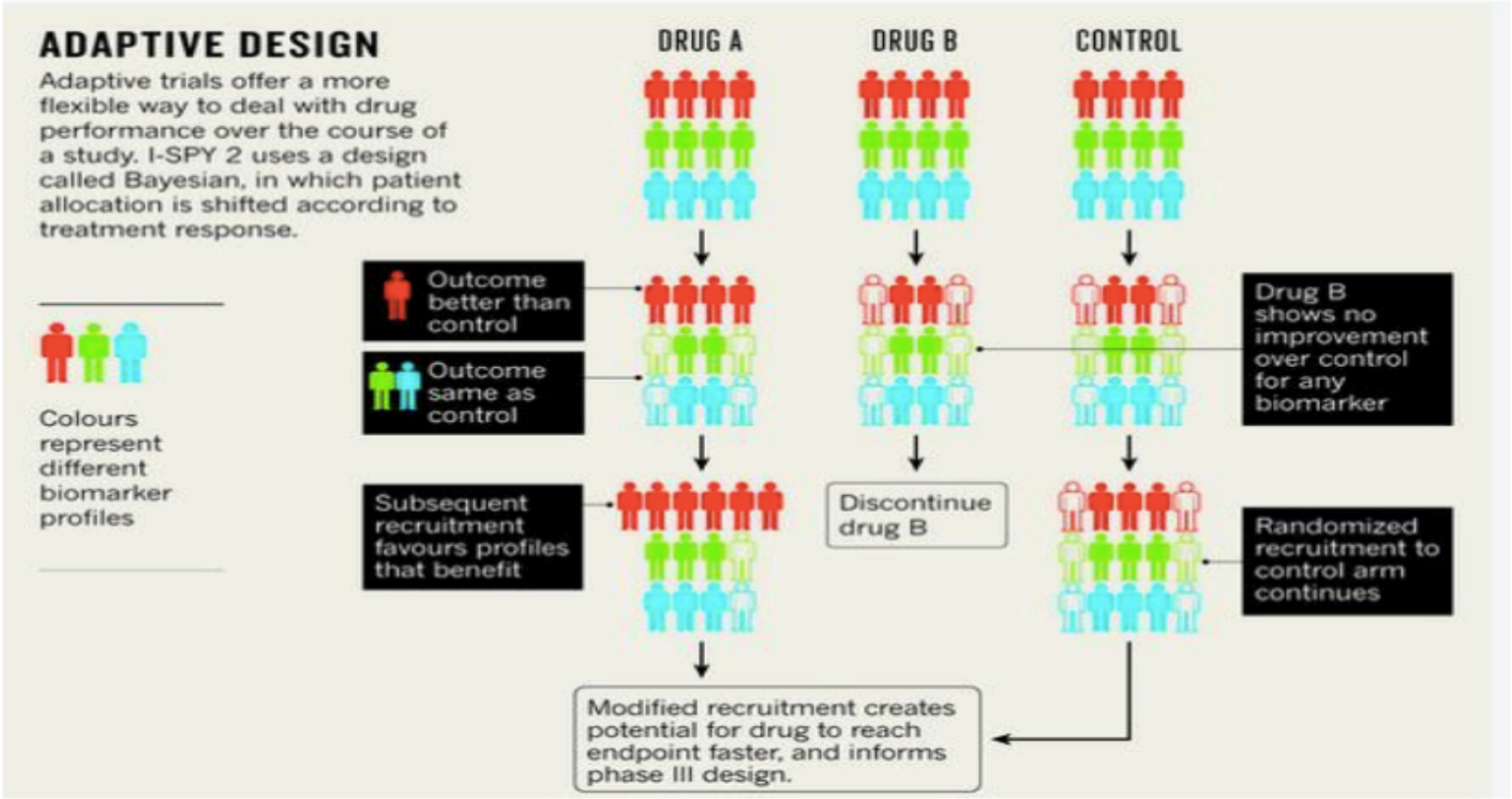
SELECTED NEW DESIGNS IN DRUG DEVELOPMENT BASED ON MOLECULAR BIOLOGY OR ON STRATEGY

Genotype driven	Basket trials	Test the effect of one drug on single mutation in a variety of cancer types
	Umbrella	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 with necessity to have an active IDMC. **A platform trial** is a type of adaptive trial designed to evaluate multiple treatments efficiently.
	Windows of opportunity	Assessing the administration of an investigational agent over a short period of time
	Randomized discontinuation design	phase I : all patients are openly treated with the medication phase II: Those who have responded are randomly assigned to continue the same treatment or switch to placebo. particularly useful in studying the effect of long-term, non-curative therapies
	N of 1 trials	Clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions.


Novel precision medicine trial designs
Umbrella trial
1 type of cancer
Different genetic mutations (●●●)
Test drug 1
Test drug 2
Test drug 3
Basket trial
Multiple types of cancer
1 common genetic mutation (●)
Test drug

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

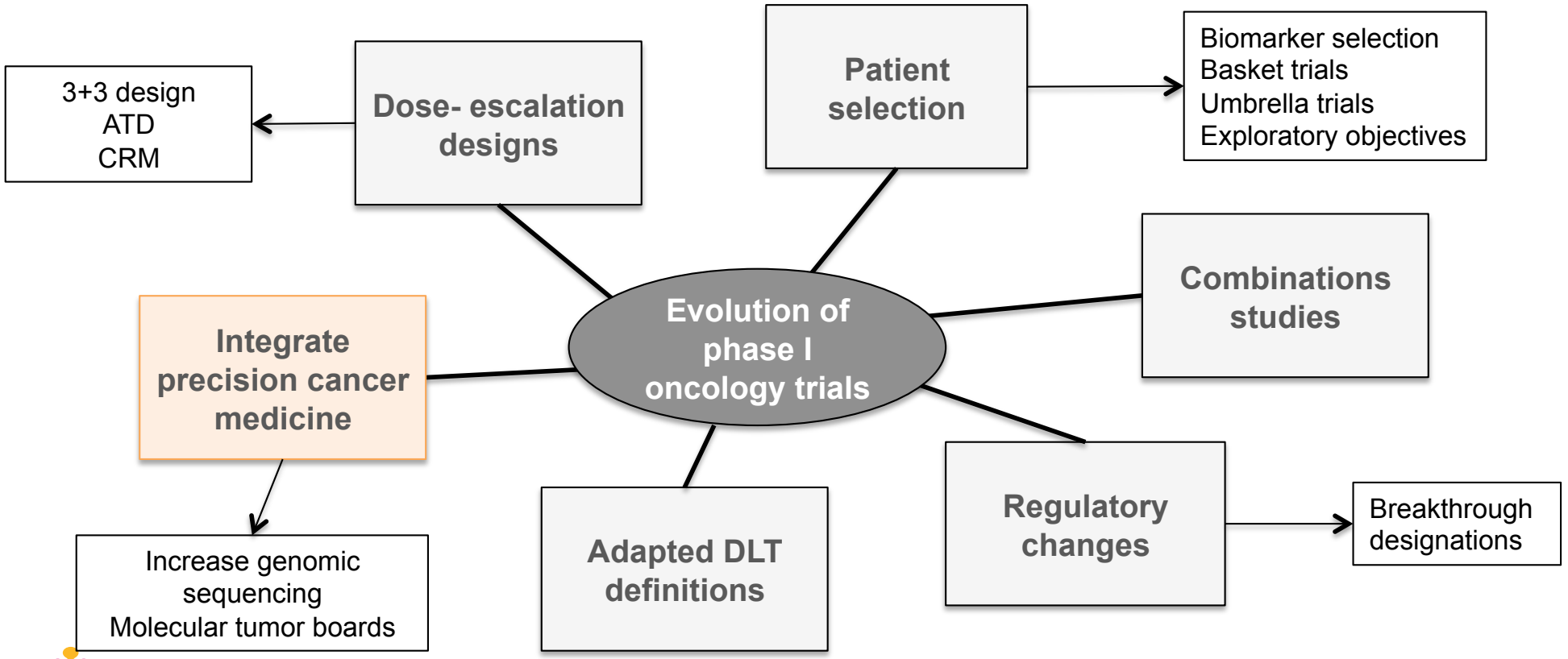
Genotype driven	Basket trials	Test the effect of one drug on single mutation in a variety of cancer types
	Umbrella	Test the impact of different drugs in different mutations in a single type of cancer
New designs	Adaptive trial	Allows the modification of some parameters of the trial as data accrue, e.g. sample size reassessment, stop for early efficacy/ futility, drop an arm with necessity to have an active IDMC. **A platform trial** is a type of adaptive trial designed to evaluate multiple treatments efficiently.
	Windows of opportunity	Assessing the administration of an investigational agent over a short period of time
	Randomized discontinuation design	phase I : all patients are openly treated with the medication phase II: Those who have responded are randomly assigned to continue the same treatment or switch to placebo. particularly useful in studying the effect of long-term, non-curative therapies
	N of 1 trials	Clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions.


ADAPTIVE DESIGN
Adaptive trials offer a more flexible way to deal with drug performance over the course of a study. I-SPY 2 uses a design called Bayesian, in which patient allocation is shifted according to treatment response.
Colours represent different biomarker profiles
DRUG A
DRUG B
CONTROL
Outcome better than control
Outcome same as control
Subsequent recruitment favours profiles that benefit
Discontinue drug B
Drug B shows no improvement over control for any biomarker
Randomized recruitment to control arm continues
Modified recruitment creates potential for drug to reach endpoint faster, and informs phase III design.

SELECTED NEW 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	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 with necessity to have an active IDMC. **A platform trial** is a type of adaptive trial designed to evaluate multiple treatments efficiently.
	Windows of opportunity	Assessing the administration of an investigational agent over a short period of time
	Randomized discontinuation design	phase I : all patients are openly treated with the medication phase II: Those who have responded are randomly assigned to continue the same treatment or switch to placebo. particularly useful in studying the effect of long-term, non-curative therapies
	N of 1 trials	Clinical trials consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions.

Considerations for the evolution of phase I oncology trials



INSTITUT JULES BORDET INSTITUUT

Adapted from Wong et al. Nature Reviews 2016

ULB iris

INSTITUT
JULES BORDET
INSTITUUT

Precision 1
- Investigate benefits of approach
- **Interinstitutional Molecular tumor board**

Precision 2
- Establish **new evidence on efficacy in specific genotype-cancer type associations**

The Belgian Molecular Profiling Program of Metastatic Cancer for Clinical Decision and Treatment Assignment

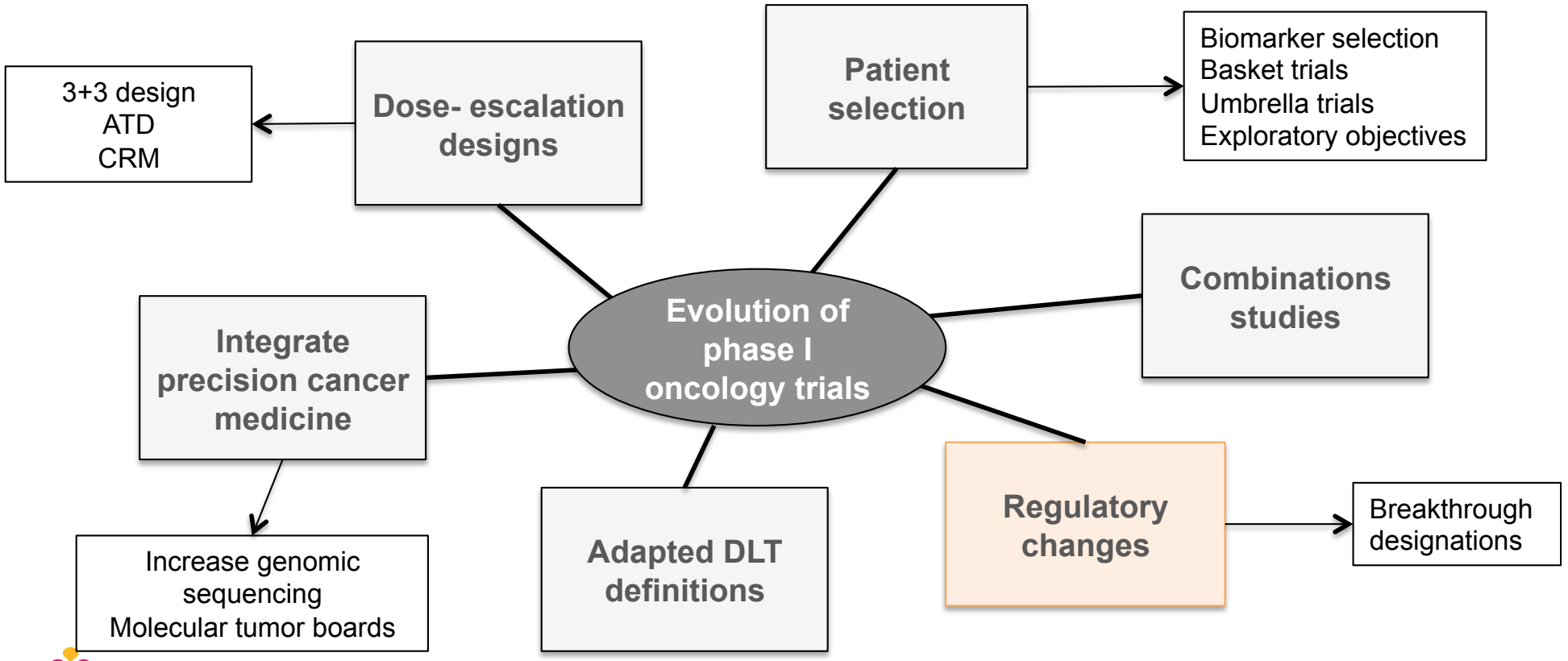
A BSMO master protocol
"PRECISION 1 and 2"

A collaboration between Belgian universities and their network hospitals

BSMO 2014-2

ULB iris

Considerations for the evolution of phase I oncology trials

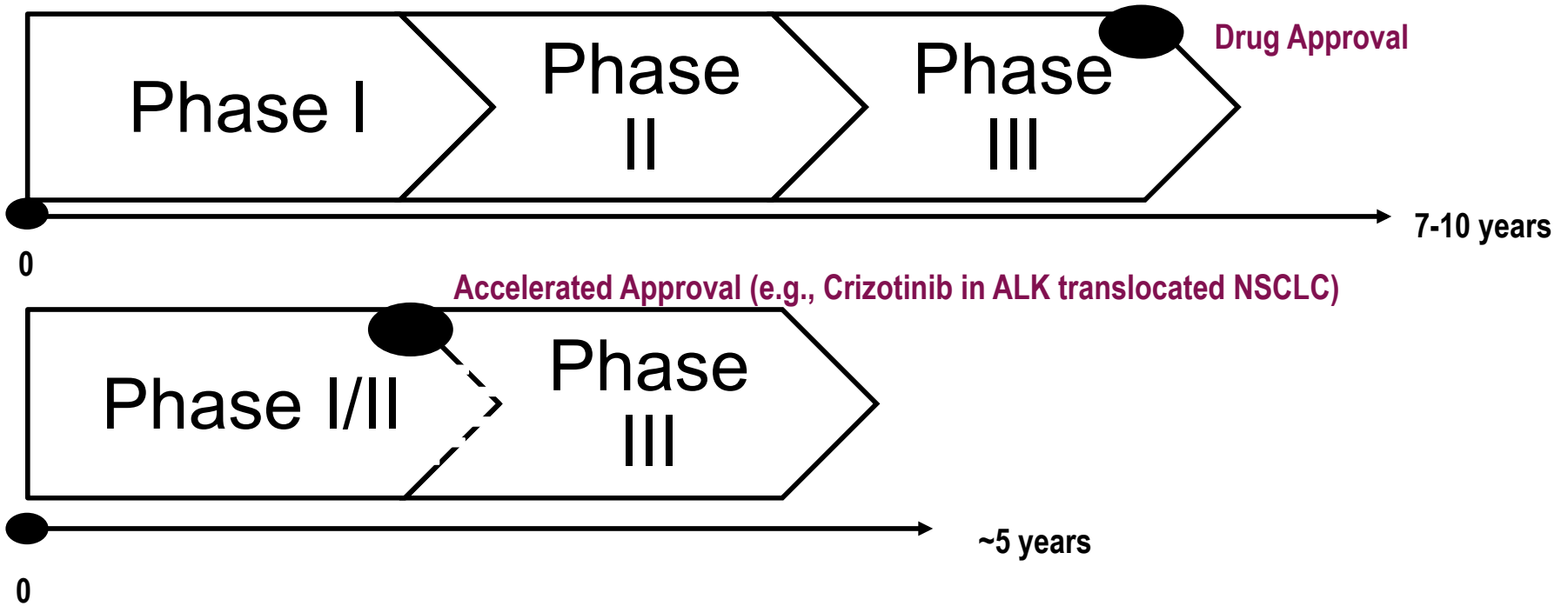


INSTITUT JULES BORDET INSTITUUT

Adapted from Wong et al. Nature Reviews 2016

ULB iris

RECENT DEVELOPMENTS IN THE CLINICAL RESEARCH METHODOLOGY AND REGULATORY CHANGES



INSTITUT JULES BORDET INSTITUUT

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

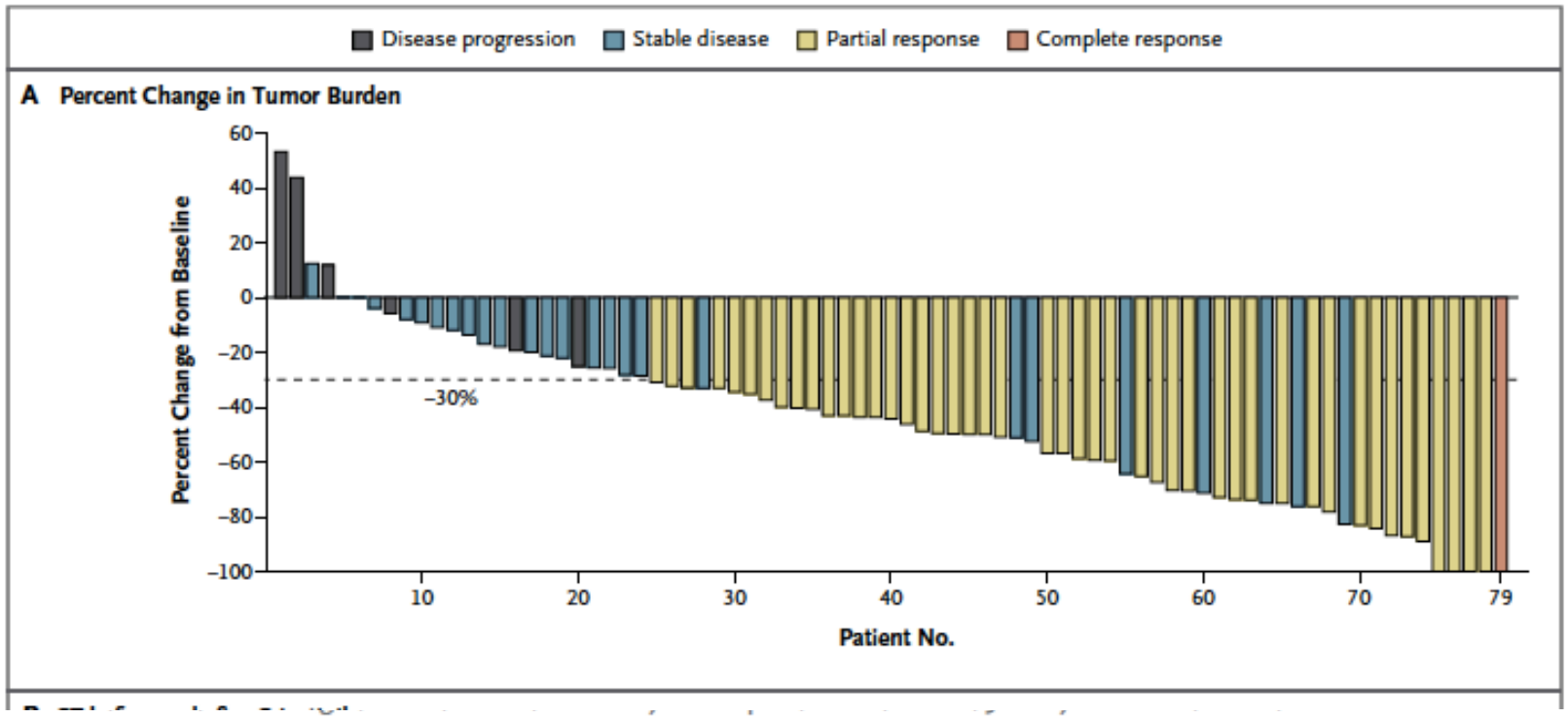
ULB iris

The NEW ENGLAND

Ana

Sai-He

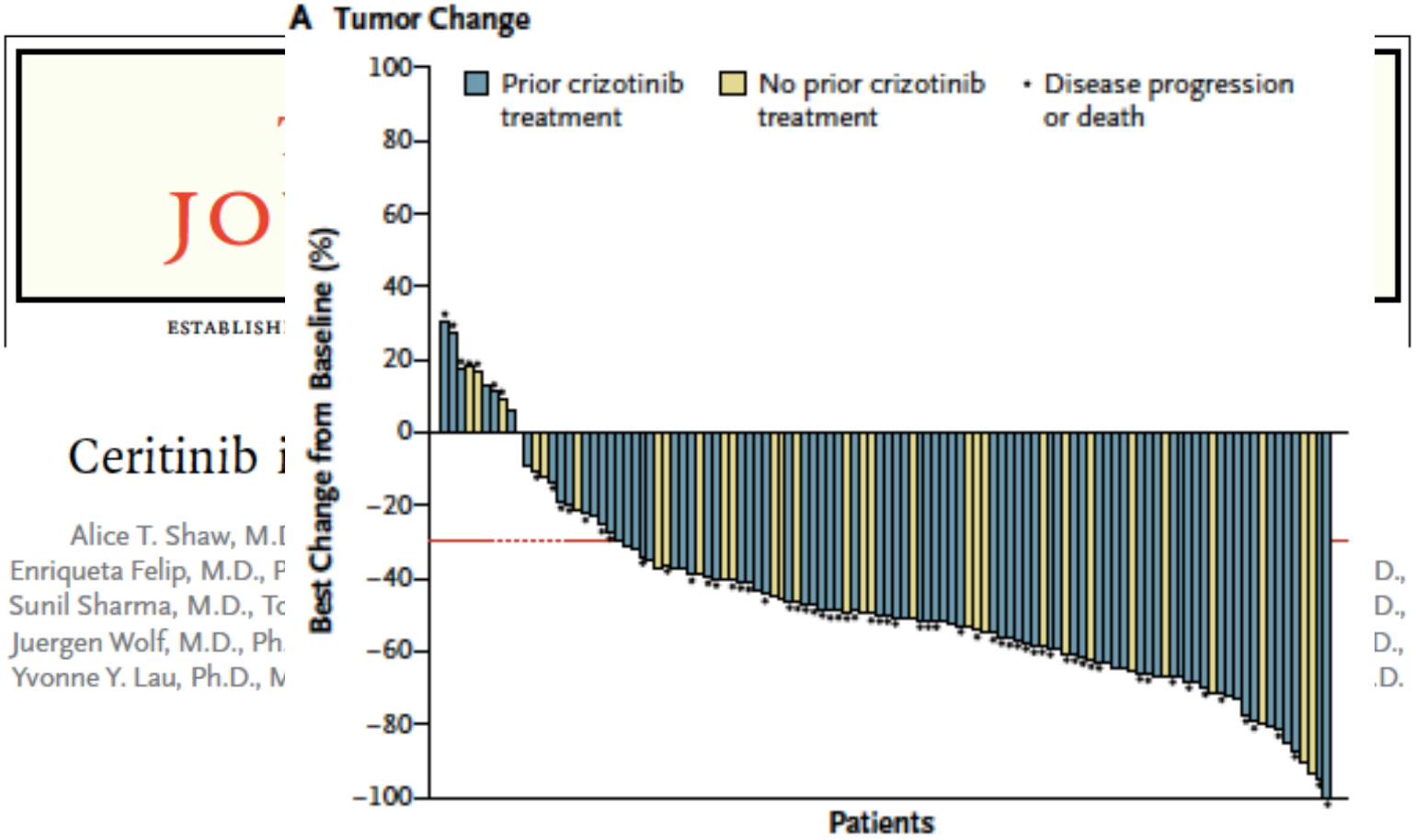
Hanr
Leena
Marl
K



and A. John Iafrate, M.D., Ph.D.

INSTITUT
JULES BORDET
INSTITUUT

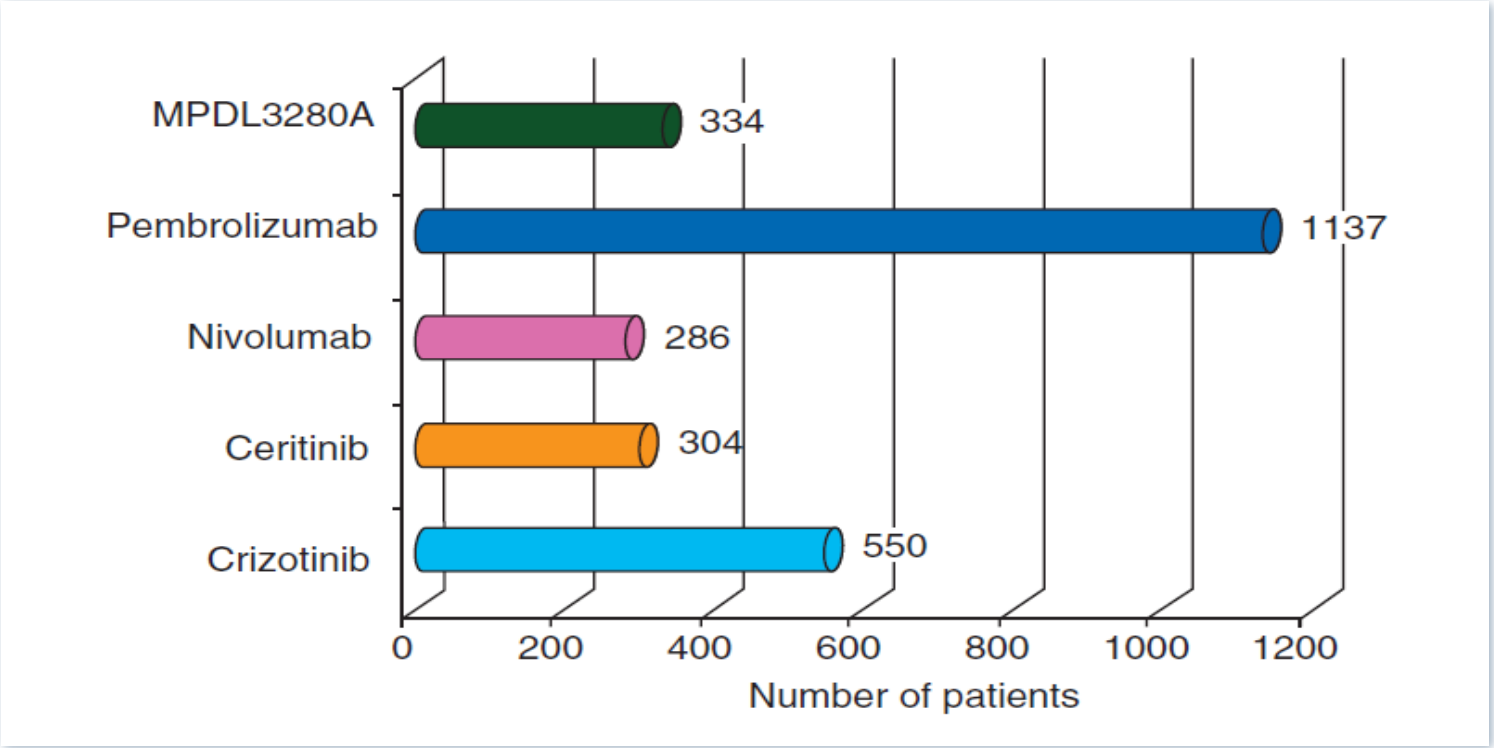
ULB
iris



INSTITUT JULES BORDET INSTITUUT

ULB iris

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

EVOLVING METHODOLOGY OF EARLY PHASE TRIALS FROM CYTOTOXICS TO IMABS

	Cytotoxic chemotherapy	Molecular-targeted agents	Immunostimulatory antibodies
Patients number	30-50 unselected pts	30-200 ''molecularly'' selected pts	100-1000 ''immunologically'' selected pts
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

INSTITUT JULES BORDET INSTITUUT

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

ULB iris

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)

INSTITUT JULES BORDET INSTITUUT

Italiano et al. NEJM 2018

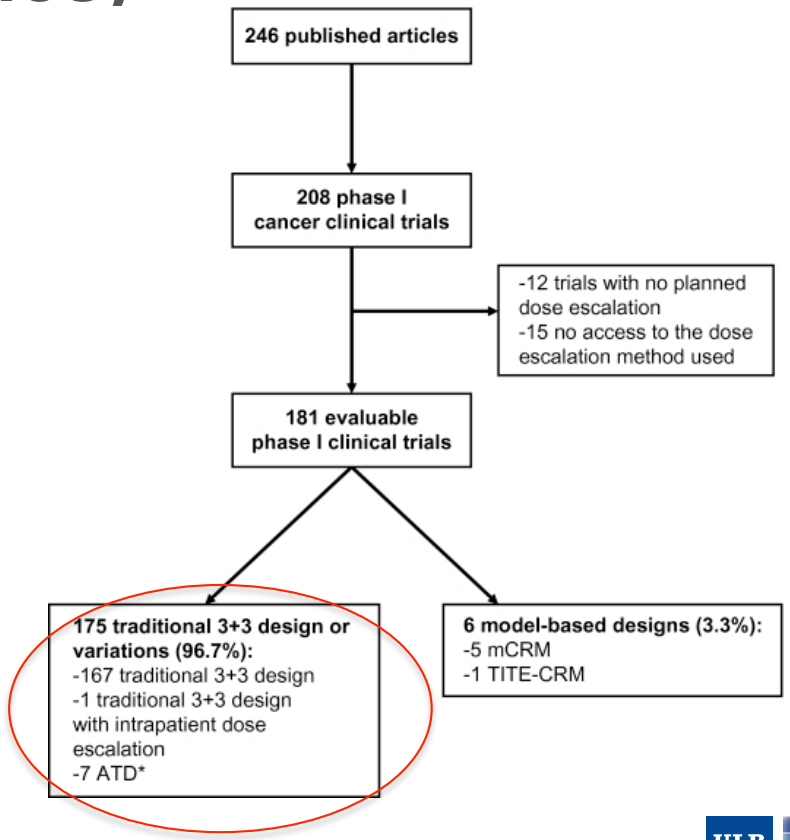
OUTLINE

- Evolving landscape in oncology: New drugs and new cancer types definitions
- Current status for new drug development and phase 1 trials in oncology
- **Challenges for clinical research in oncology**
- What do we need in drug development methodology ?

Challenges in early clinical trials methodology (2 examples)

1. Still inappropriate designs[1, 2]

2. Definition of DLT and recommended doses and schedules are often inappropriate[3]



1. X. Paoletti et al. 2014
2. C. Le Tourneau et al 2009
3. N. Kotecki et al COON 2017

INSTITUT JULES BORDET INSTITUUT

ULB iris

REVIEW

CURRENT OPINION

Inappropriate dose of multitargeted tyrosine kinase inhibitors: the original sin

Nuria Kotecki and Nicolas Penel

Purpose of review
The use of antiangiogenic tyrosine kinase inhibitors (TKIs) is challenging and often requires dose adaptation and transient or definitive treatment interruption. We believe that the inappropriate recommended dose of TKI is related to no optimal study designs in the early development of the drug.

Recent findings
As an example of this, we described herein some pitfalls made in the successive development of sunitinib, sorafenib, regorafenib, and pazopanib, but there are several other examples of early drugs development illustrating this issue.

Summary
Regarding the antiangiogenic TKI mechanism of action, we strongly feel that innovative approaches are needed such as extended dose-limiting toxicity period or a better definition of the induced toxicity. Furthermore, before classic phase II/III trials, an intermediate step may be needed to better define the recommended phase II dose, such as a randomized phase I/II trial with several expansion cohorts.

Keywords
antiangiogenic, dose, optimal study designs, tyrosine kinase inhibitors

Challenges in precision medicine

LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE

More and more biomarkers studies **(Pubmed search: 42636!)** but very few were validated for clinical use.

>> Importance of selective and well designed clinical trials integrating high level of translational research with potential for clinical practice

>>Importance of using a proper statistical stategy for validation.

>> Need for quality assurance and reproducibility

Challenges in precision medicine

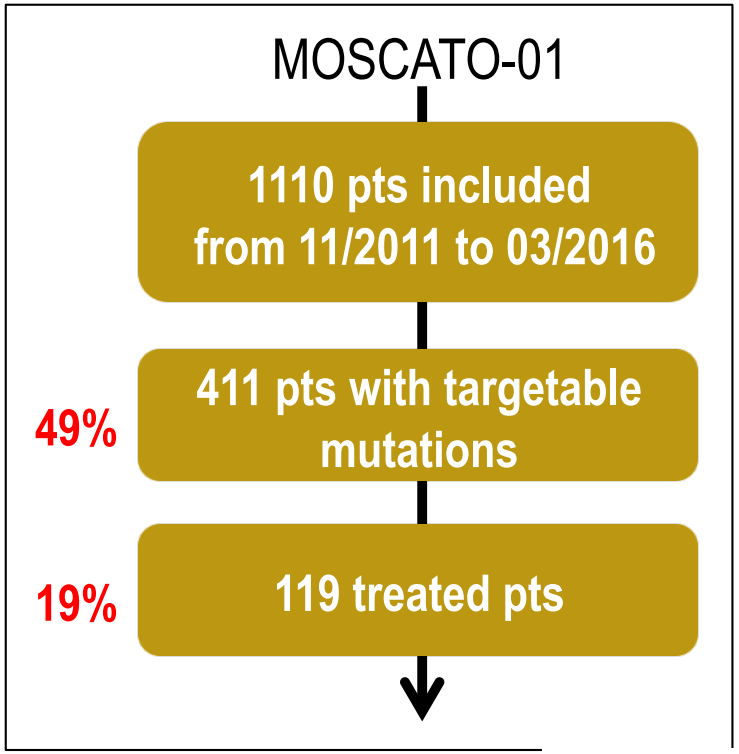
- High promotion of Precision Medicine among medical team and patients

but

- Limited number of actionable/targetable mutations
- Limited access or not available clinical trials or marketed targeted agents

⬇

High attrition rate and ethical issues



Adapted from Massart et al. Cancer Discovery 2017

INSTITUT JULES BORDET INSTITUUT

ULB iris

Tumor-Agnostic treatment for cancer

Example of TRK fusions

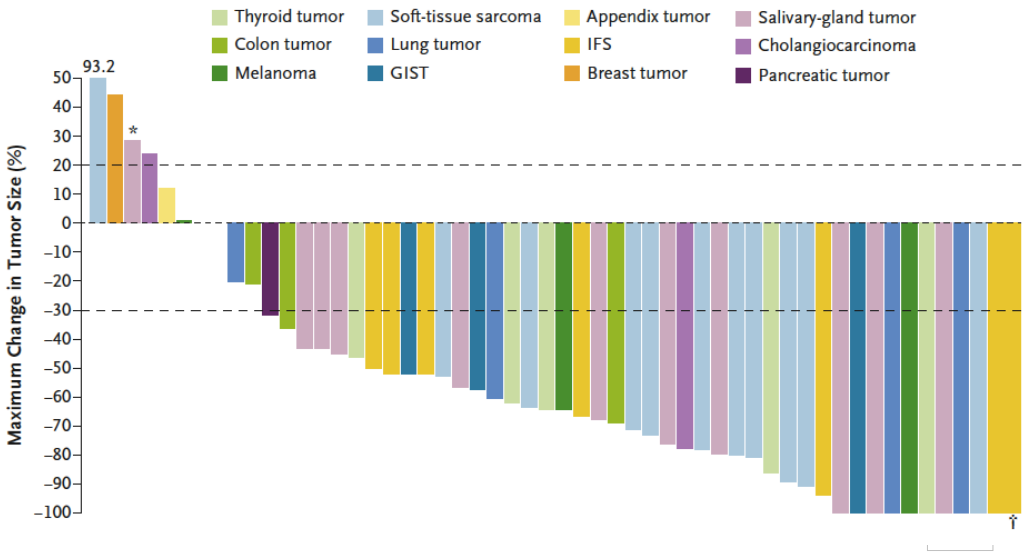
- Can be harbored by **1%** of all cancers
- Targeted treatments are very potent

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

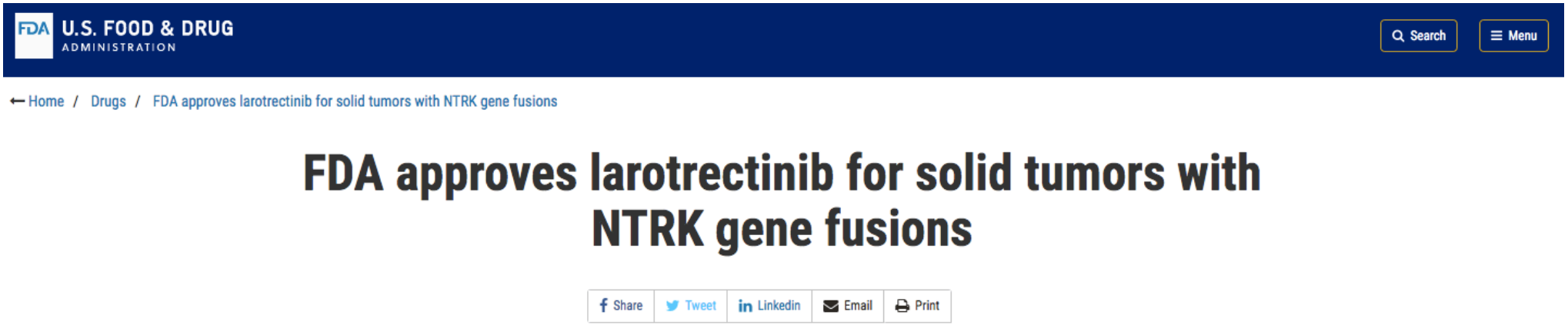
Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

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

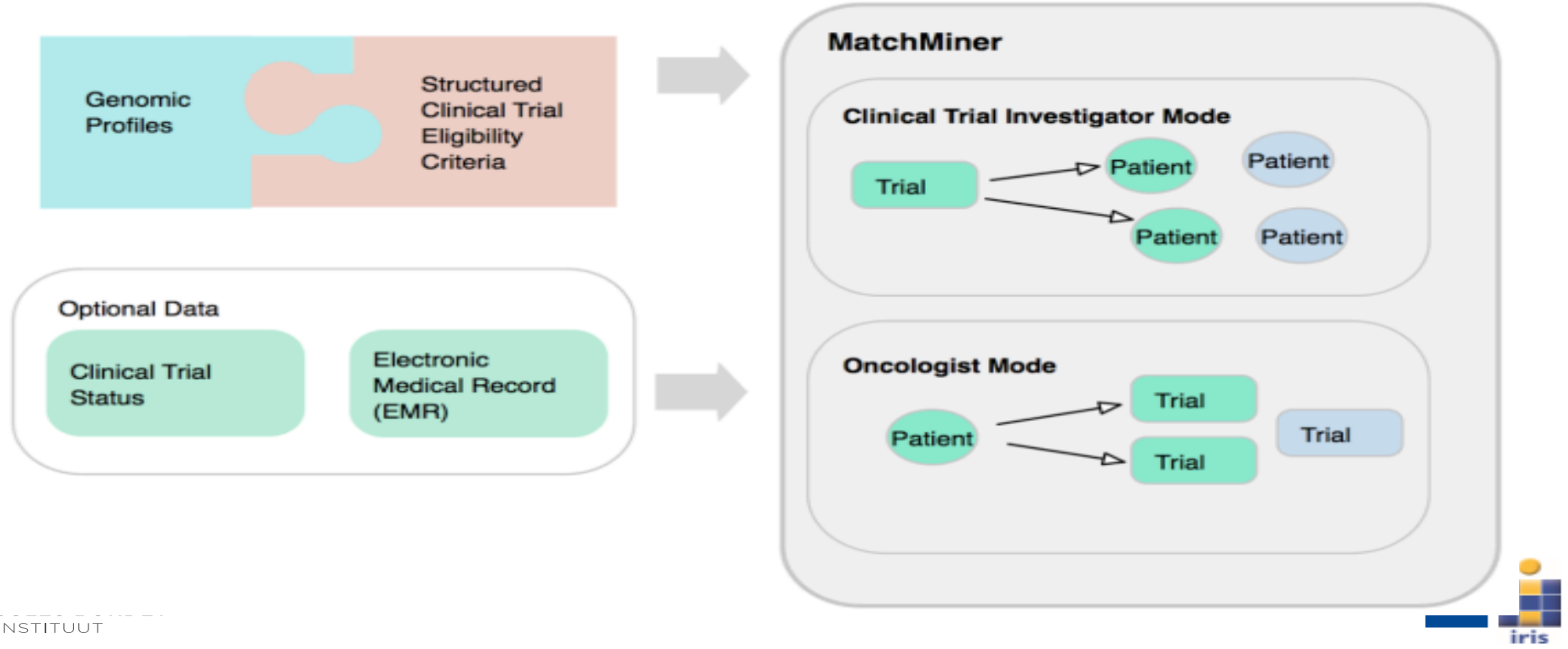
Tumor-Agnostic treatment for cancer

Example of TRK fusions

- How can patients be screened without universal molecular screening?
- **Is recruitment possible in clinical trials without clinical and genomic data sharing?**

MatchMiner

Developed at Dana Farber Cancer Institute



INSTITUUT

iris

Challenges for immunotherapy trials

Optimal dose and schedule selection

- > Minimal immunologically active dose (dose is not linearly associated with efficacy and toxicity)
- > Optimal dose for prolonged exposure

Optimal sequence/rechallenge

- > Maximize benefit for patients and minimize economic burden

Identify resistant/sensitive disease to immunological approaches

- > Biomarkers (immunoscore, Immunomics, …)

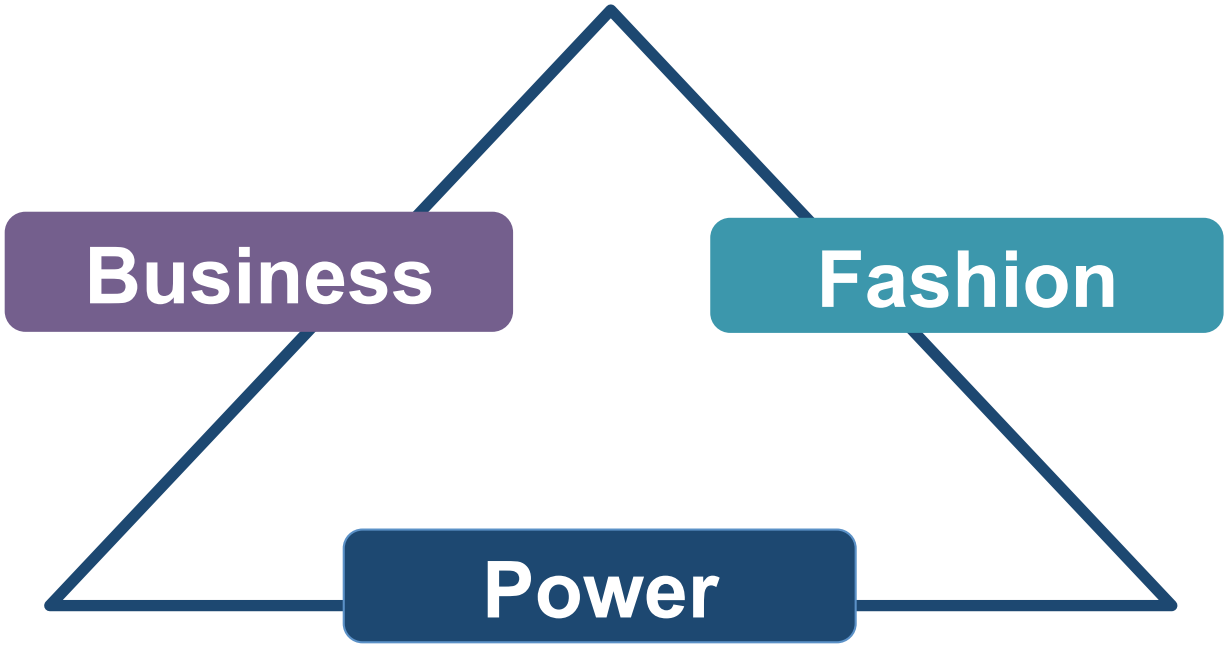
New patterns/definitions of tumor assessment and disease progression

Combinations issues

INSTITUT
JULES BORDET
INSTITUUT

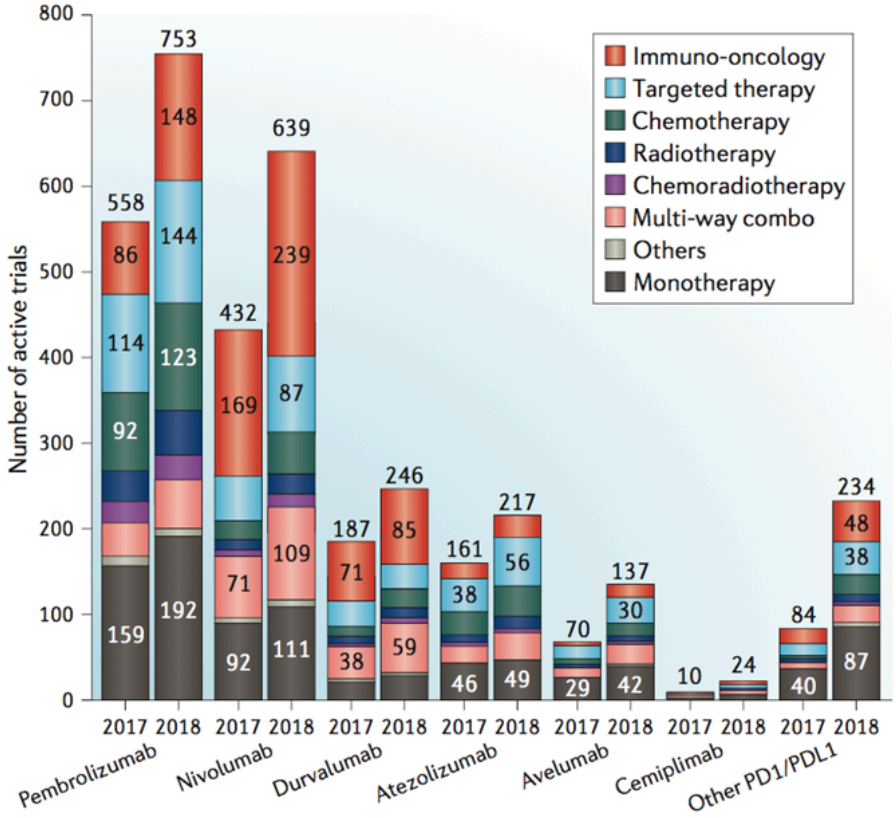
ULB iris

Current strategy of solid cancers clinical research is dominated by:



More “market and regulatory oriented” trials and less patients directed or based on unmet need in diseases or settings!

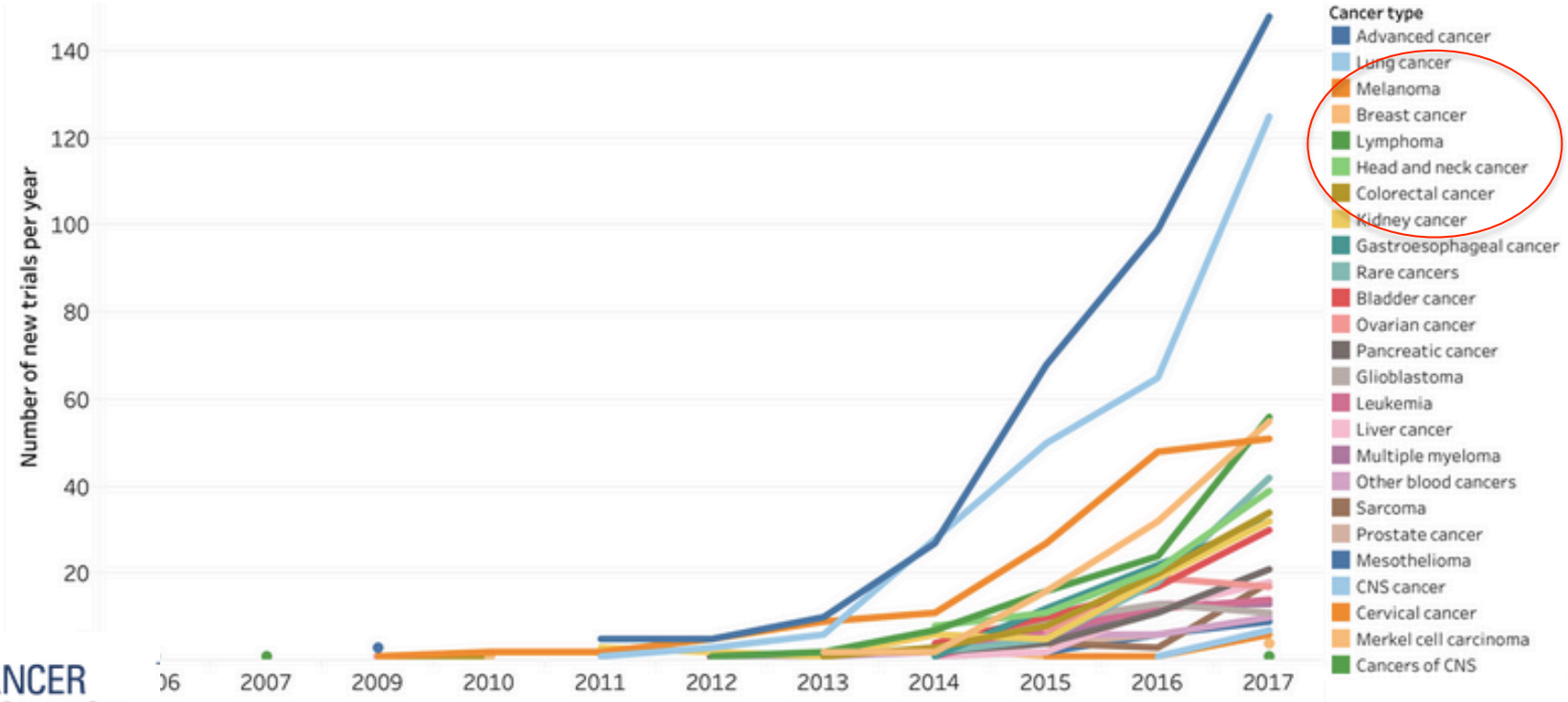
Huge redundancy in the development of agents: Number of active trials with PD1/PDL1 Ab



CANCER RESEARCH INSTITUTE

ULB iris

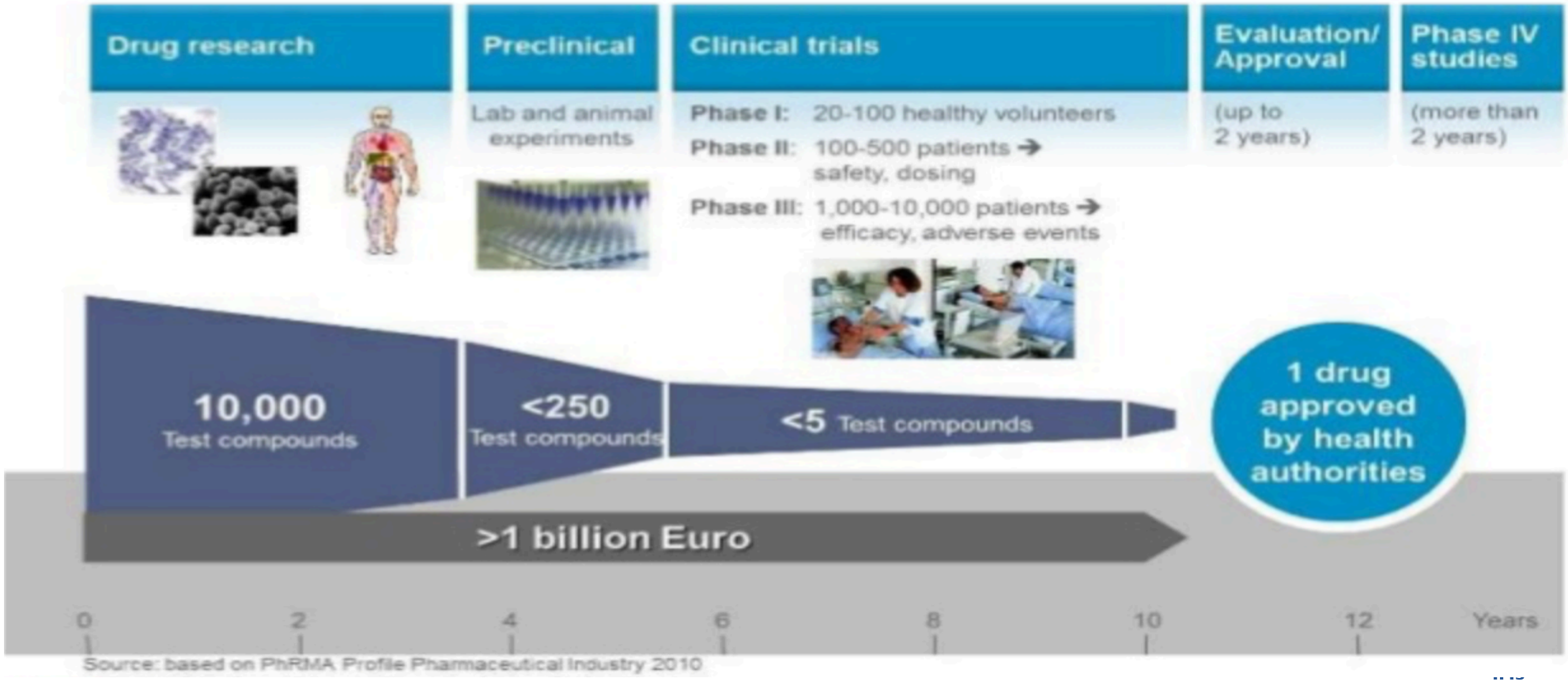
Evolution of PD-1/PDL-1 trials by different cancer types



CANCER RESEARCH INSTITUTE

ULB iris

High cost and attrition rate



Source: based on PhRMA Profile Pharmaceutical Industry 2010

Current strategy of clinical research

- New chemotherapy agents are less and less developed *(except antibody drugs conjugates (ADC))* but chemotherapy has proven to cure patients

↓

- Molecular-targeted therapies (and ADC) have been developed but rarely have cured patients *(except for endocrine agents and trastuzumab in breast cancer)*

↓

- Recently the hype of immunotherapy slows significantly the development of other anti-cancer treatments

From empirical oncology to molecular and immunological therapeutic approaches

Does the current design of oncology trials meet the need of patients?

YES	NO
• **Several new anticancer agents reached clinical practice** much faster than in the past • **Often improvement in PFS** (but rarely in survival (metastatic setting)) • **Often improvement in DFS** (but rarely in OS (early setting))	• **still Inapropriate design and DLT definitions** • **Commonly used endpoints are not relevant** for immunotherapy or other new agents • **Redundancy** in the development of agents • **Competitive trials** in the same setting • Few studies looking to a therapeutic strategy • Few studies in **unmet need clinical settings** or focusing on **rares cancers** • More biomarkers studies but **limited validated biomarkers** for clinical use

Still a huge gap between clinical research & the need in clinical practice !!

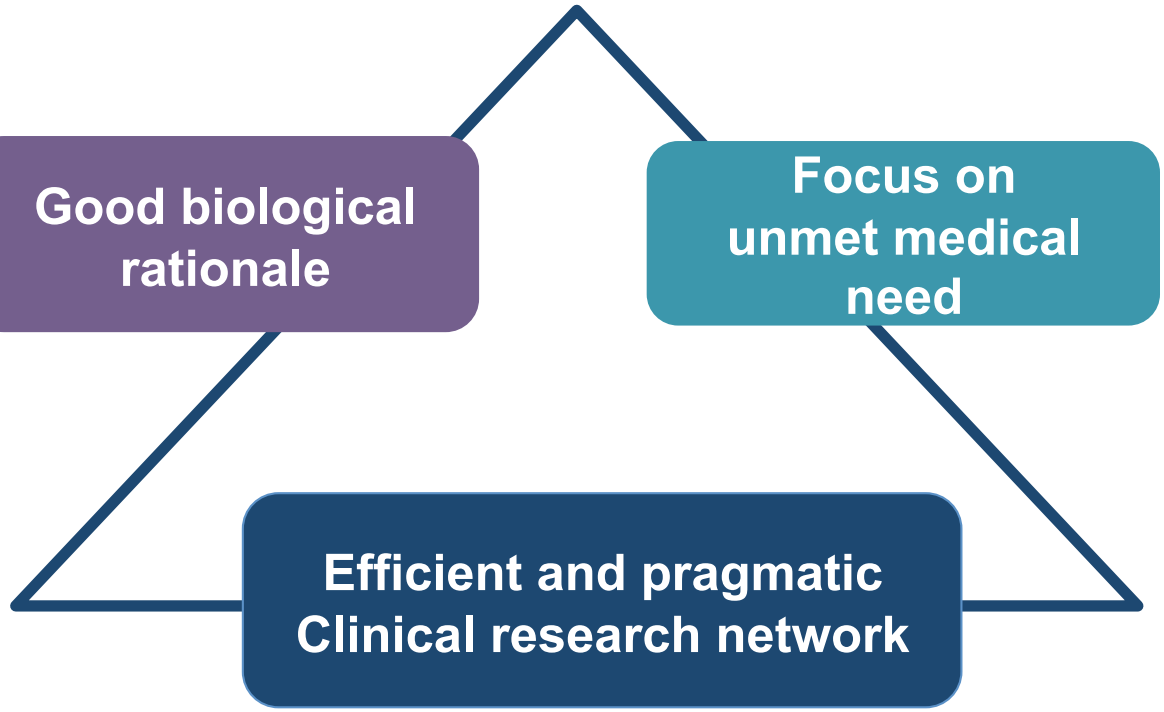
OUTLINE

- Evolving landscape in oncology: New drugs and new cancer types definitions
- Current status for new drug development and phase 1 trials in oncology
- Challenges for clinical research in oncology
- **What do we need in drug development methodology ?**

What do we need in drug development methodology ?

1. More innovative approaches and trials design in drug development
2. Targeting unresolved scientific questions and settings of unmet need for patients
3. More selective and well designed biomarkers studies with clinical utility integrating high level translational research approaches
4. Creating new models of clinical research networks and collaboration between pharma, cooperative groups and investigators

What do we need in drug development methodology ?



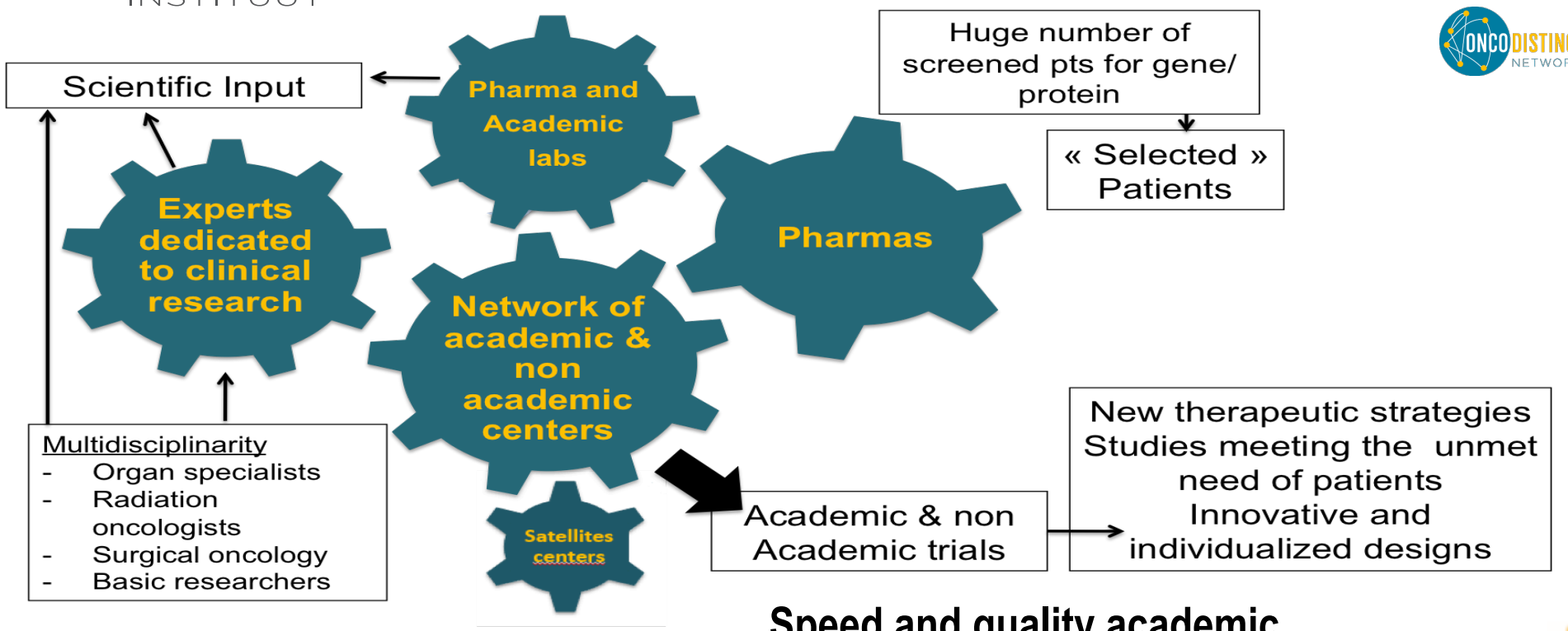
INSTITUT JULES BORDET INSTITUUT

ONCODISTINCT NETWORK

ULB iris

INSTITUT
JULES BORDET
INSTITUUT

ACADEMIC MODEL OF CLINICAL RESEARCH COLLABORATION BASED ON THE PROGRESS ON MOLECULAR BIOLOGY AND METHODOLOGICAL ISSUES



Speed and quality academic and non academic trials

www.oncodistinct.net

A new model of clinical research collaboration

"working together and not as different groups"

Academic centres, non-academic centres with expertise in research, early and late drug developers, monospecialized and multispecialized investigators, clinicians, laboratory workers and patients

Scientific input
High number of screened patients
Speed in performance of trials
Able to perform early (2-3 centres) to late phase trials within the network (several centres)

INSTITUT JULES BORDET INSTITUUT

ULB iris

Aknowledgements

Pr Ahmad Awada
Dr Philippe Aftimos
Dr Christiane Jungels
And the Oncodistinct network investigators

MAIN CONTACT:

ahmad.awada@bordet.be
nuria.kotecki@bordet.be

ADDRESS:

Oncodistinct, Dr Ahmad Awada,
Boulevard de Waterloo, 121
1000 Brussels Belgium

FOLLOW US ON TWITTER

INSTITUUT