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GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

DRUGS DEVELOPMENT METHODOLOGY

The unavoidable break with the past

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DISCLOSURES

- Ahmad Awada has reported no conflicts of interest
- Nuria Kotecki has reported no conflicts of interest
- Alex A Adjei has reported no conflicts of interest
- Guillem Argiles has reported no conflicts of interest
- Dirk Arnold has reported consulting and advisory services, speaking or writing engagements, public presentations for Roche, Merck Serono, Bayer Healthcare, Servier, BTG, Terumo, Sanofi Oncology and Eli Lilly
- Jean-Yves Blay has reported to have received research support and honoraria from Roche, BMS GSK, Novartis, Pharmamar, MSD, Lilly, Ignyta and Deciphera
- Olivier Collignon has reported no conflicts of interest
- Christian Dittrich has reported no conflicts of interest
- Felip Janku has reported to have a research support from Novartis, Deciphera, Symphogen, Piqur, Roche, BioMed Valley Discoveries and Upsher-Smith Laboratories; he is on the Scientific Advisory Boards of Deciphera, Illumina and Guardant Health, he provides paid consulting for Immunoment, IFM Therapeutics and Trovagene and has ownership interest in Trovagene.
- Denis Lacombe has reported no conflicst of interest
- Nicolas Penel has reported no conflicts of interest
- Josep Tabernero has reported to have served on Advisory Boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho and Takeda

DRUGS DEVELOPMENT METHODOLOGY IN SOLID TUMOURS

The unavoidable break with the past

KEY POINTS: What do we need in drug development methodology?

- Targeting settings with unmet need for patients
- More innovative approaches and trials design in drug development with the aim to individualise clinical research
- Selective and well-designed biomarker studies (rather predictive of intrinsic tumour resistance?!) with high potential for clinical utility
- New ways of collaboration and functioning between pharma, cooperative groups and on-site investigators
- Creating new models of clinical research networks, taking into consideration the recent molecular biology advances

OUTLINE

1. Research in oncology: Historical view and current strategy
2. Does the current design of oncology trials meet the need of patients?
3. Recent developments in the clinical research methodology
4. Challenges of the recent clinical research methodology
5. What do we need?

1. RESEARCH IN ONCOLOGY

Historical view and current strategy

RESEARCH IN ONCOLOGY

A historical view

DRUG-/TARGET-ORIENTED CLINICAL RESEARCH IN SOLID CANCERS

Percentage of the studies at the Jules Bordet Institute in June 2017

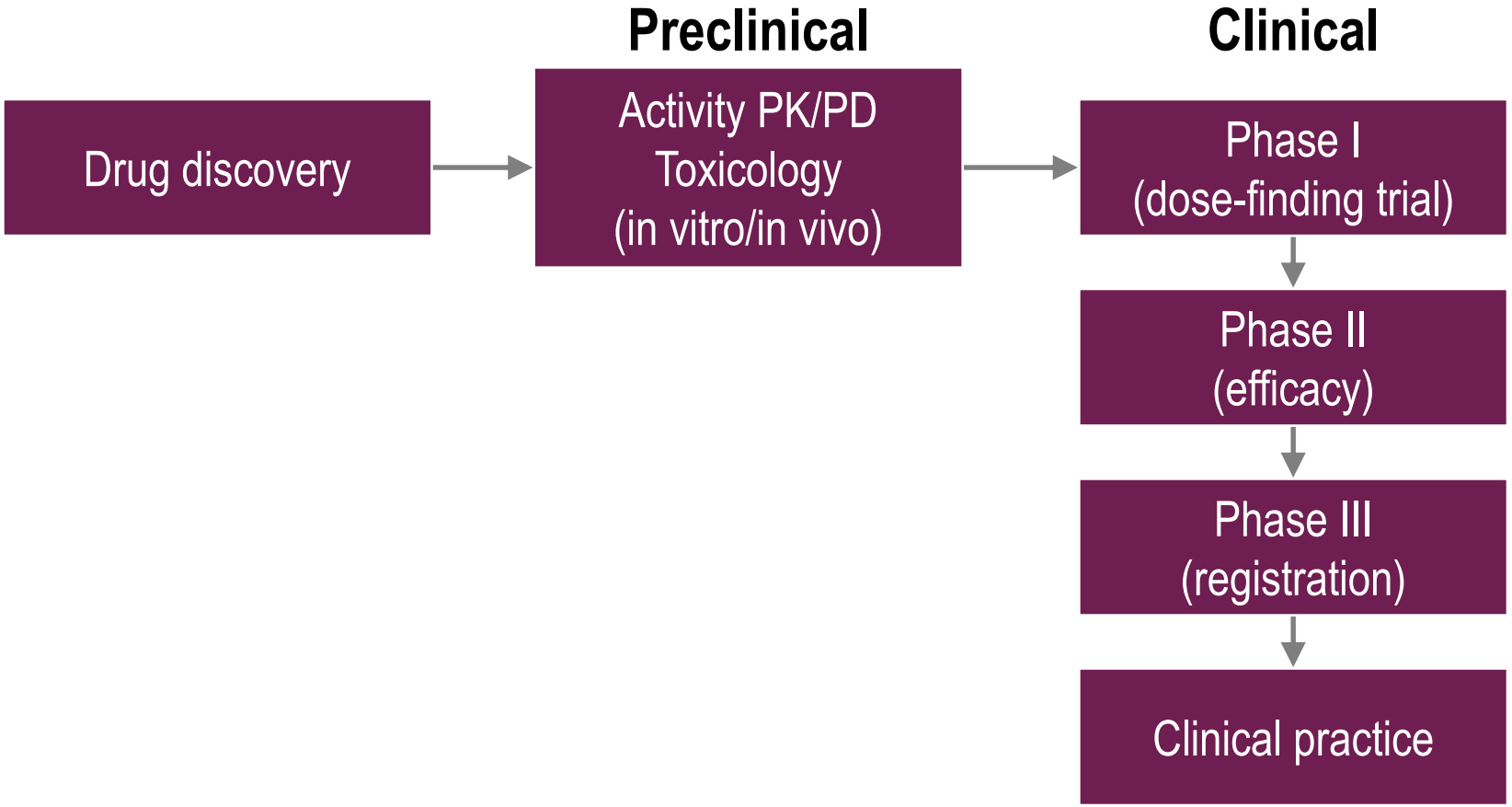
Pharmaceutical industry-based clinical research: **70%**

Academic clinical research in « partnership » with the pharmaceutical industry: **20%**

« Pure » academic research: **10%**

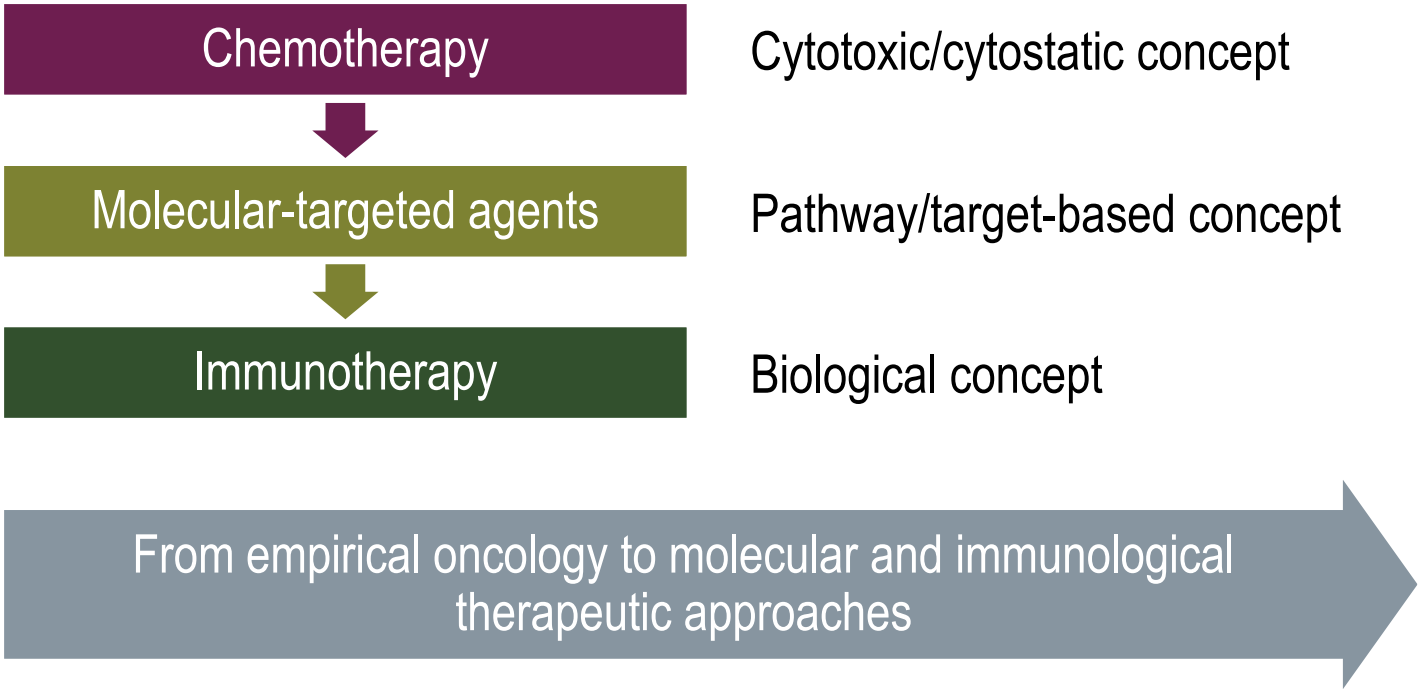
Number of patients**: Pharma (450); Academic (377)**

CLASSICAL APPROACH OF DRUG DEVELOPMENT



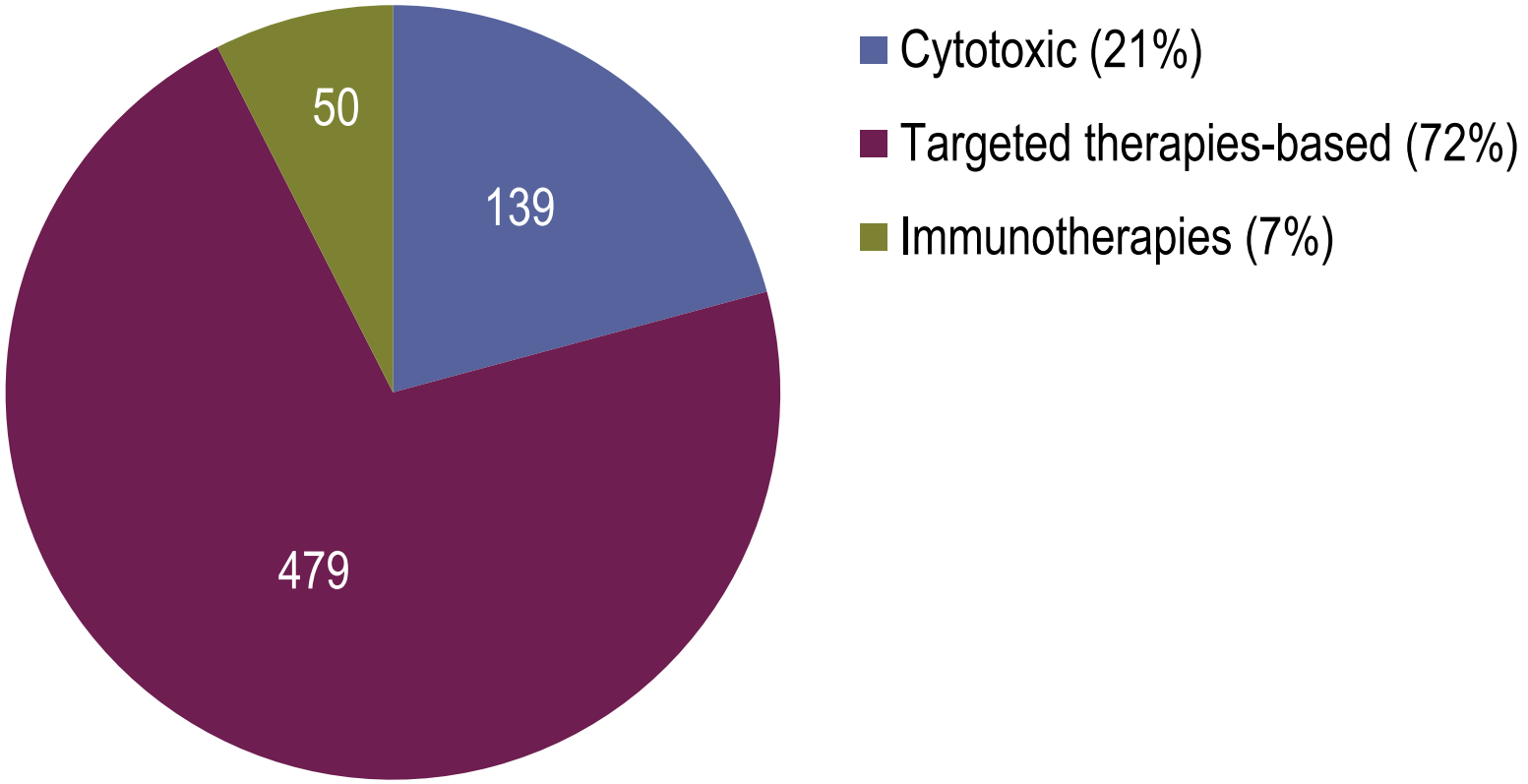
EVOLVING THERAPEUTIC CONCEPTS IN ONCOLOGY

Based on molecular biology understanding



TYPES OF CLINICAL TRIALS

In advanced breast cancer (2007–2011)



Dogan S, *et al.,* Curr Opin Oncol. 2013;25:625–9

CURRENT STRATEGY OF BREAST CANCER CLINICAL RESEARCH

New chemotherapy agents are less and less developed *(except antibody drug conjugates [ADC])* but chemotherapy is proven to cure patients – A very risky developmental strategy

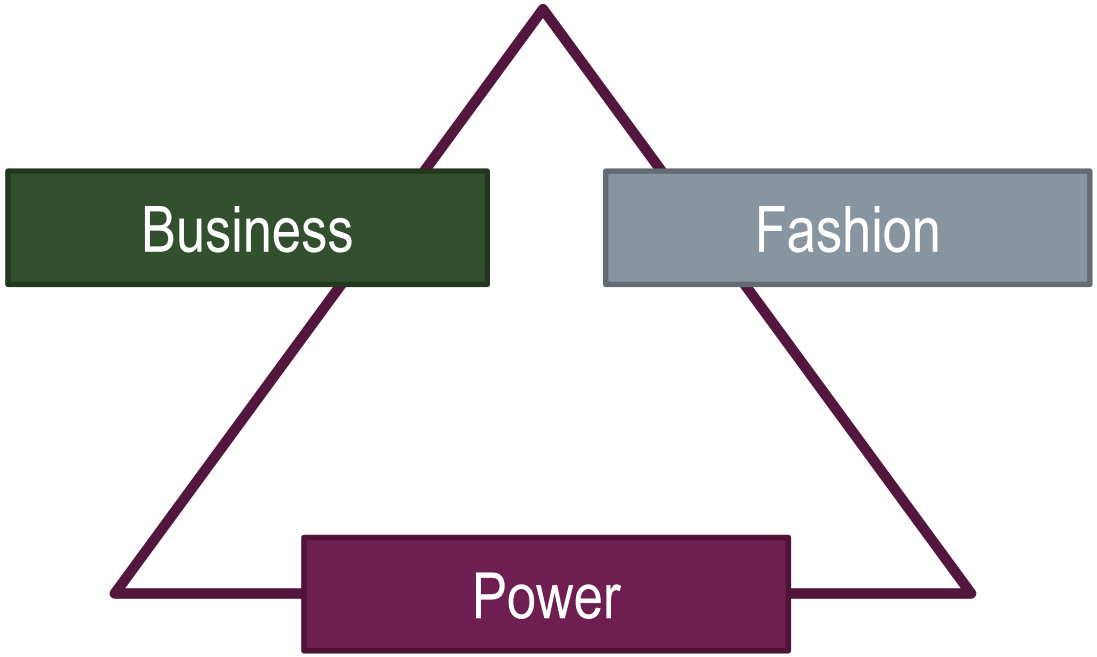
Molecular-targeted therapies (and ADC) have been developed but rarely have cured patients (*except for **endocrine** agents and trastuzumab in breast cancer*)

Recently, the hype of immunotherapy has slowed down significantly the development of other anticancer treatments

From empirical oncology to molecular and immunological therapeutic approaches

CURRENT STRATEGY OF SOLID CANCER

Clinical research is dominated by:



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

2. DOES THE CURRENT DESIGN OF ONCOLOGY TRIALS MEET THE NEED OF PATIENTS?

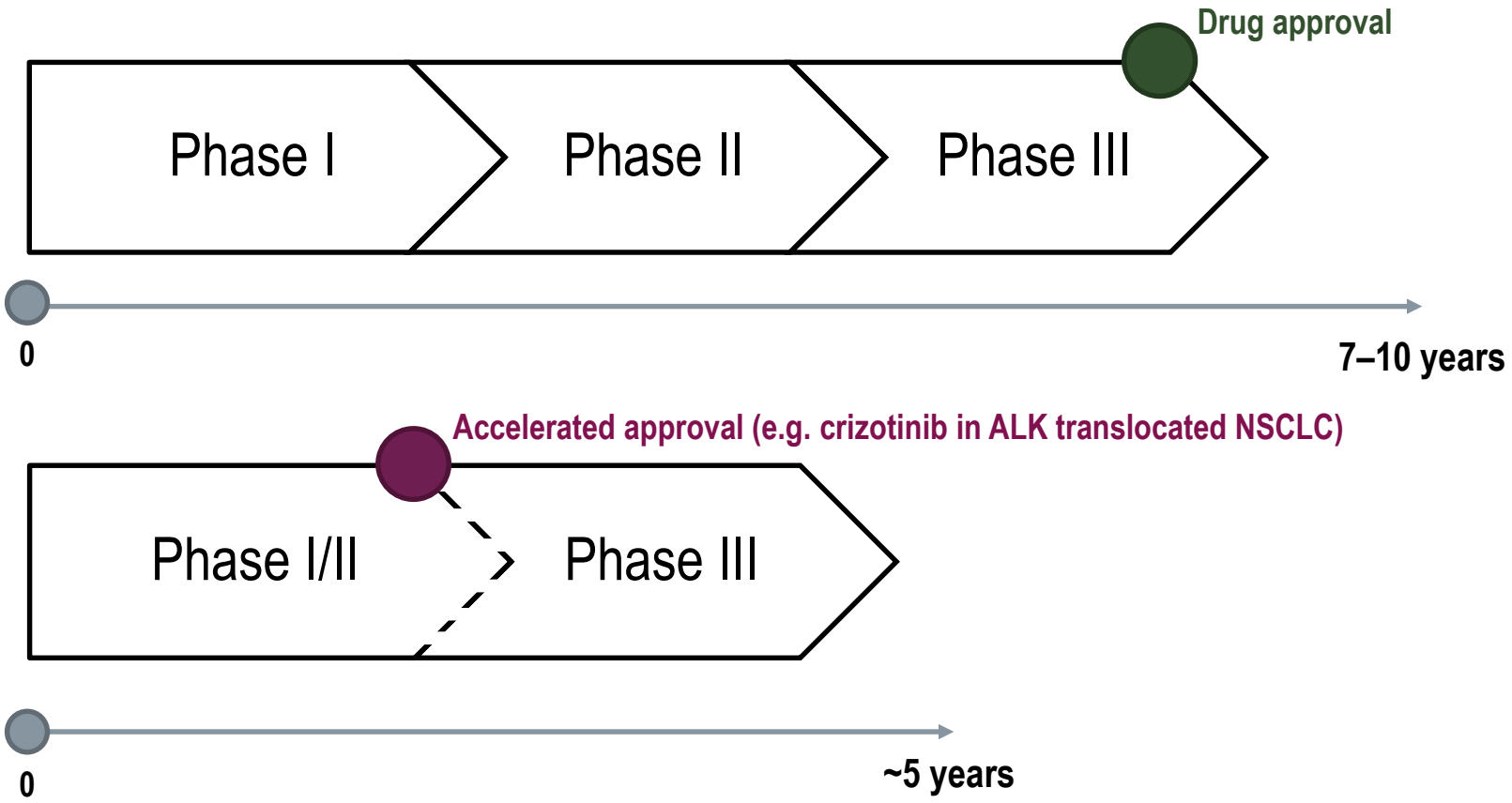
DOES THE CURRENT DESIGN OF ONCOLOGY TRIALS MEET THE NEED OF PATIENTS?

YES	NO
♦ **Several new anticancer agents reached clinical practice** much faster than in the past (the interval from Phase I to registration has shortened from ~8–10 years to **<5 years** nowadays)	♦ **Redundancy** in the development of agents
♦ **Often improvement in PFS** (but rarely in survival [metastatic settings])	♦ **Commonly used endpoints are not relevant** for immunotherapy
♦ **Often improvement in early DFS** (but rarely in OS [early settings])	♦ Many **competitive trials** in the same setting
	♦ Few studies looking at a therapeutic strategy
	♦ Few studies in **unmet need clinical settings** or focusing on **rare cancers**
	♦ More and more biomarker studies **but limited validated biomarkers** for clinical use
	♦ Principles of analytical validation and clinical utility are often not properly taken into account in drug development models

Still a huge gap between clinical research and the need in clinical practice

3. RECENT DEVELOPMENTS IN THE CLINICAL RESEARCH METHODOLOGY

NO CLEAR FRONTIER BETWEEN PHASE I, PHASE II AND PHASE III



Adapted from Postel-Vinay S, *et al.*, Ann Oncol 2016;27:214–24

EVOLVING METHODOLOGY OF EARLY-PHASE TRIALS

From cytotoxics to imAbs

	Cytotoxic chemotherapy	Molecular-targeted agents	Immunostimulatory monoclonal antibodies (imAbs)
Patients number	30–50 unselected patients	30–200 ''molecularly'' selected patients	100–1000 ''immunologically'' selected patients
Administration	IV > Oral	Oral > IV	IV
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

MTD, maximum tolerated dose
Adapted from Postel-Vinay S, *et al.,* Ann Oncol 2016;27:214–24

EVOLUTION OF CLINICAL RESEARCH LANDSCAPE

Adjuvant setting (1)

PAST

- Large RCTs
- Thousands of unselected patients
- Small benefits

PRESENT and FUTURE

- « Selected » groups of patients* (challenging)
- Number of patients is variable
- Large benefits requested!
- Need of biomarkers for selection/ surrogate markers for efficacy

*By clinical, pathological or molecular criteria

EVOLUTION OF CLINICAL RESEARCH LANDSCAPE

Metastatic setting (2)

PAST

- RCTs
- Hundreds of unselected patients
- OS is the main endpoint (less PFS)
- Small benefits

PRESENT and FUTURE

- RCTs or single arm trials aiming to demonstrate a large effect on ORR based on historical controls
- Need for databases of historical control arms
- Selected groups of patients*
- Basket and umbrella studies
- Lower number of patients treated but huge number screened
- PFS as preponderate endpoint
- Large benefits requested!

*By clinical, pathological or molecular criteria

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
	Randomised 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

4. CHALLENGES OF THE RECENT CLINICAL RESEARCH METHODOLOGY

CHALLENGES OF THE RECENT CLINICAL RESEARCH METHODOLOGY

Challenges of early clinical trials methodology

Challenges of precision medicine

Challenges of more recently-developed immunotherapy trials

CHALLENGES OF EARLY CLINICAL TRIALS METHODOLOGY (2 EXAMPLES)

1. Inappropriate designs[1,2]
2. Definition of dose-limiting toxicities and recommended doses and schedules are often inappropriate[3]

1. Paoletti X, *et al.,* Ann Oncol 2015 26:1808–2; 2. Le Tourneau C, *et al.,* PLoS One 2012;7:e51039;
3. Kotecki N, *et al*., Curr Opin Oncol 2016;28:437–40

CHALLENGES OF PRECISION MEDICINE (1)

The desperate hunt for biomarkers:

More and more biomarker studies (Pubmed search: 42,636!) 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 strategy for validation**
- Need for quality assurance for reproducibility and interpretation of complex datasets

LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE (1)

Target	Tumour	Inhibitor	Predictive markers of sensitivity/resistance	Disease setting
ER	Breast	Tamoxifen, aromatase inhibitors (AI), fulvestrant	ER expression ER mutation (resistance)	Adjuvant and advanced disease
EGFR	Head and neck	Cetuximab	-	Locally-advanced head and neck cancer
EGFR	NSCLC	Gefitinib/erlotinib/afatinib osimertinib	EGFR activating mutation EGFR T790M mutation	Metastatic NSCLC
EGFR	NSCLC squamous	Necitumumab	EGFR expression	Metastatic squamous NSCLC
K-/N-Ras B-Raf	Colorectal	Cetuximab, panitumumab	K-/N-Ras mutations/B-Raf mutation (resistance)	Metastatic colorectal cancer
HER-2/neu	Breast Gastric	Trastuzumab, pertuzumab lapatinib, neratinib, T-DM1 trastuzumab	HER-2/neu amplification	Breast: Adjuvant and advanced disease Gastric: Metastatic disease

LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE (2)

Target	Tumour	Inhibitor	Predictive markers of sensitivity	Disease setting
VEGF	NSCLC, colorectal, renal, breast, ovary, cervix	Bevacizumab, aflibercet (colon)		Advanced disease
VEGFR	Hepatocellular, colorectal, gastric, NSCLC	Sorafenib, regorafenib, ramucirumab, ramucirumab	-	Advanced disease
VEGF(R); M-TOR	Renal	MTKs, bevacizumab everolimus, temsirolimus	-	Advanced disease
VEGFR; M-TOR'	Neuroendocrine (pancreas), soft tissue sarcomas	Sunitinib, everolimus, pazopanib	-	Advanced disease
VEGFR, RET	Thyroid	Vandetanib, sorafenib lenvatinib	-	Advanced disease
M-TOR	Breast	Everolimus	-	Advanced disease
CDK 4/6	Breast	Palbociclib, ribociclib, abemaciclib	-	Advanced disease

LIMITED AVAILABILITY OF BIOMARKERS IN CLINICAL PRACTICE (3)

Target	Tumour	Inhibitor	Predictive markers of sensitivity/resistance	Disease setting
KIT	GIST	Imatinib, sunitinib, regorafenib	KIT mutation PDGFR mutation	High risk or metastatic GIST
EML4-ALK ROS1	NSCLC	Crizotinib, ceritinib, alectinib, crizotinib	EML4-ALK translocation ROS1 rearrangement	Advanced NSCLC
RANKL	Bone metastases, giant cell tumours	Denosumab	-	Advanced disease
Hedgehog	Basal cell carcinoma	Vismodegib	PTCH mutations	Advanced disease
BRAF, MEK	Melanoma	Vemurafenib, dabrafenib. trametinib	BRAF mutation on V600	Advanced disease
PARP	Breast, ovary (BRCA tumours)	Olaparib, niraparib, rucapanib	BRCA mutation	Advanced disease
CTLA4	Melanoma	Ipilimumab		Advanced disease
PD-1/PD-L1	Melanoma, NSCLC, RCC, gastric, head and neck, urothelial, …	Nivolumab, pembrolizumab,...	PD-L1 protein in NSCLC	Advanced disease
Androgen receptor	Prostate	Abiraterone, enzalutamide,		Advanced disease

CHALLENGES OF PRECISION MEDICINE (2)

High promotion of precision medicine among medical team and patients

but

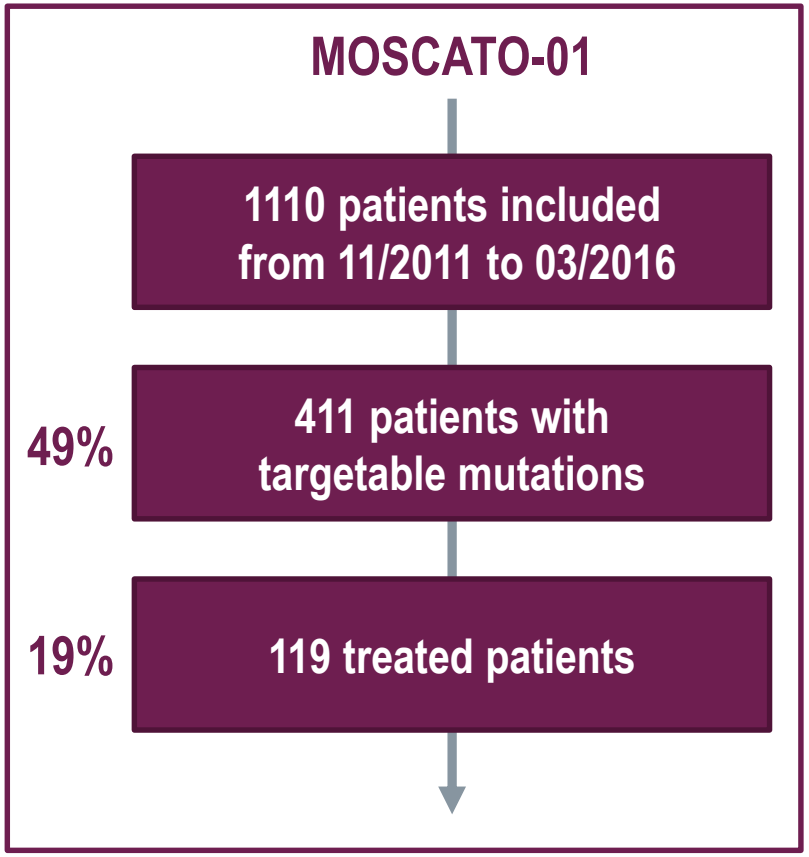
Limited number of actionable/targetable mutations

Limited access or unavailable clinical trials or marketed targeted agents

→ High attrition rate

↓

Ethical issues



Adapted from Massard C, *et al.*, Cancer Discov 2017;7:586–95

CHALLENGES FOR IMMUNOTHERAPY TRIALS

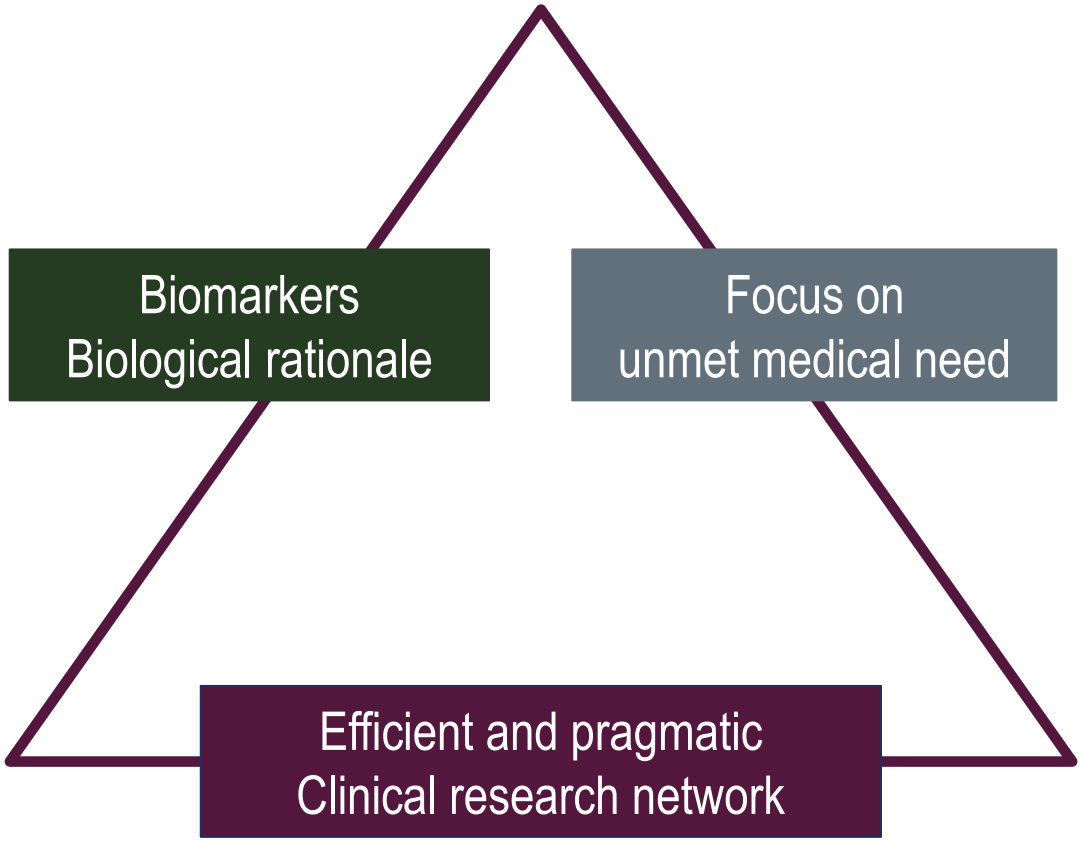
1. Optimal dose and schedule selection
   Minimal immunologically active dose (dose is not linearly associated with efficacy and toxicity)
   - Optimal dose for prolonged exposure
2. Optimal sequence/re-challenge
   - Maximise benefit for patients and minimise economic burden
3. Identify resistant/sensitive disease to immunological approaches
   - Biomarkers (immunoscore, immunomics, …)
4. New patterns/definitions of tumour assessment and disease progression
   (Champiat S, *et al*., Clin Cancer Res 2016;23:1920–8)
5. Combinations issues

5. WHAT DO WE NEED?

OVERALL, WHAT DO WE NEED ?

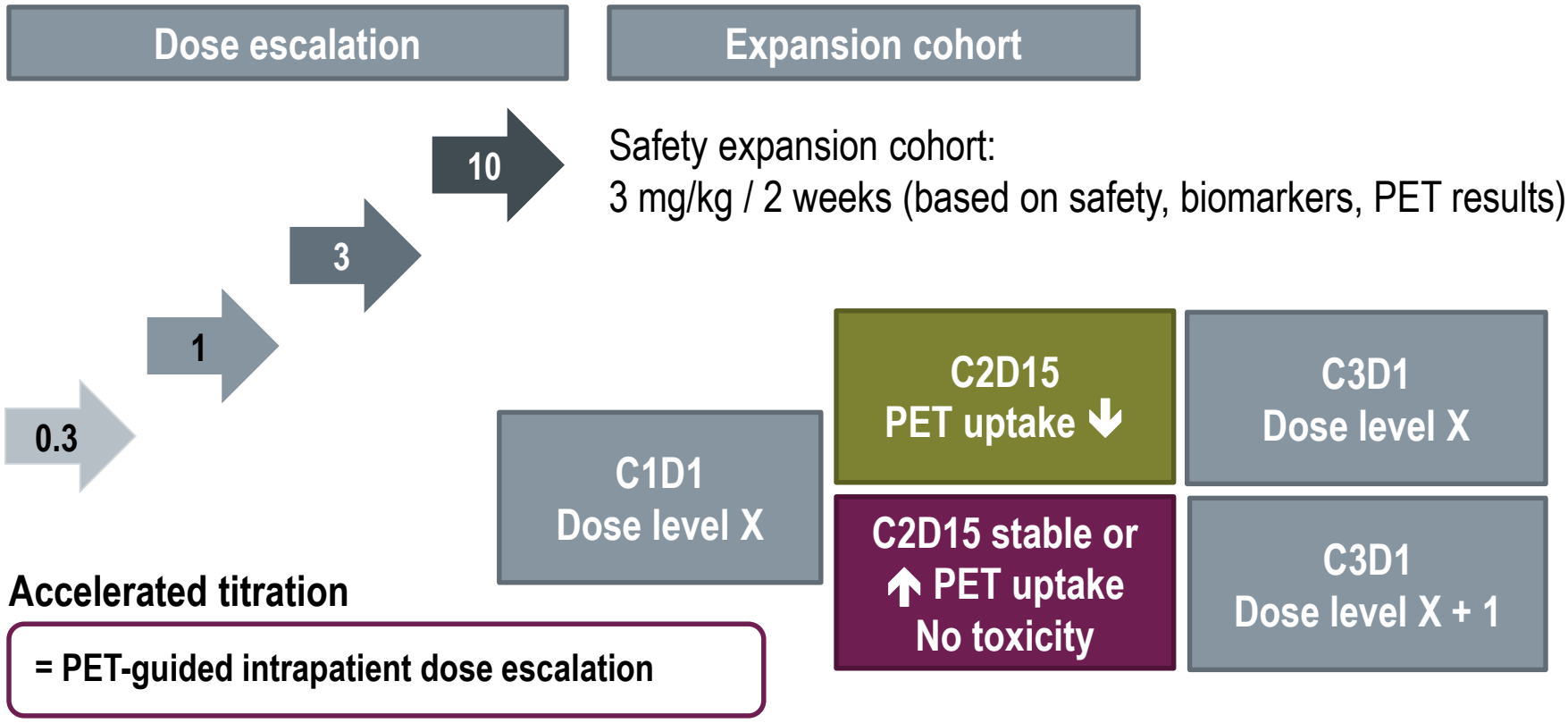
1. Continue to perform pivotal trials (regulatory purpose)
2. More innovative approaches and trial designs in drug development → Individualising clinical research!
3. Targeting the unmet need for patients in the context of nosological fragmentations of the diseases
4. More selective and well-designed biomarker studies (rather predictive of tumour resistance, such as **K/N-Ras** mutations in colorectal cancer) with high potential for clinical practice
5. Creating new models of clinical research networks (e.g. Oncodistinct.net…) and collaboration between pharma, cooperative groups and investigators

WHAT DO WE NEED ?



CLINICAL RESEARCH INDIVIDUALISATION: EXAMPLE

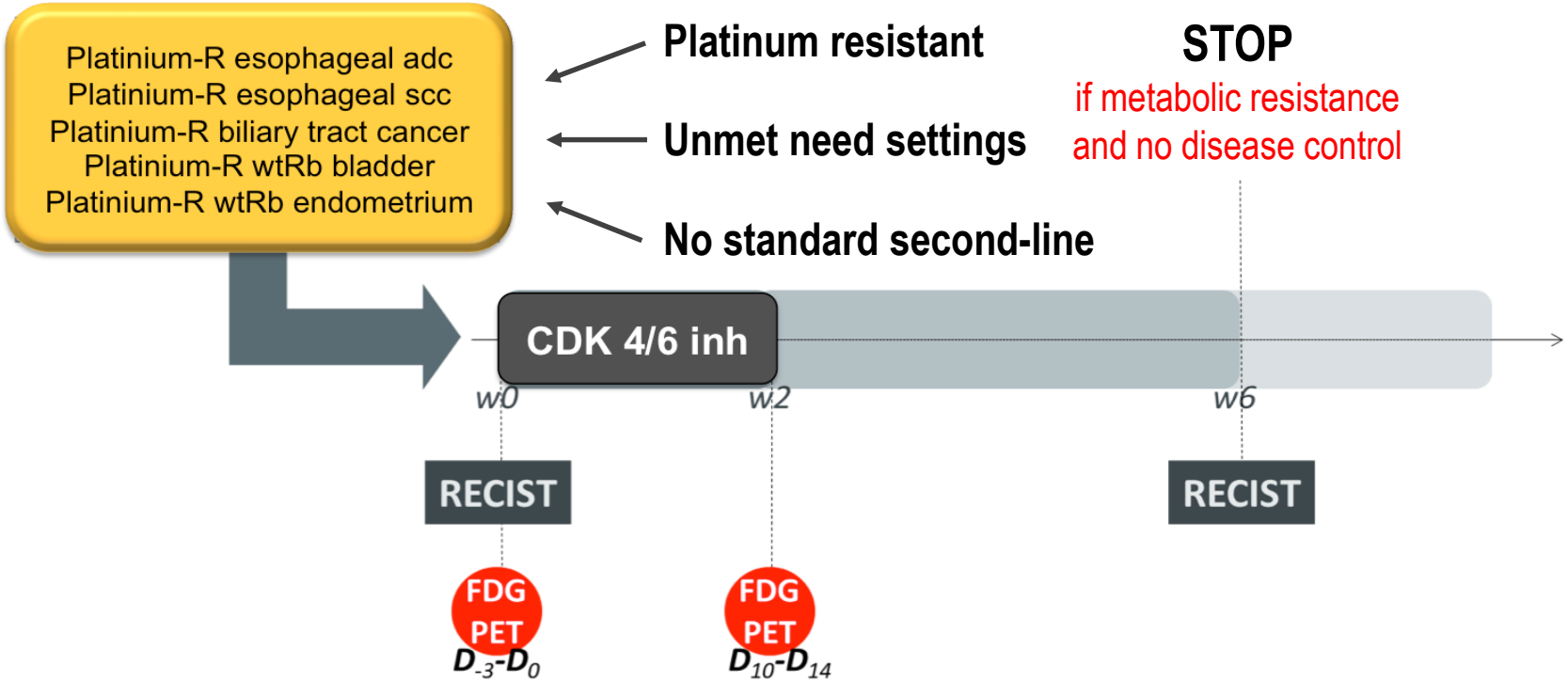
A Phase Ib Study of ARGX-111 (c-Met mAb) in patients with advanced solid cancer



clinicaltrials.gov: ClinicalTrials.gov Identifier: NCT02055066

MORE INNOVATIVE APPROACHES AND TRIAL DESIGNS IN DRUG DEVELOPMENT

Example

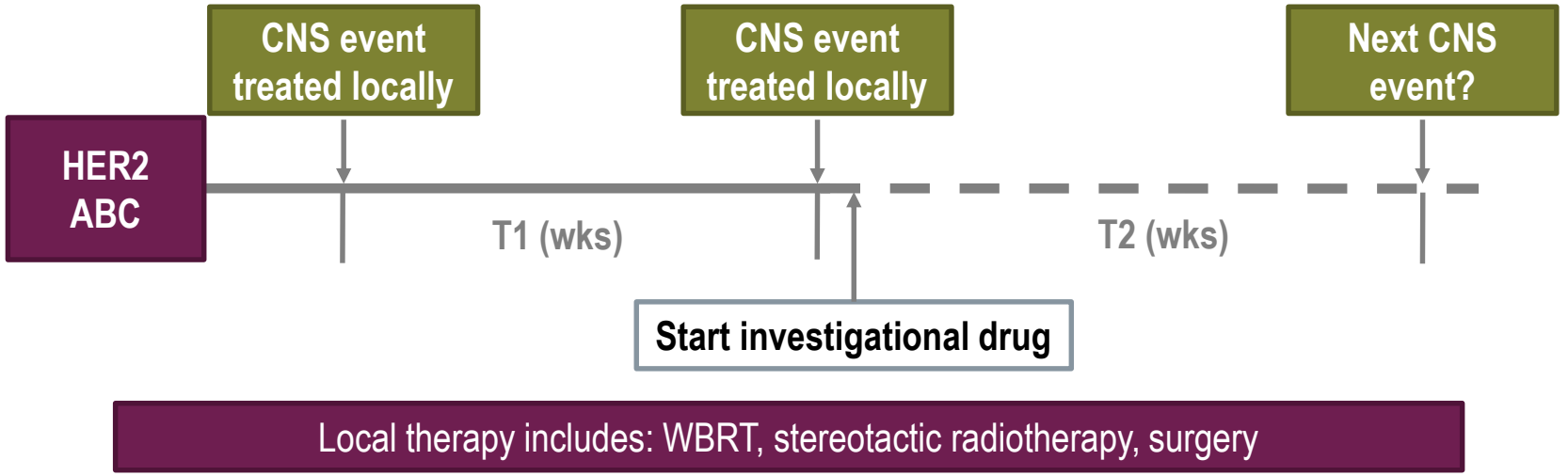


Oncodistinct 002/MIME TRIAL: Multiorgan Metabolic imaging response assessment of a CDK4/6 inhibitor in solid tumours (other than breast)

TARGETING UNMET NEED FOR PATIENTS

Brain METS – Example

A Phase II trial to evaluate a HER2-targeted investigational agent crossing the BBB for **prevention of subsequent CNS event** in HER2 advanced breast cancer (ABC)



The time period between the 2 local treatments should be known (T2/T1 > 1.3)

BIOMARKERS RESULTS

“ON LIVE” with high potential for clinical research and practice use: Biocartis platform as an example

Idylla™: fully automated, real-time PCR

Offer fast and easy access to molecular biomarker results (blood, tumour…)

Time frame of 35 to 150 minutes

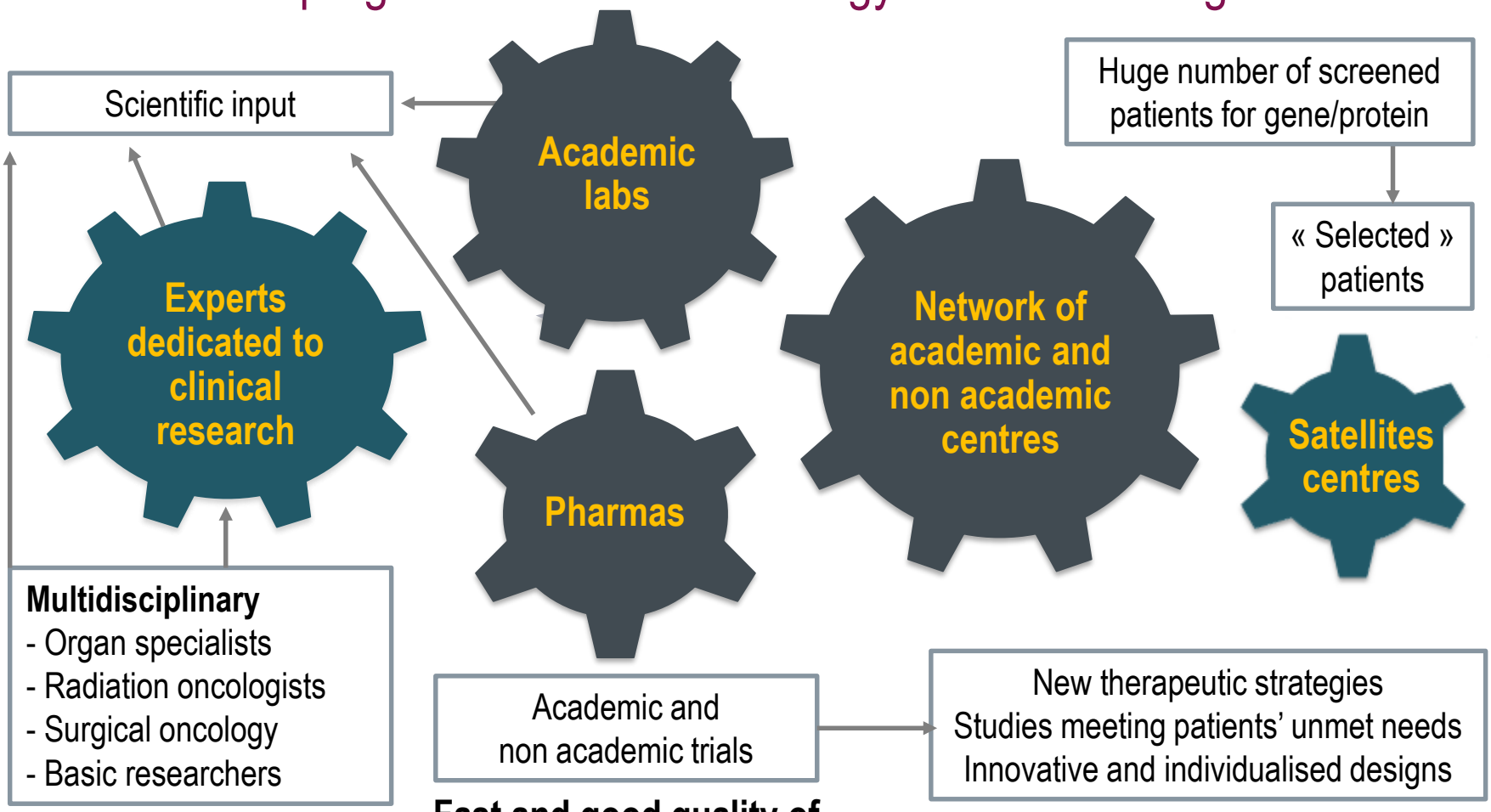
Analyse both RNA and DNA

Available cartridges:
EGFR mutation assay,
BRAF mutation test
KRAS mutation test
NRAS-BRAF-EGFRS492R mutation assay
ctBRAF mutation assay
ctKRAS mutation assay
NRAS-BRAF mutation test

Others under preparation

A NEW ACADEMIC MODEL OF CLINICAL RESEARCH COLLABORATION

Based on the progress on molecular biology and methodological issues



Fast and good quality of academic and non academic trials

THANK YOU!

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