Oncology as an example of applied precision medicine

Prof. Christophe Le Tourneau, MD, PhD

Institut Curie
Département d'Essais Cliniques Précoces
Equipe de recherche INSERM U900
Université Paris-Saclay

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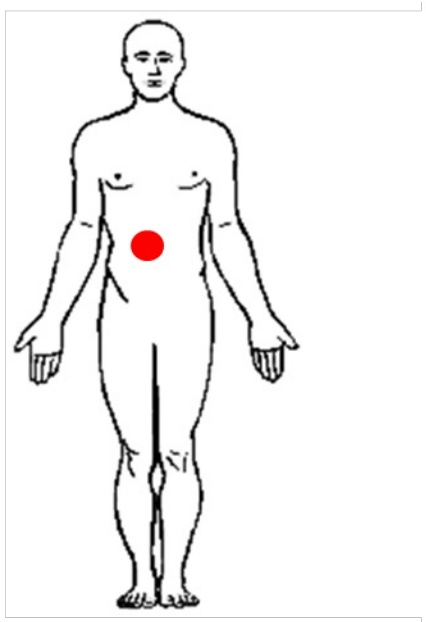
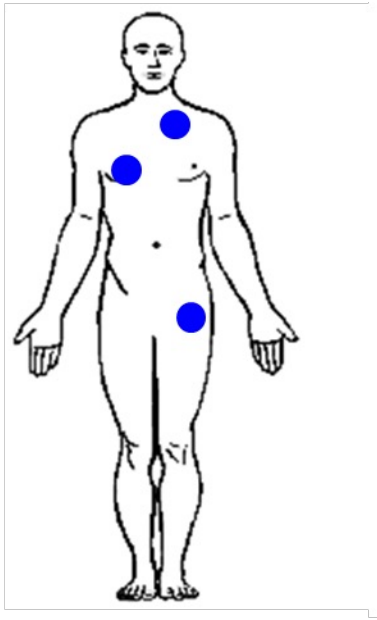
Treatment of cancer

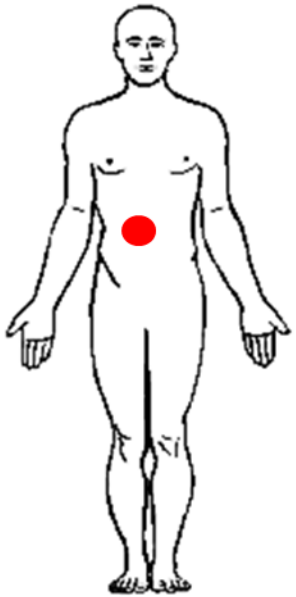




● Primary tumor

● Metastases

Treatment of cancer



Surgery

Radio-therapy

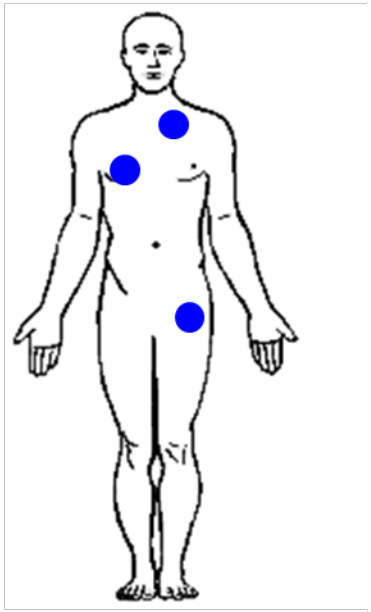
Local treatments

Drugs

For a limited time

→ Aim = cure

Treatment of cancer



Drugs

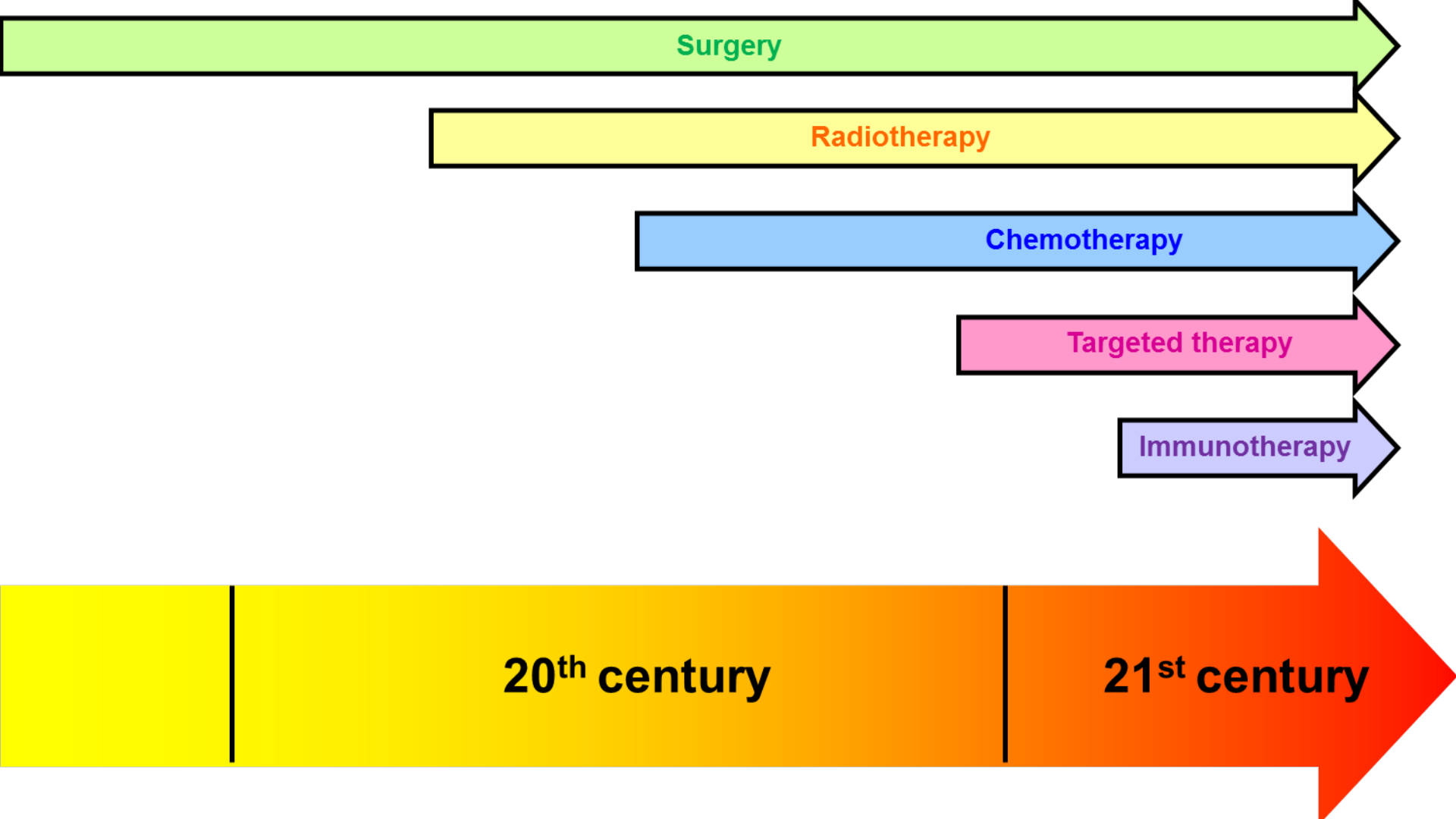
Treatment for life

Surgery

Radio-therapy

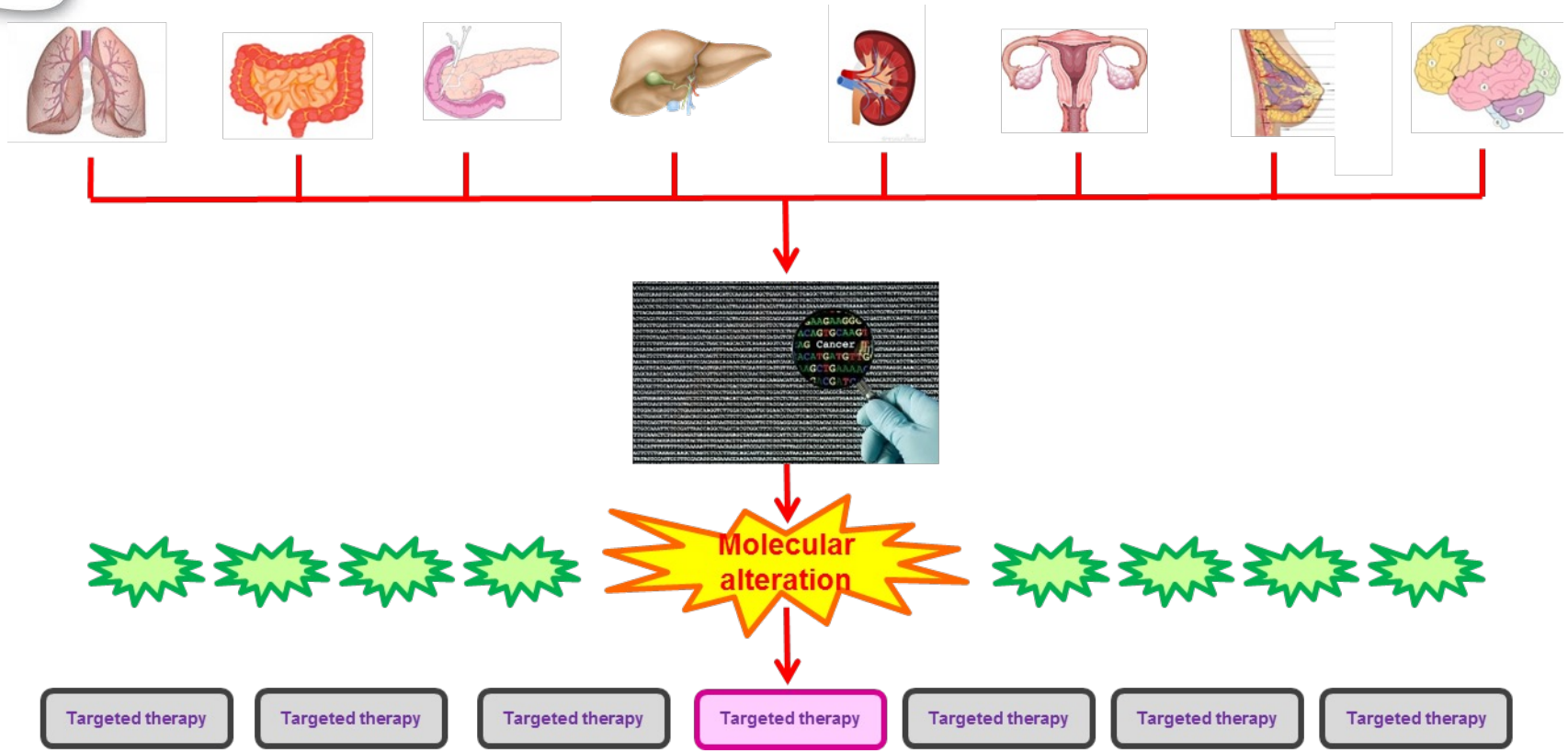
Curable situation in ~5% of cases (exception of germline tumors [95%])

Chronic disease


Surgery
Radiotherapy
Chemotherapy
Targeted therapy
Immunotherapy
20th century
21st century

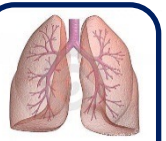
Precision medicine

Precision medicine concept

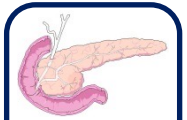


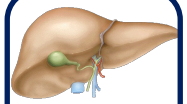
Ancestral paradigm

All comers


Chemo-therapy
Targeted therapy
Immuno-therapy

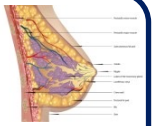

Chemo-therapy
Targeted therapy
Immuno-therapy

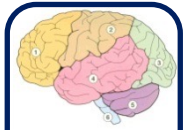

Chemo-therapy
Targeted therapy


Chemo-therapy
Targeted therapy
Immuno-therapy

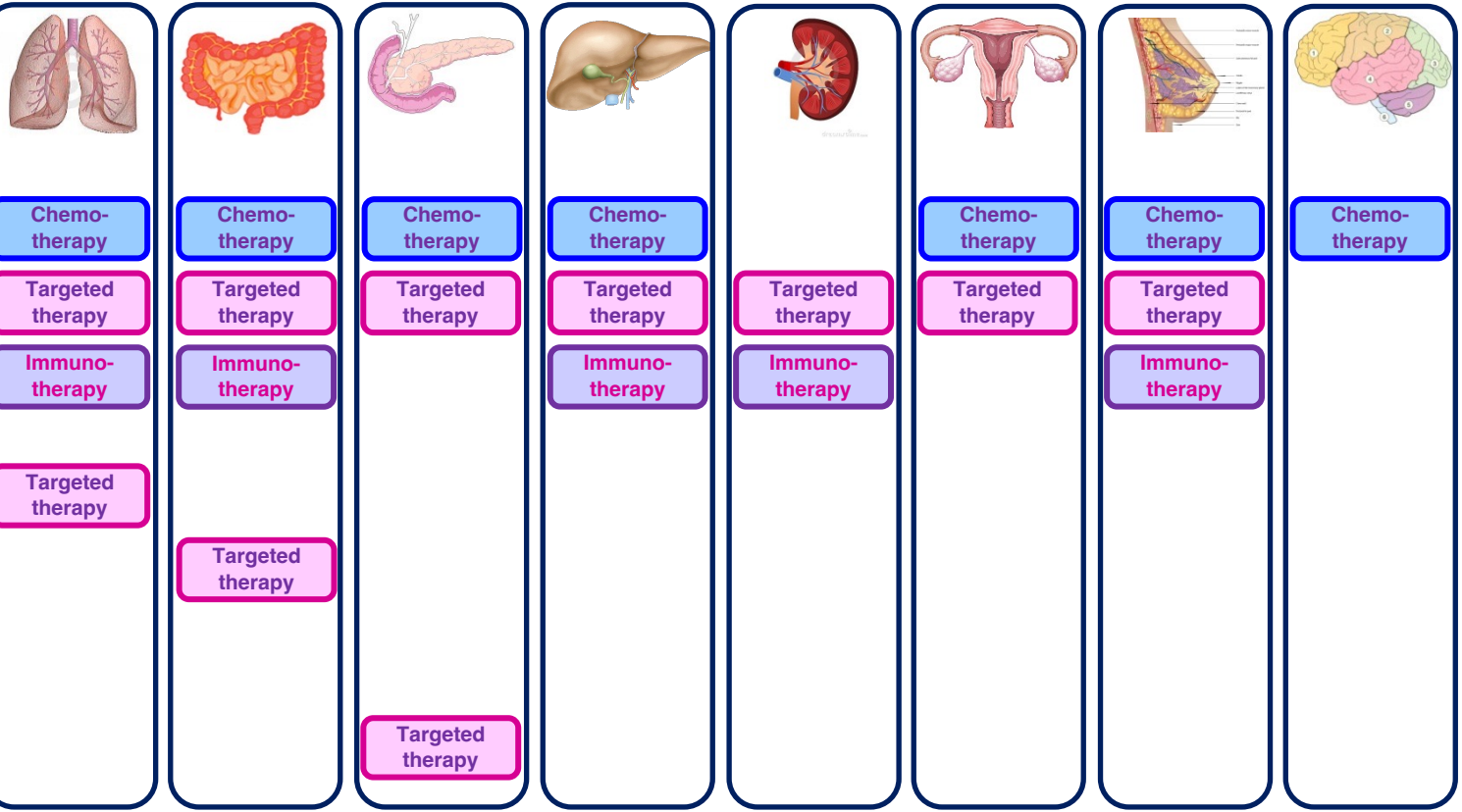

Targeted therapy
Immuno-therapy


Chemo-therapy
Targeted therapy

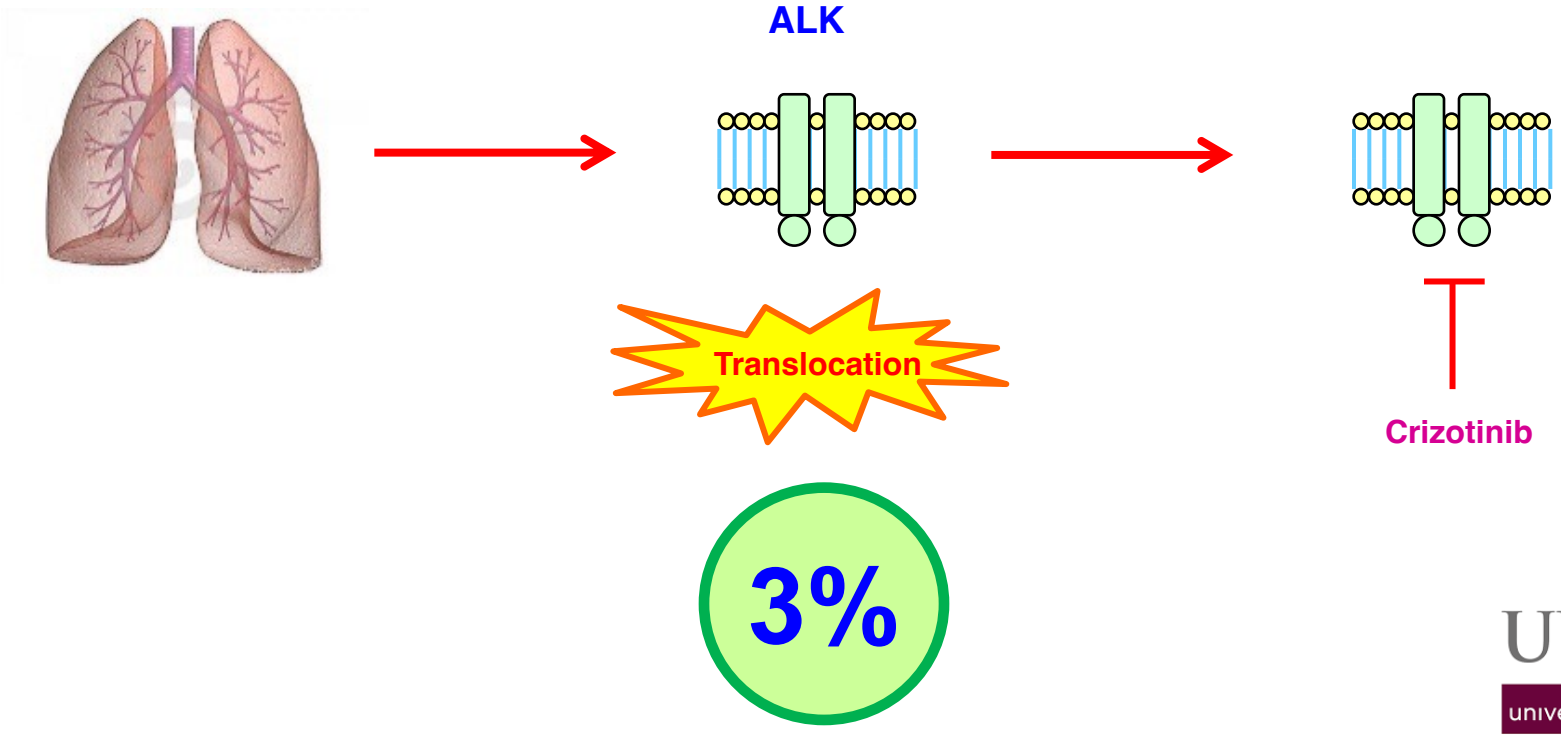

Chemo-therapy
Targeted therapy
Immuno-therapy


Chemo-therapy

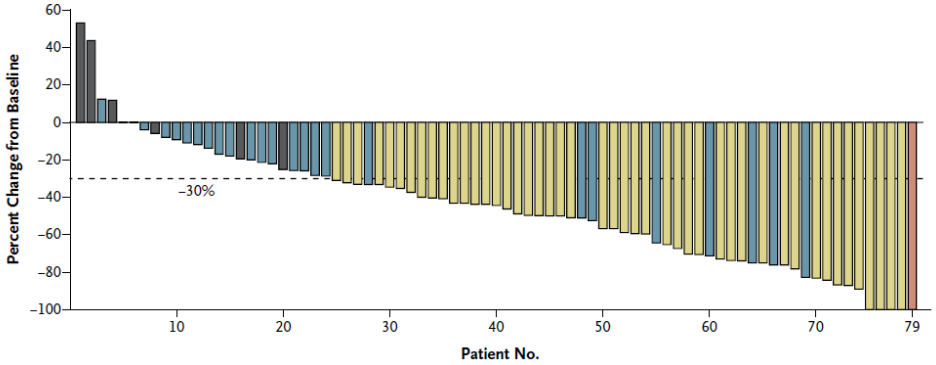
Biomarker-driven drug development

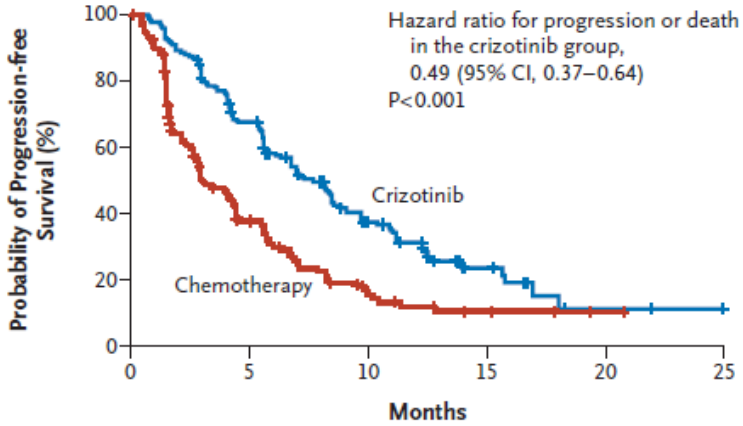


Biomarker-driven drug development



Biomarker-driven drug development



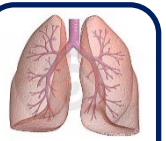


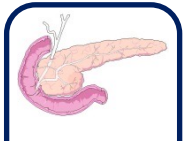
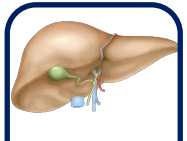
No. at Risk

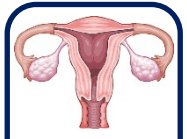
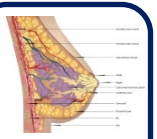
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Kwak et al. NEJM 2010;363:1693-1703; Shaw et al. NEJM 2013;368:2385-94

Biomarker-driven drug development




Target A

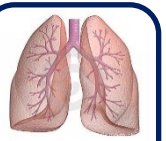
Target B

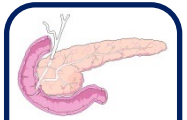
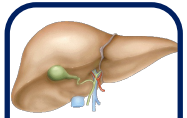
Target C

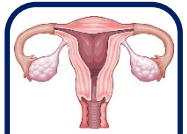
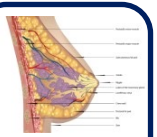
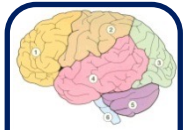
Target X

Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy

Biomarker-driven drug development

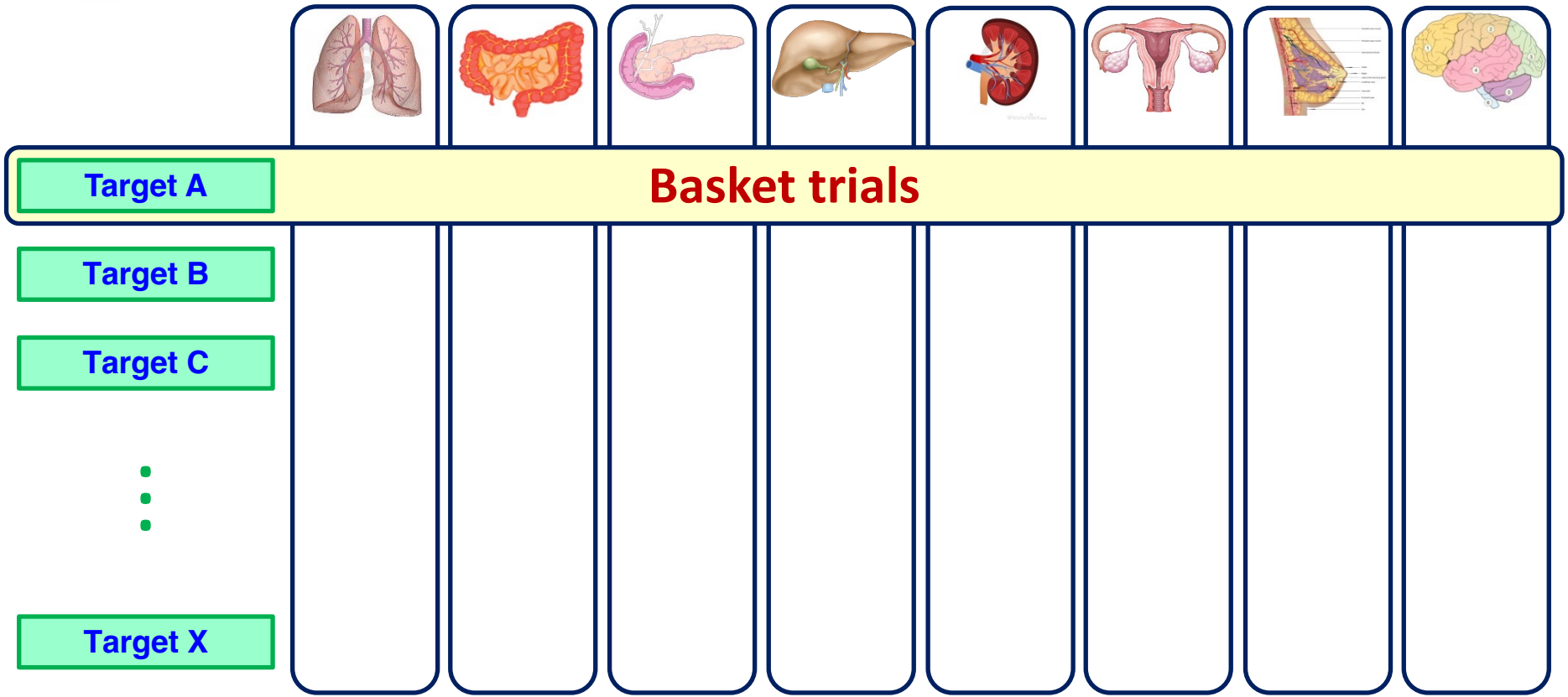


Target A	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy
Target B								
Target C								
⋮								
Target X								

Biomarker-driven drug development



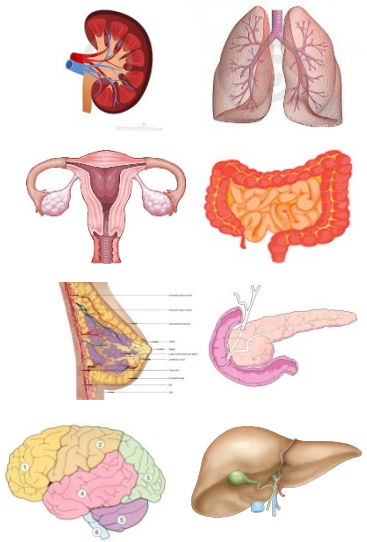
Basket trials

- Allow to evaluate a drug **concomitantly** in multiple tumor types
- Most often designed as paralel **phase II** trials
- **Main challenges:**

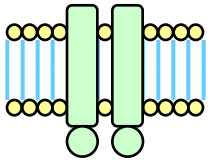
  - low **incidence**

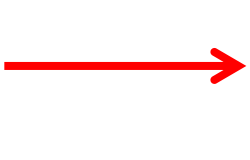
  - **tissue-agnostic** drug approval

Basket trials



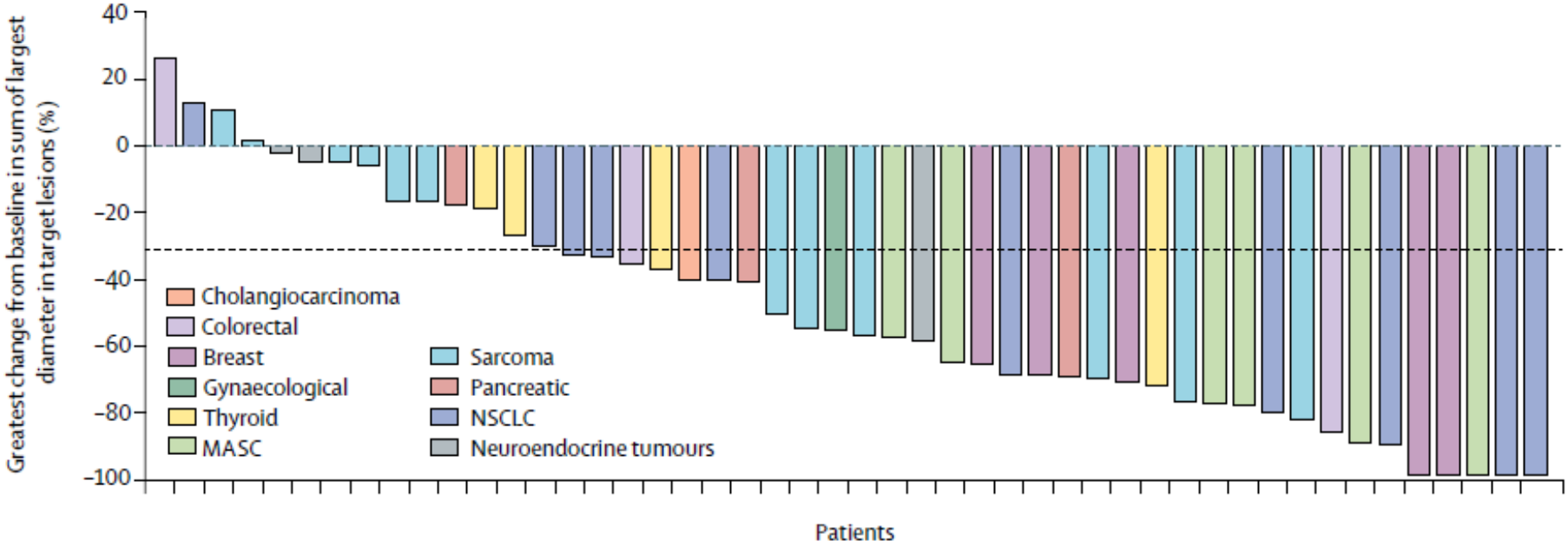
NTRK





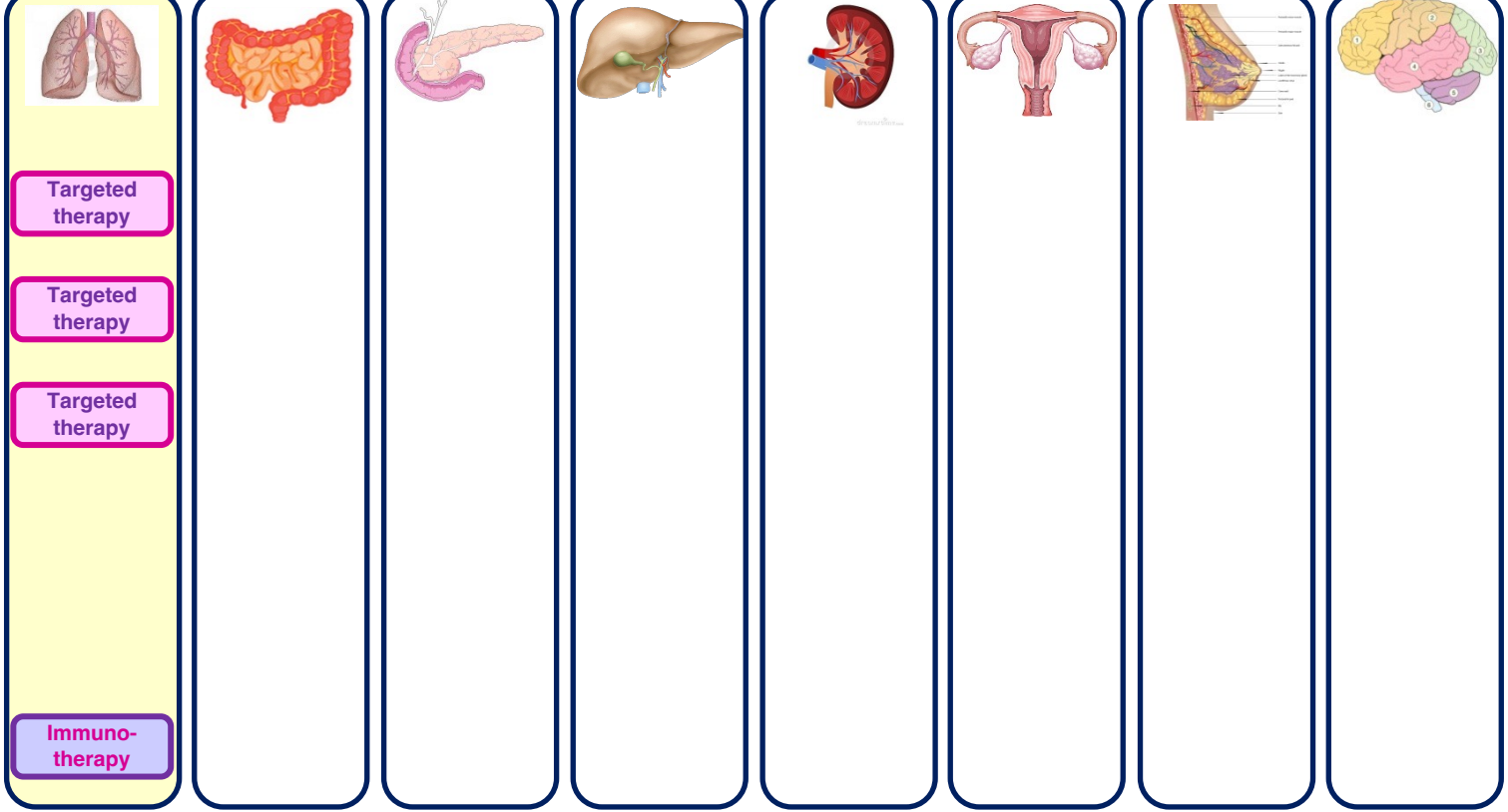
Larotrectinib
Entrectinib

Basket trials



Drilon et al. NEJM 2018;378:731-9; Doebele et al. Lancet Oncol 2020;21;271-82

Biomarker-driven drug development



Biomarker-driven drug development

Target A

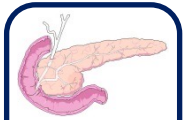
Target B

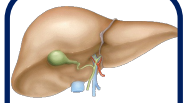
Target C

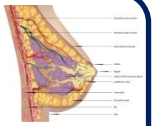
...

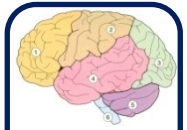
Target X

Umbrella trials









Umbrella trials

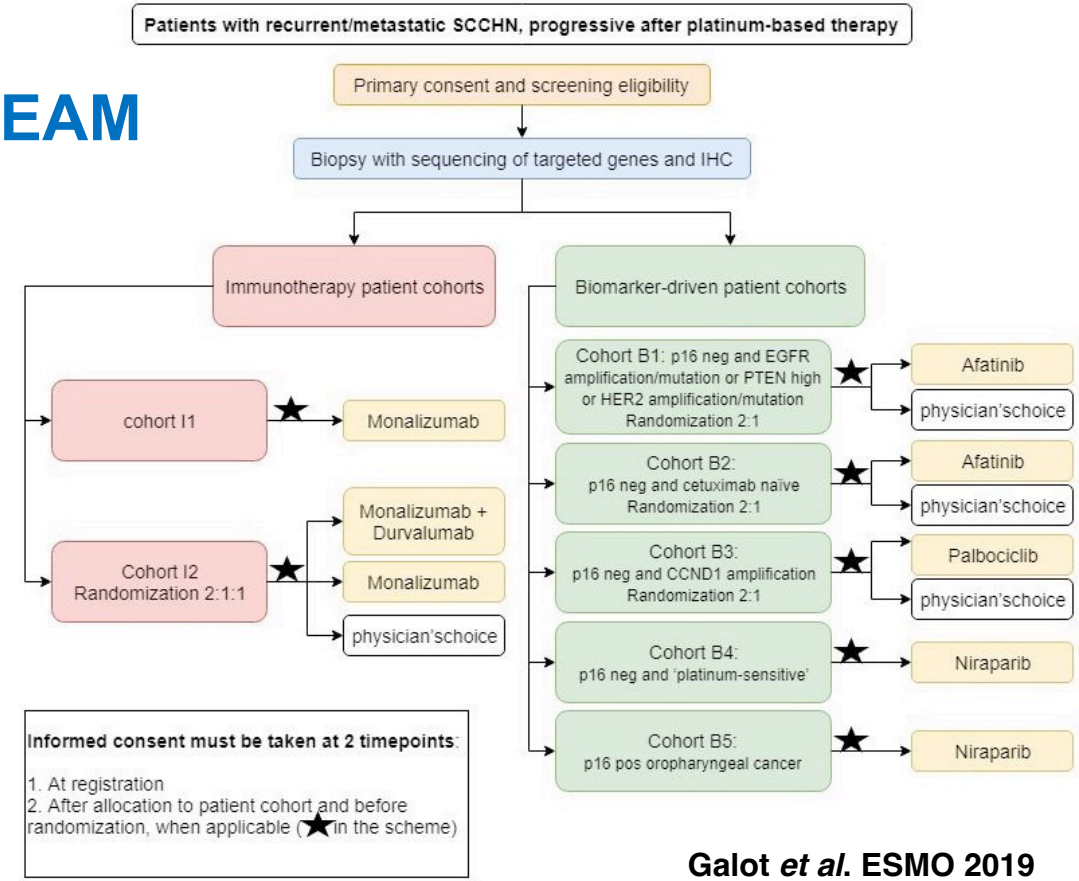
- Usually offer a **treatment option** in all cases
- Most often designed as paralel **phase II** trials
- **Mains challenges:**

  - **priorization** in case of several alterations

  - some **cohorts** might not be filled

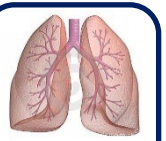
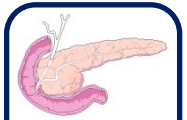
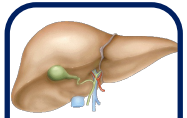
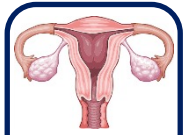
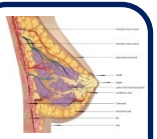
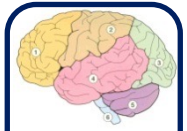
Umbrella trials

- **UP-STREAM**

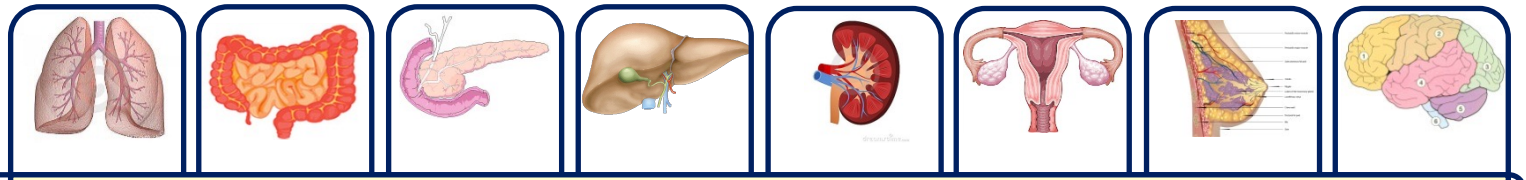


Galot *et al.* ESMO 2019

Biomarker-driven drug development

								
Target A	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy
Target B	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy
Target C	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy	Targeted therapy
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
Target X	Immuno-therapy	Immuno-therapy	Immuno-therapy	Immuno-therapy	Immuno-therapy	Immuno-therapy	Immuno-therapy	Immuno-therapy

Biomarker-driven drug development



- Target A
- Target B
- Target C
- ⋮
- Target X

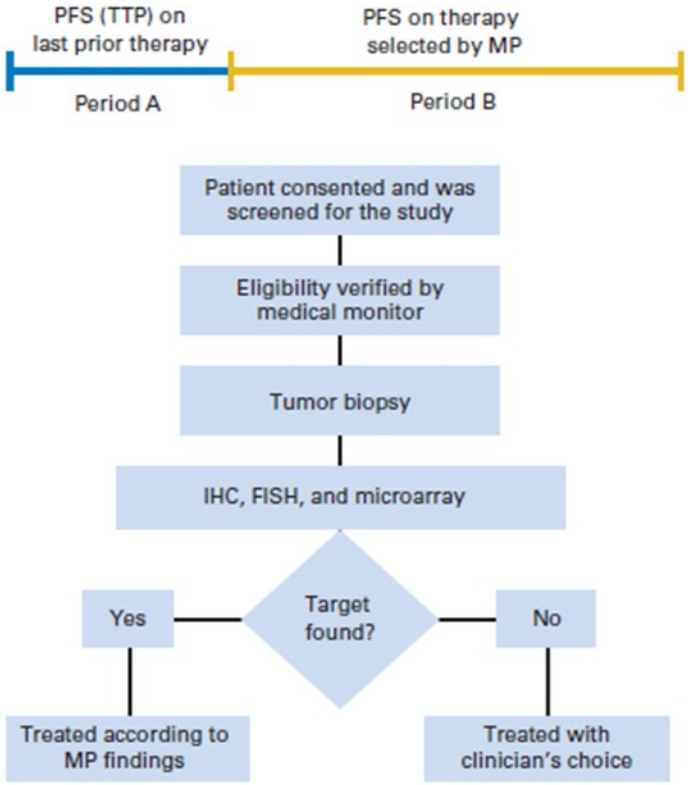
Algorithm-testing trials

Algorithm-testing trials

- Mix multiple **tumor types**, **molecular alterations**, and **drugs**
- Can only conclude on the **efficiency** of the **treatment algorithm** to allocate treatments
- Cannot assess the **efficacy** of any of the **drugs** in any **histologically**- or **molecularly**-defined **subgroup** of patients

Non-randomized trials

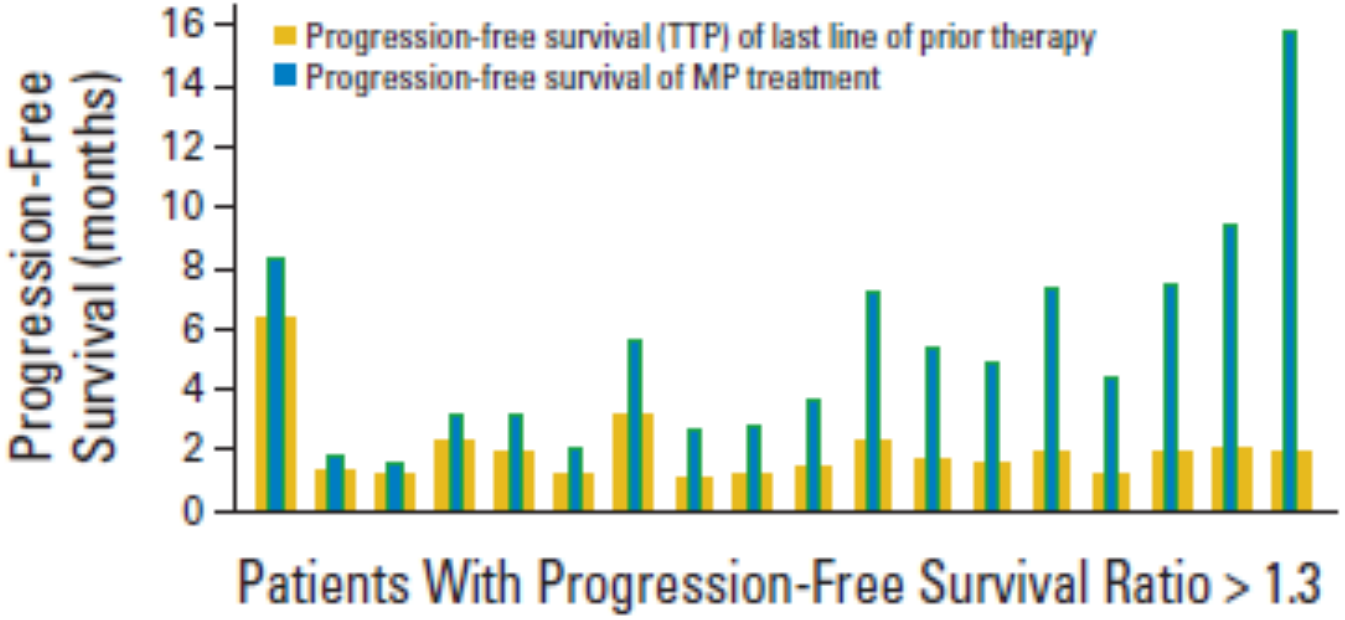
- **Pilot study**



von Hoff et al. JCO 2010;28:4877-83

Non-randomized trials

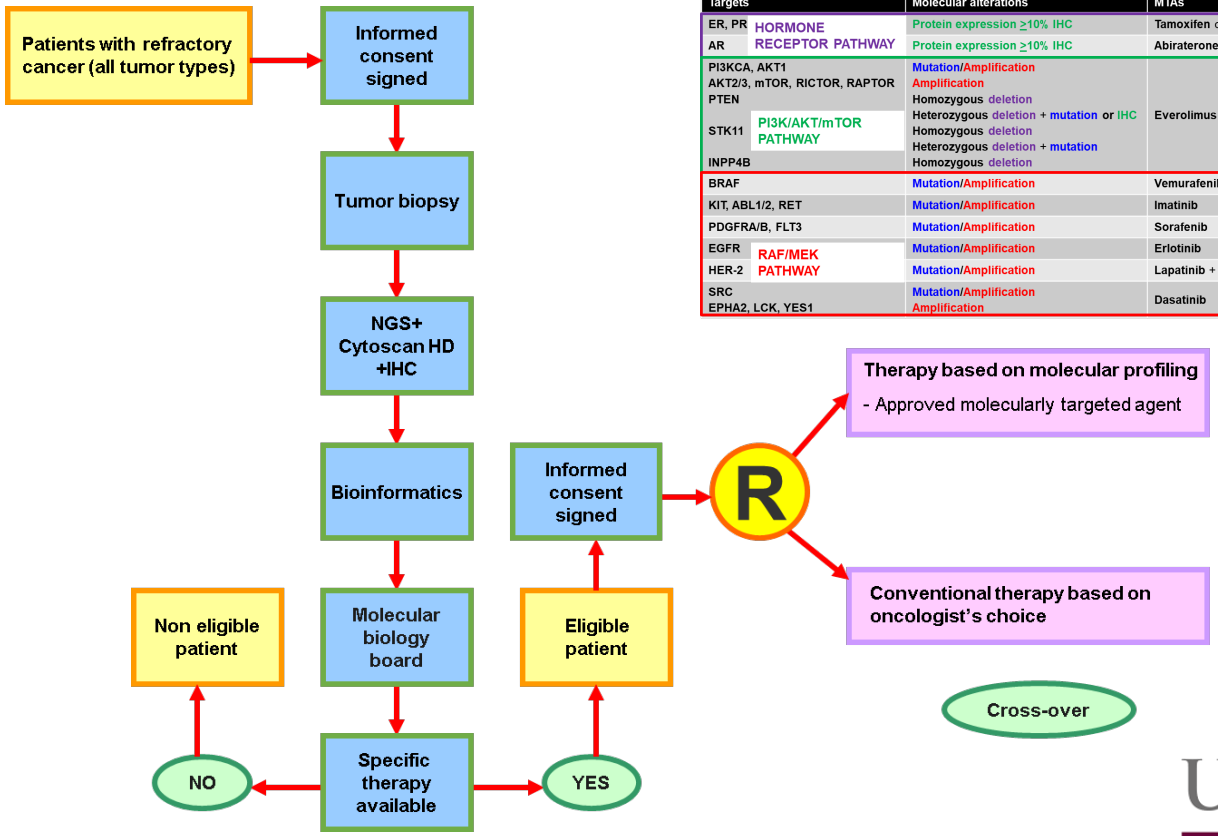
- 18/66 patients (27%): ratio>1.3



von Hoff et al. JCO 2010;28:4877-83

Randomized trials

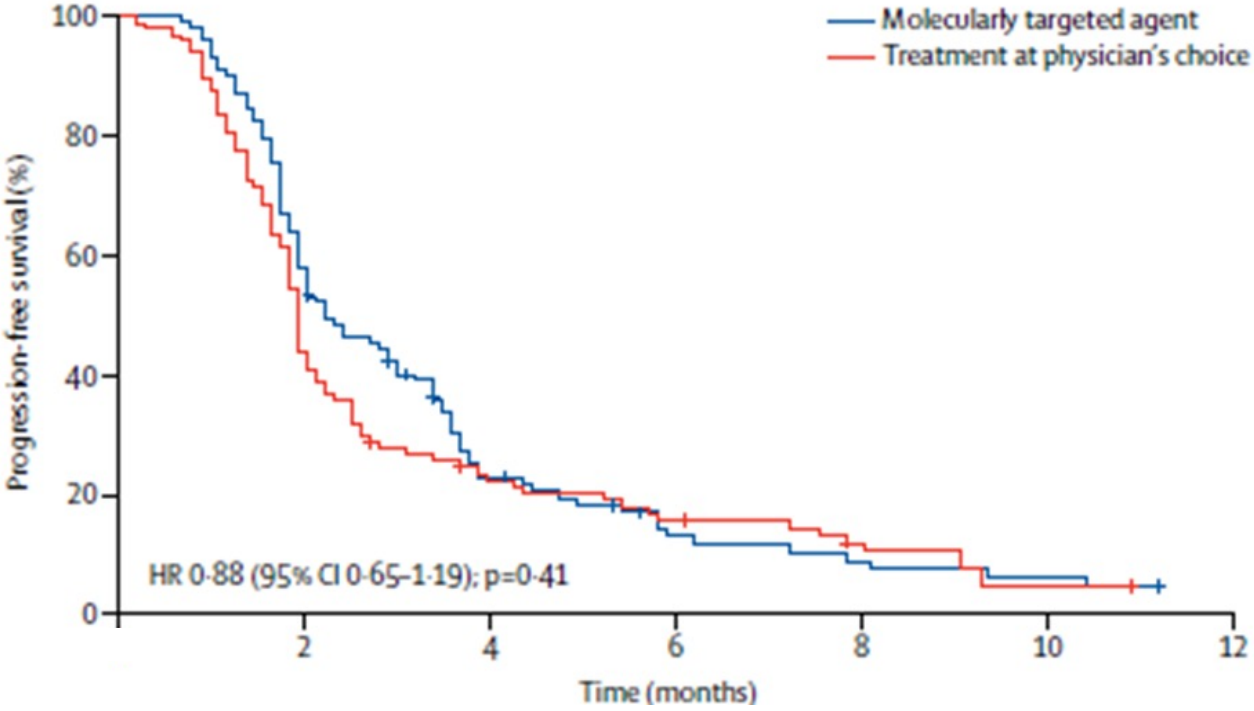
- **SHIVA01**

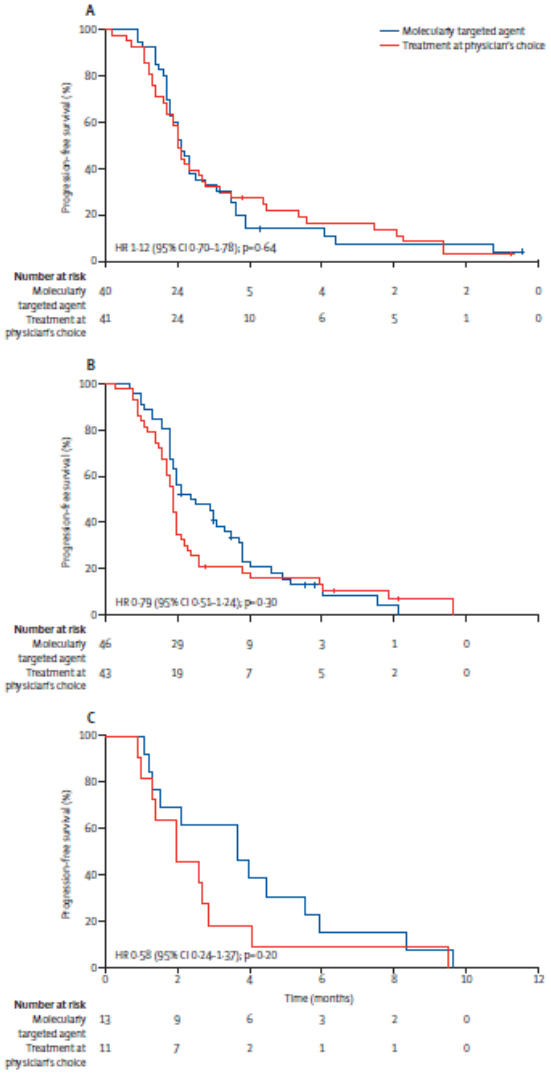


Targets		Molecular alterations	MTAs
ER, PR	HORMONE RECEPTOR PATHWAY	Protein expression ≥10% IHC	Tamoxifen or Letrozole
AR		Protein expression ≥10% IHC	Abiraterone
PI3KCA, AKT1	PI3K/AKT/mTOR PATHWAY	Mutation/Amplification	Everolimus
AKT2/3, mTOR, RICTOR, RAPTOR		Amplification	
PTEN		Homozygous deletion	
STK11		Heterozygous deletion + mutation or IHC Homozygous deletion	
INPP4B		Heterozygous deletion + mutation Homozygous deletion	
BRAF	RAF/MEK PATHWAY	Mutation/Amplification	Vemurafenib
KIT, ABL1/2, RET		Mutation/Amplification	Imatinib
PDGFRA/B, FLT3		Mutation/Amplification	Sorafenib
EGFR		Mutation/Amplification	Erlotinib
HER-2		Mutation/Amplification	Lapatinib + Trastuzumab
SRC EPHA2, LCK, YES1		Mutation/Amplification Amplification	Dasatinib

Le Tourneau et al. Lancet Oncol 2015;16:1324-34

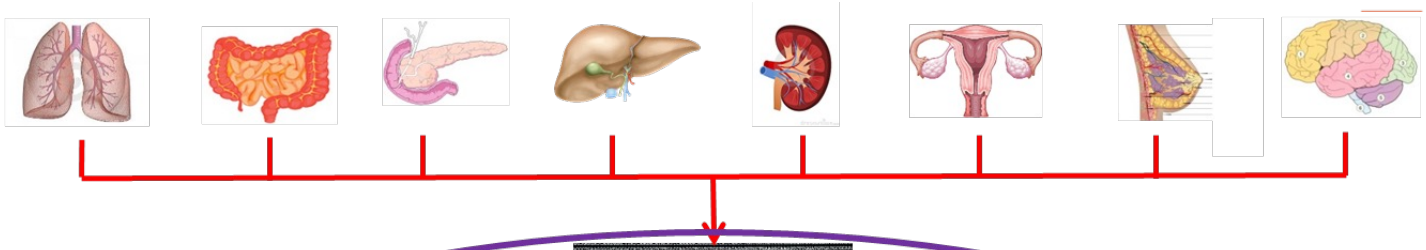
Randomized trials





Le Tourneau et al. Lancet Oncol 2015;16:1324-34

Challenges



Molecular

= TREATMENT ALGORITHM

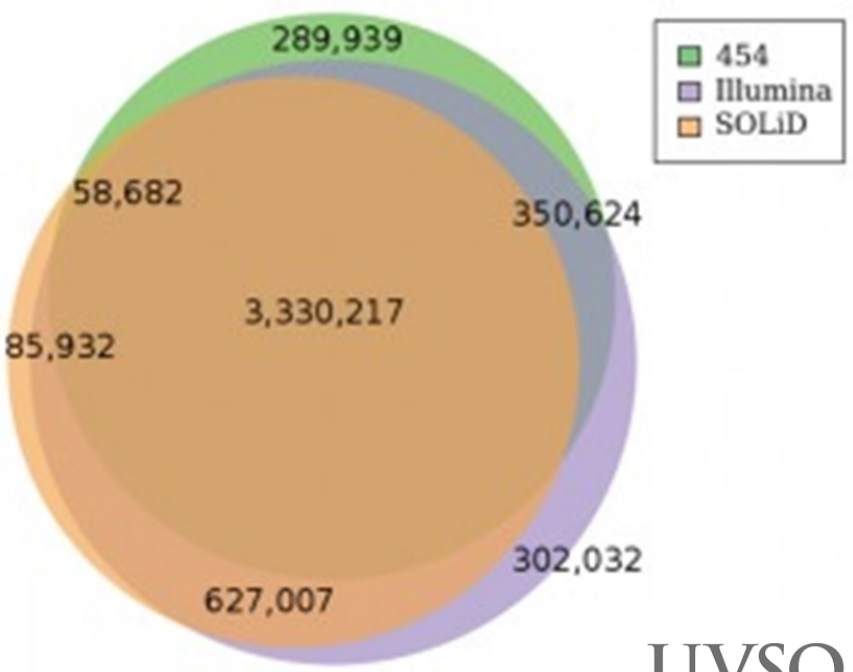
Targeted agent | Targeted agent | Targeted agent | Targeted agent | Targeted agent | Targeted agent | Targeted agent

Le Tourneau et al. JNCI 2015;108:4

Challenges

- **Treatment algorithm:**

  - **technology** used to identify molecular alterations



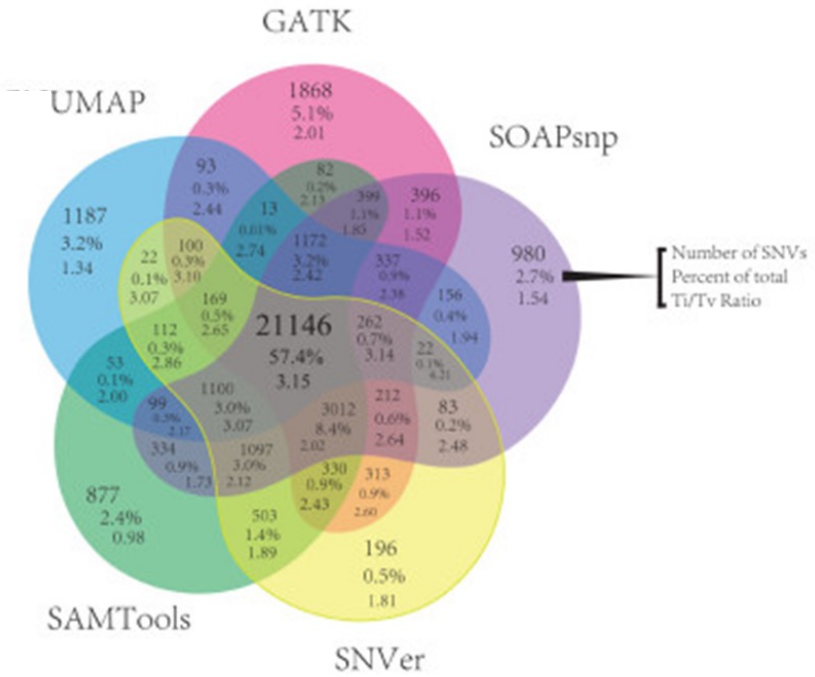
Ratan et al. Plos One 2013;8

Challenges

- **Treatment algorithm:**

  - **technology** used to identify molecular alterations

  - **thresholds** used



O'Rawe et al. Genomic Medicine 2013;5:28

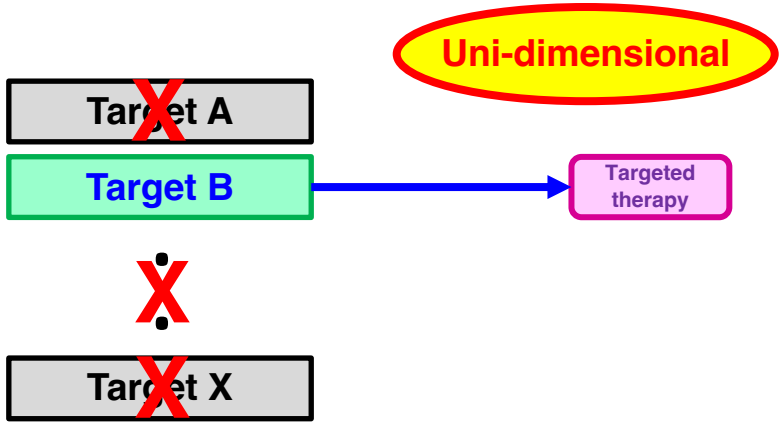
Challenges

- **Treatment algorithm:**

  - **technology** used to identify molecular alterations

  - **thresholds** used

  - molecular alterations/drugs **matching**



Challenges

- **Treatment algorithm:**

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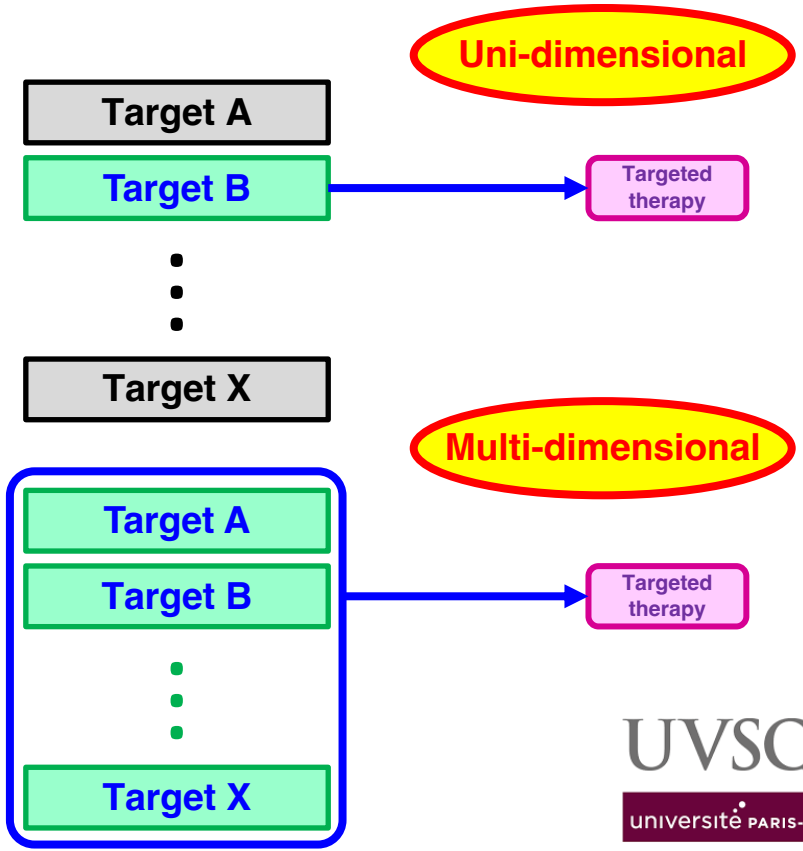


Challenges

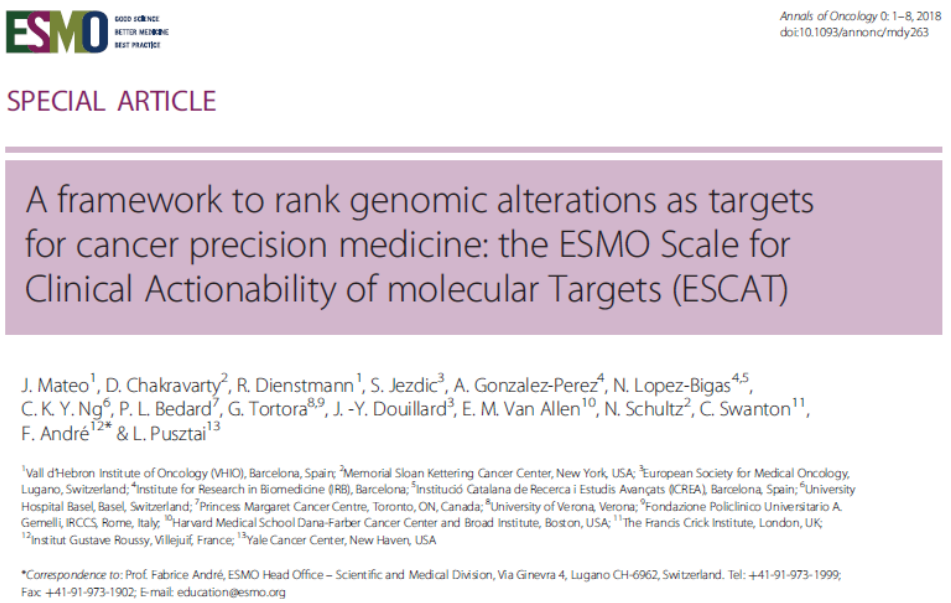
- **Treatment algorithm:**

  - **technology** used to identify molecular alterations

  - **thresholds** used

  - molecular alterations/drugs **matching**

  - molecular alterations **priorization**



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–8, 2018
doi:10.1093/annonc/mdy263

SPECIAL ARTICLE

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J. -Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

[1]Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [2]Memorial Sloan Kettering Cancer Center, New York, USA; [3]European Society for Medical Oncology, Lugano, Switzerland; [4]Institute for Research in Biomedicine (IRB), Barcelona; [5]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain; [6]University Hospital Basel, Basel, Switzerland; [7]Princess Margaret Cancer Centre, Toronto, ON, Canada; [8]University of Verona, Verona; [9]Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [10]Harvard Medical School Dana-Farber Cancer Center and Broad Institute, Boston, USA; [11]The Francis Crick Institute, London, UK; [12]Institut Gustave Roussy, Villejuif, France; [13]Yale Cancer Center, New Haven, USA

*Correspondence to: Prof. Fabrice André, ESMO Head Office – Scientific and Medical Division, Via Ginevra 4, Lugano CH-6962, Switzerland. Tel: +41-91-973-1999; Fax: +41-91-973-1902; E-mail: education@esmo.org

Mateo et al. Ann Oncol 2018;29:1895

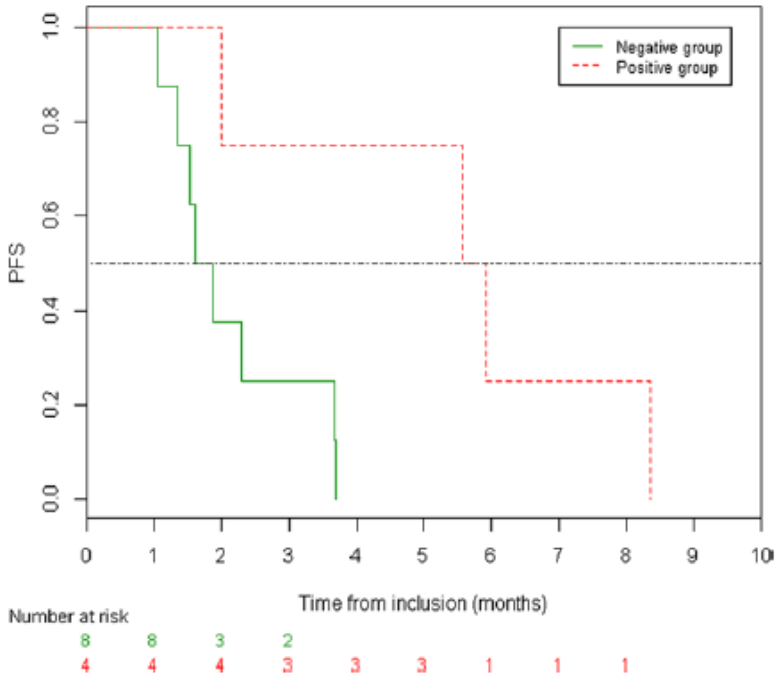
Perspectives

- **Improve treatment algorithms**

Perspectives

- **Improve treatment algorithms:**

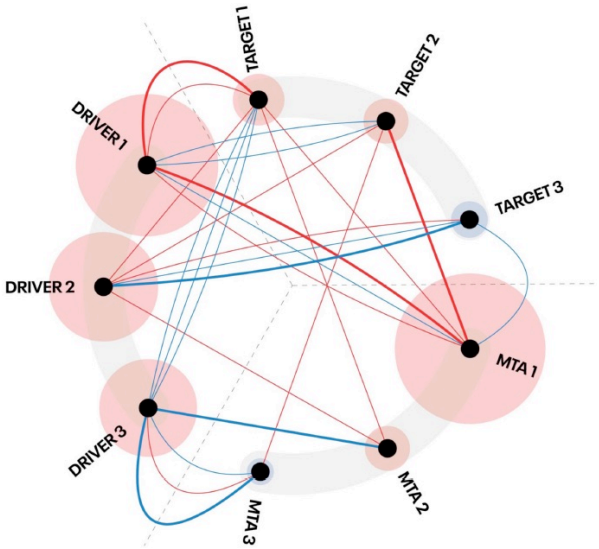
  - Use of **functional** assays

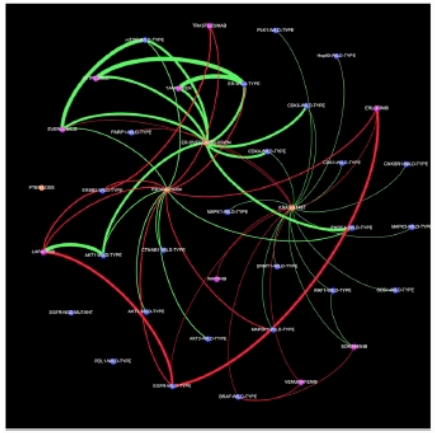


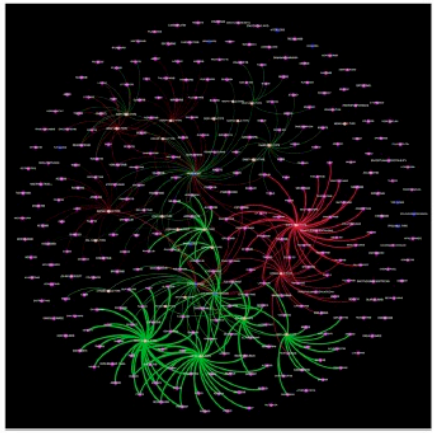
Kamal et al. Mol Oncol 2018;12:594-601

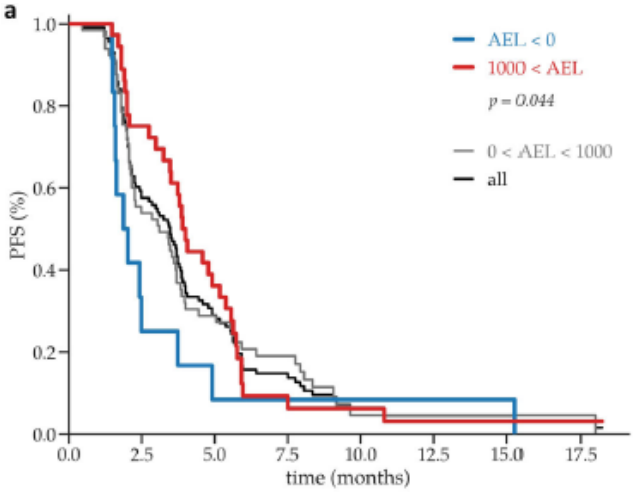
Challenges

- **Improve treatment algorithms:**
  - Use of **functional** assays
  - Use of **AI**







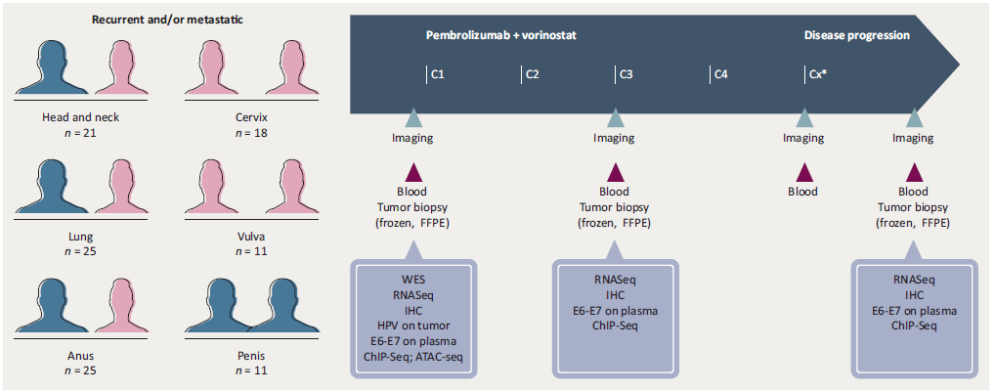


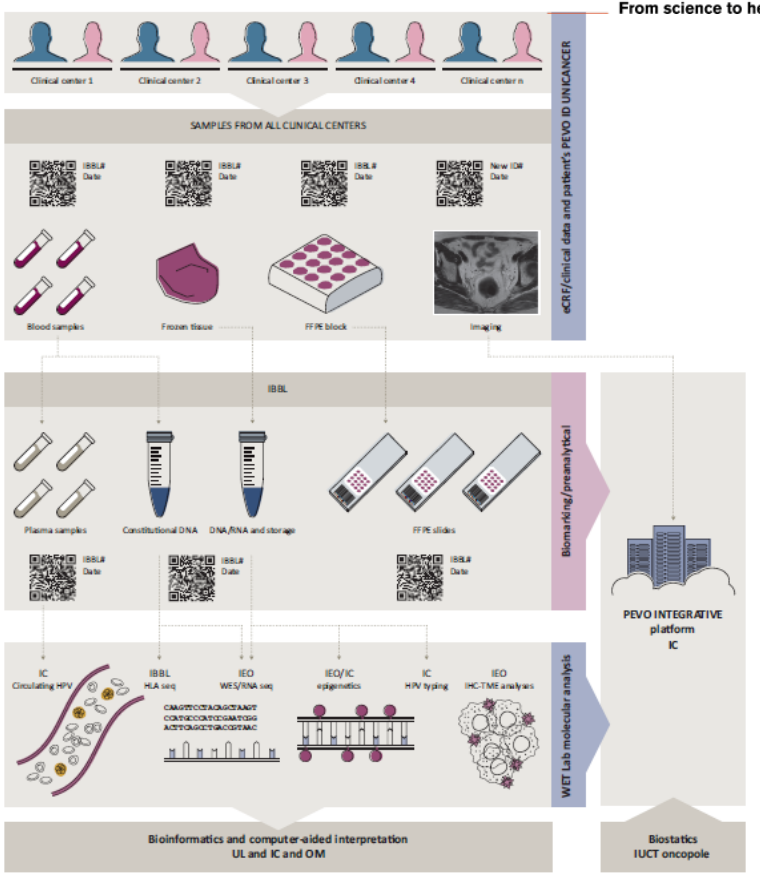
Petak et al. NPJ Precis Oncol 2021;5:59

Perspectives

- **Improve treatment algorithms:**
  - Use of **functional** assays
  - Use of **AI**
  - Reintegrate **pathology**!

PEVOdata





PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

MSD

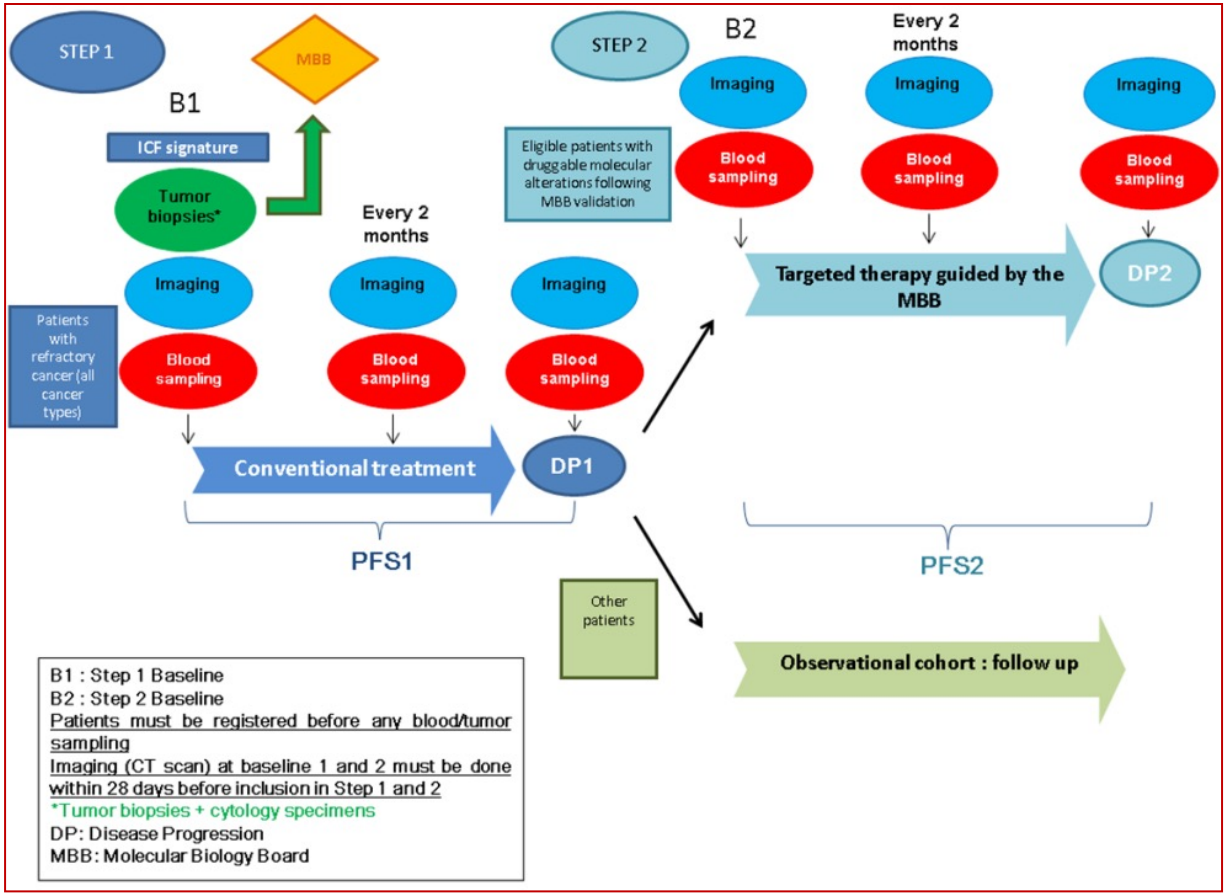
de Guillebon et al. ESMO Open 2021;6:100106

Perspectives

- **Improve treatment algorithms**
- **Overcome the challenge small patient populations**

  - PFS ratio

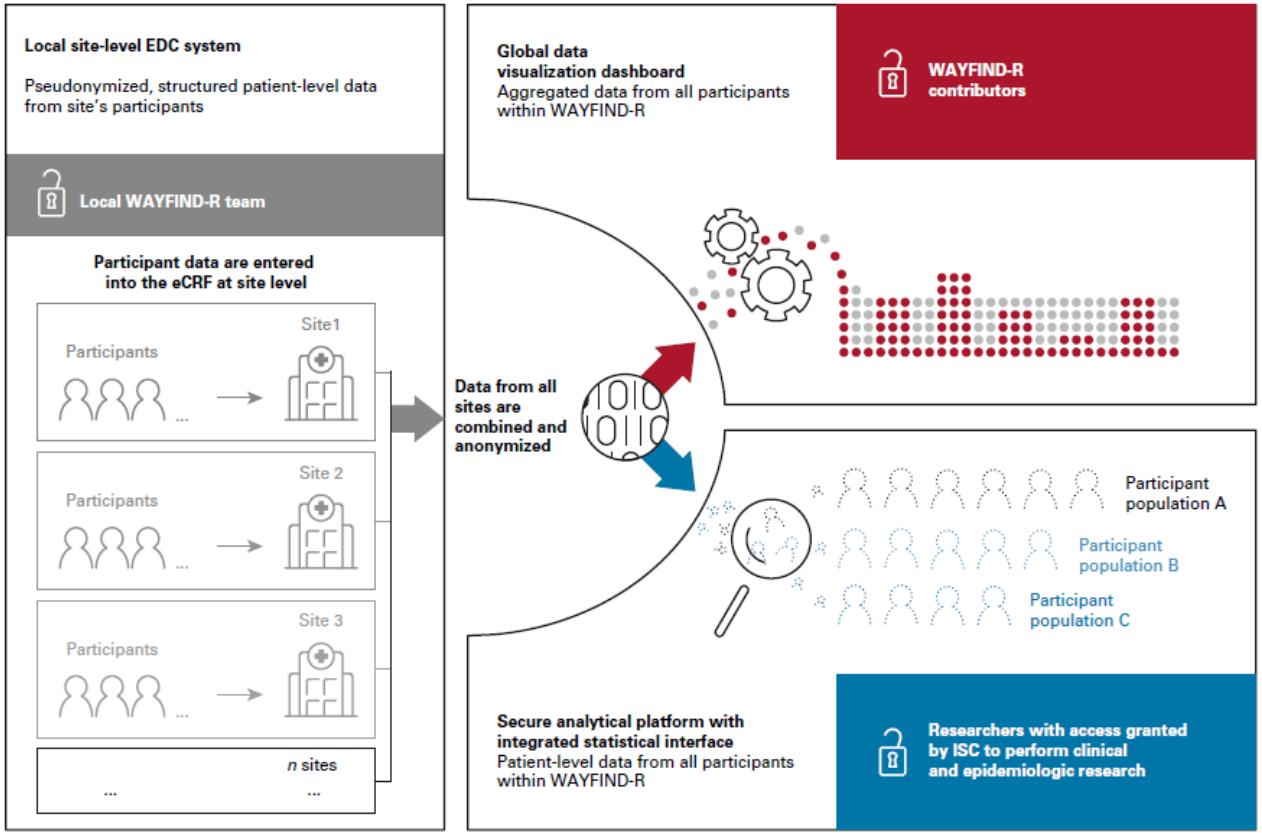
SHIVA02


STEP 1
MBB
B1
ICF signature
Tumor biopsies*
Every 2 months
Imaging
Blood sampling
Patients with refractory cancer (all cancer types)
Conventional treatment
DP1
PFS1
STEP 2
B2
Eligible patients with druggable molecular alterations following MBB validation
Every 2 months
Targeted therapy guided by the MBB
DP2
PFS2
Other patients
Observational cohort : follow up
B1 : Step 1 Baseline
B2 : Step 2 Baseline
Patients must be registered before any blood/tumor sampling
Imaging (CT scan) at baseline 1 and 2 must be done within 28 days before inclusion in Step 1 and 2
*Tumor biopsies + cytology specimens
DP: Disease Progression
MBB: Molecular Biology Board

Perspectives

- **Improve treatment algorithms**
- **Overcome the challenge small patient populations**
  - PFS ratio
  - Real World Data

WAYFIND-R



Le Tourneau et al. JCO Precis Oncol 2022; 6:e2200019

Conclusions

- The **ancestral** paradigm of **drug development** per **cancer type** remains **valid** for most of drugs under development

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Conclusions

- The **ancestral** paradigm of **drug development** per **cancer type** remains **valid** for most of drugs under development
- **Relevant** molecular alterations **across cancer types** have challenged this paradigm, opening the door to **precision medicine** in oncology
- **AI** and **RWD** will certainly play a major role in the future to move from **stratified medicine** to **precision medicine**

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Department of Drug Development and Innovation (D3i)
Christophe.LeTourneau@curie.fr

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