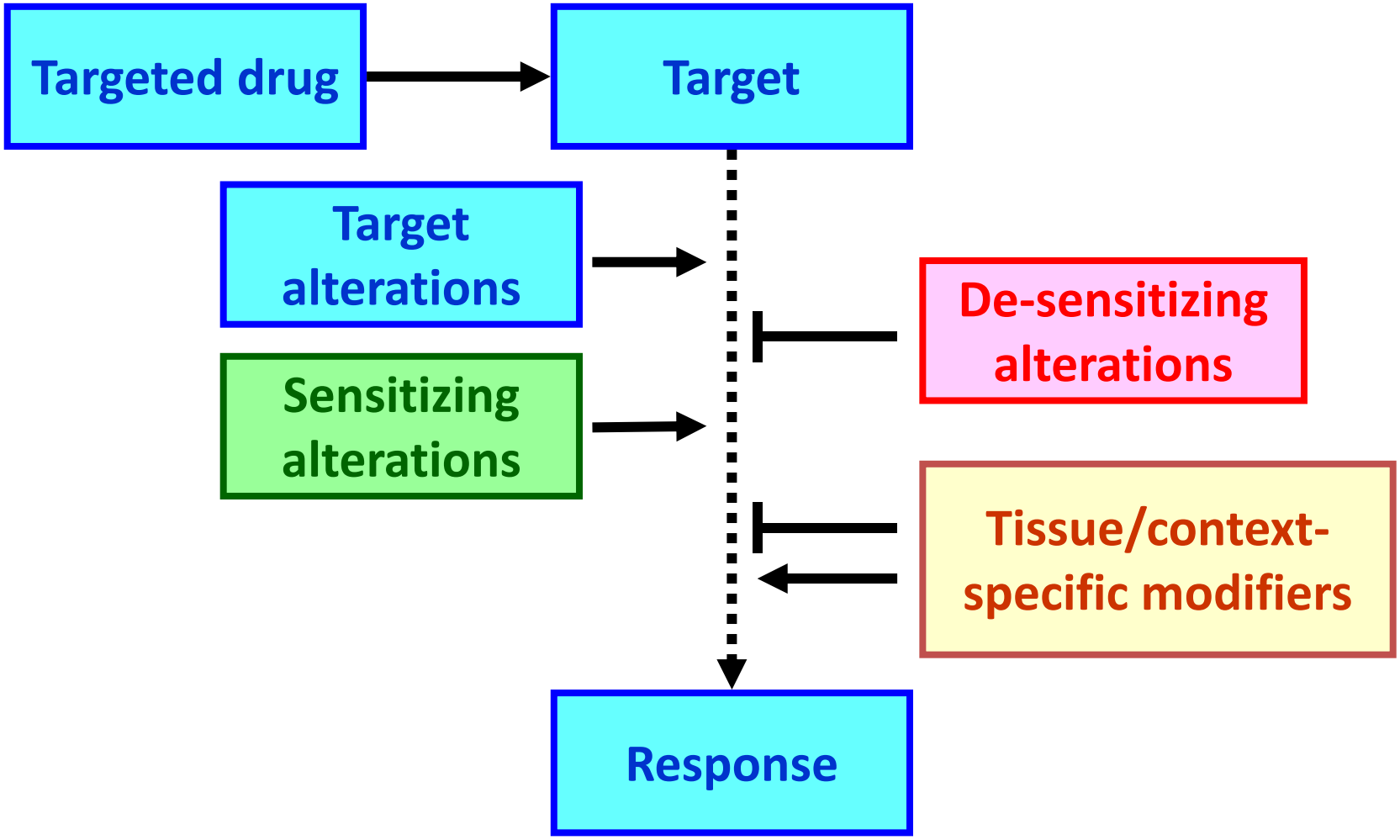
Patient-Derived Xenograft (PDX) models as an emerging way to personalized medicine in translational cancer research

Enzo Medico

EurOPDX Consortium

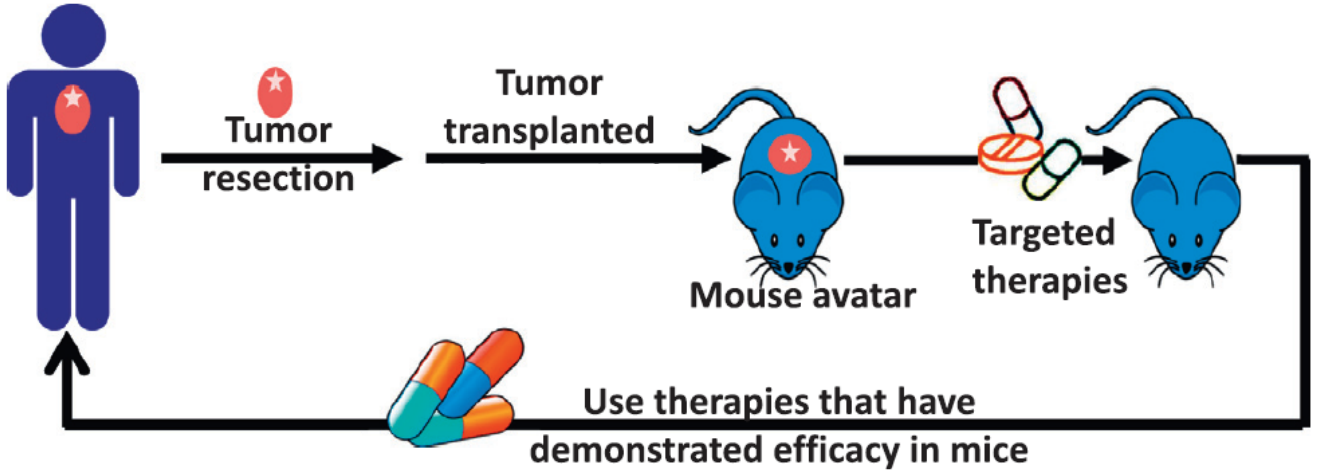
Towards precision cancer medicine



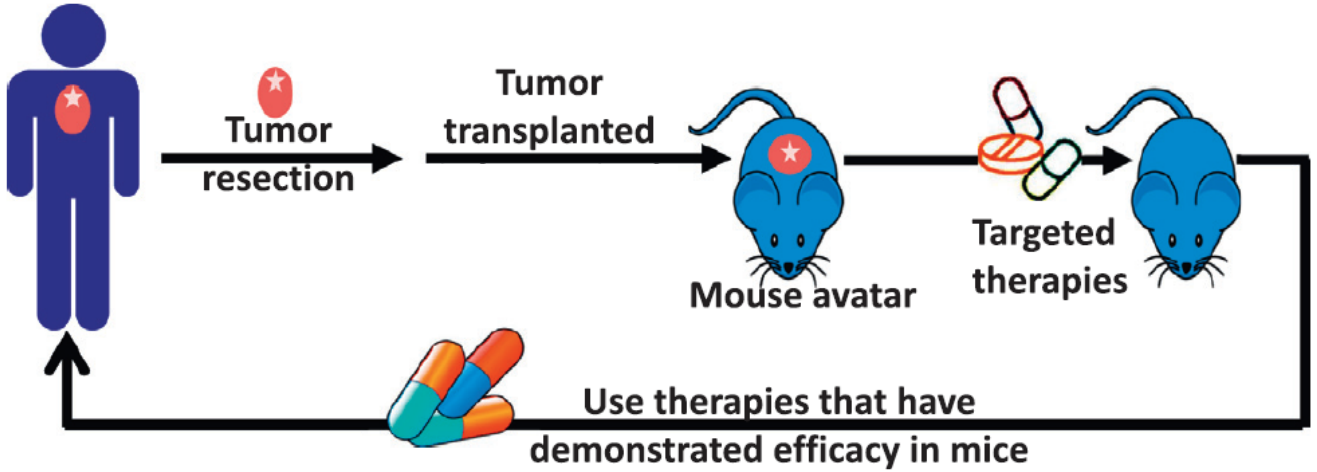
Further elements of complexity

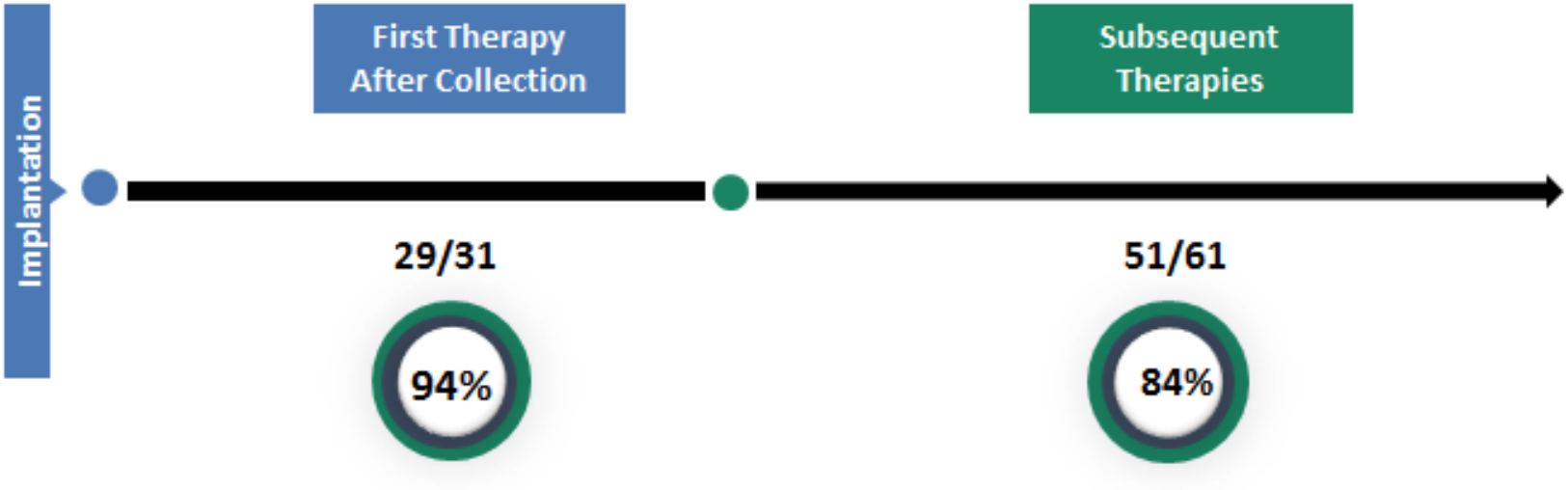
- Intratumoral heterogeneity
  - De-sensitizing lesions only present in a fraction of the cancer cells may lead to early recurrence
- Intracellular signaling is governed by networks
  - Dynamic adaptation to altered signaling.
- Tumor-host interactions
  - Tumor growth and response also depends on stroma, vasculature, inflammation and immune response

Patient-Derived mouse Xenografts (PDXs): the “Avatar” concept

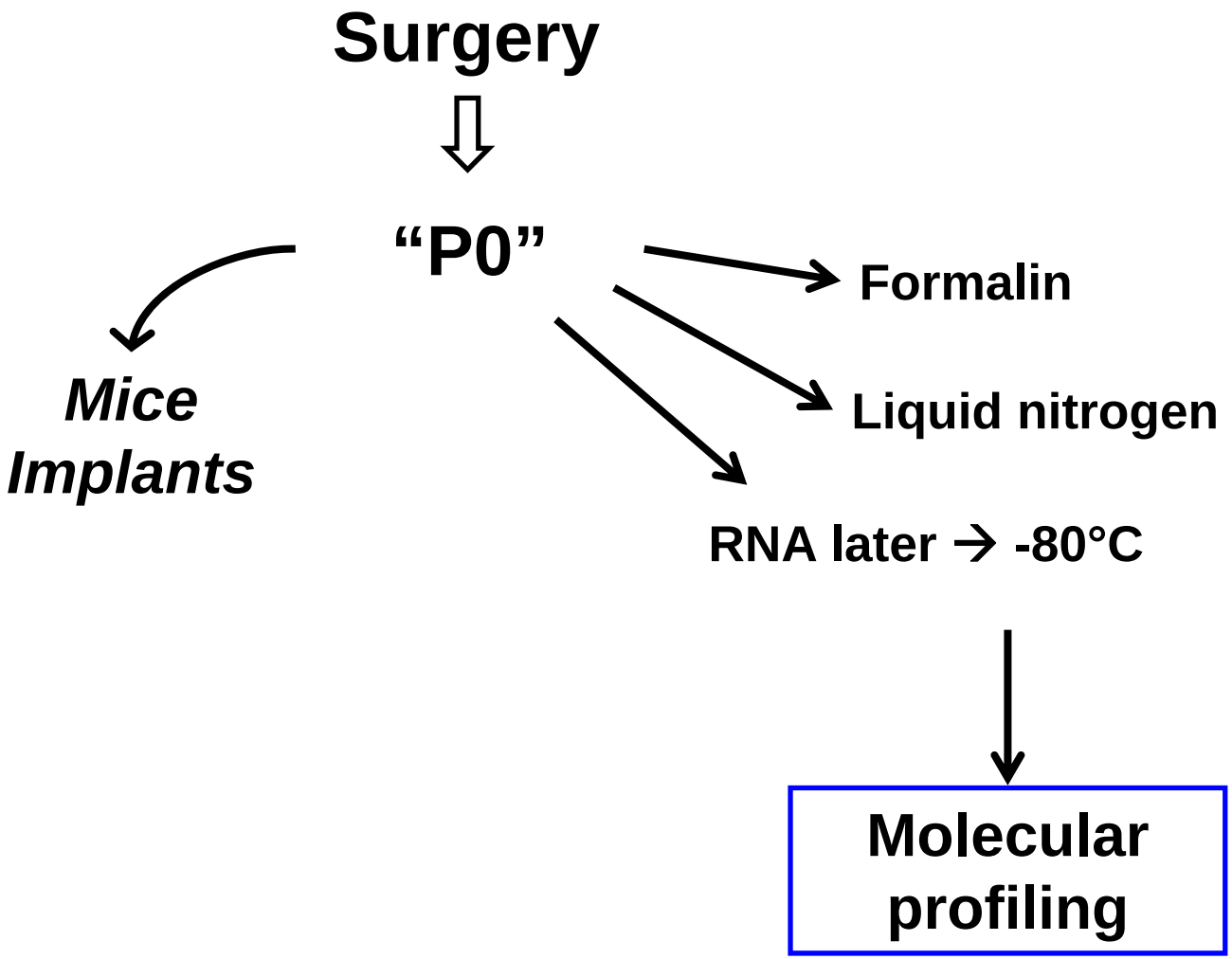


Patient-Derived mouse Xenografts (PDXs): the “Avatar” concept

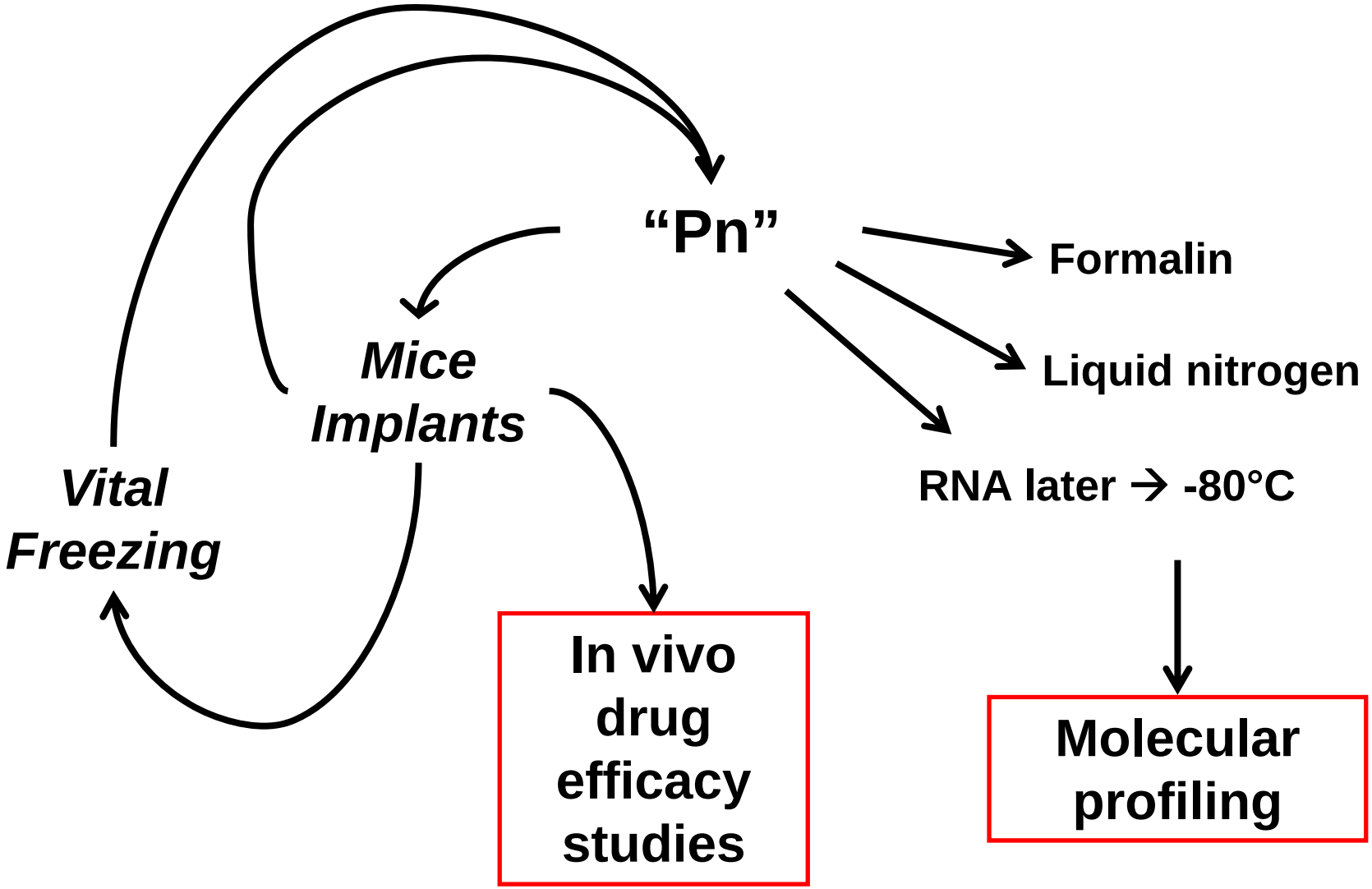




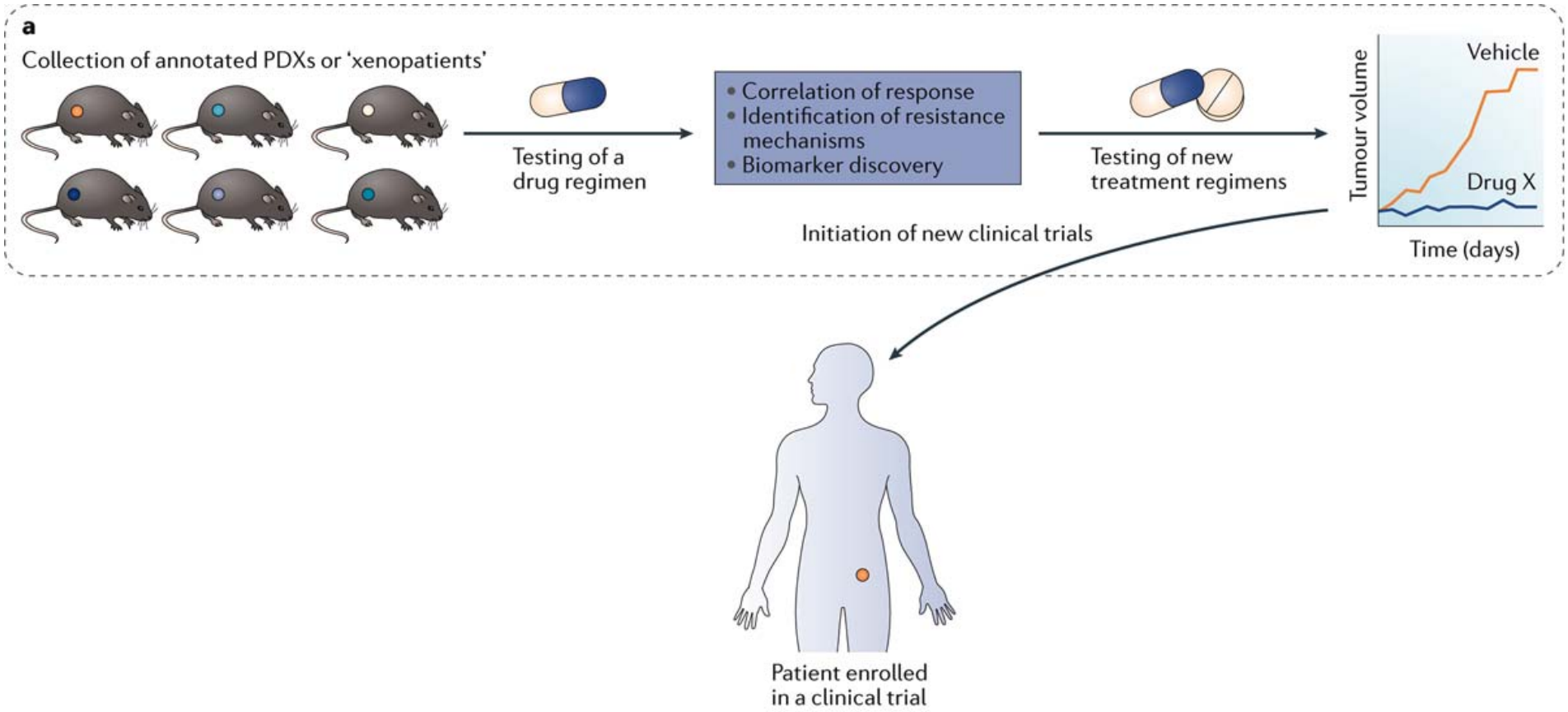
Propagation, biobanking and profiling of PDXs



Propagation, biobanking and profiling of PDXs

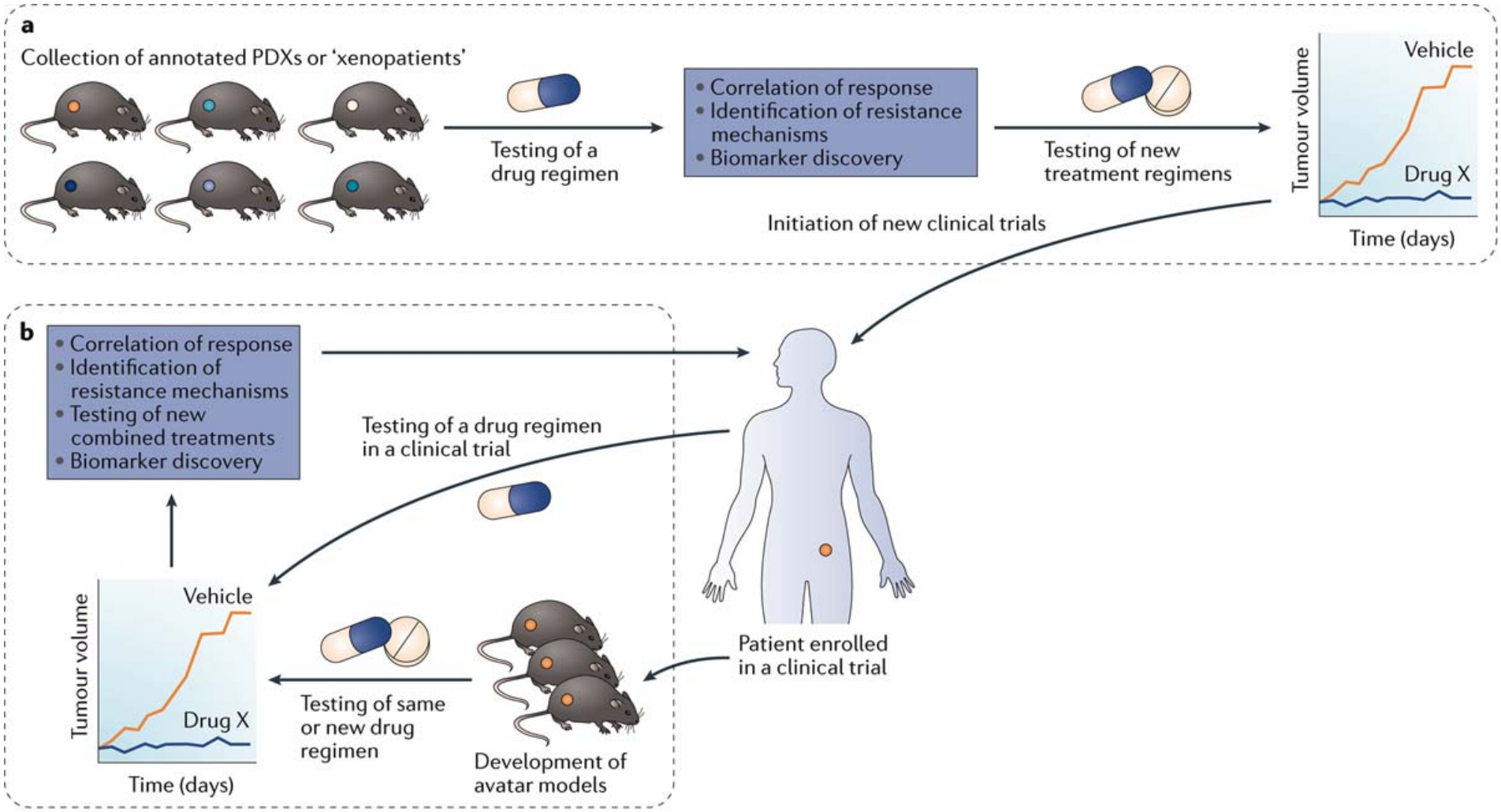


PDX preclinical study designs



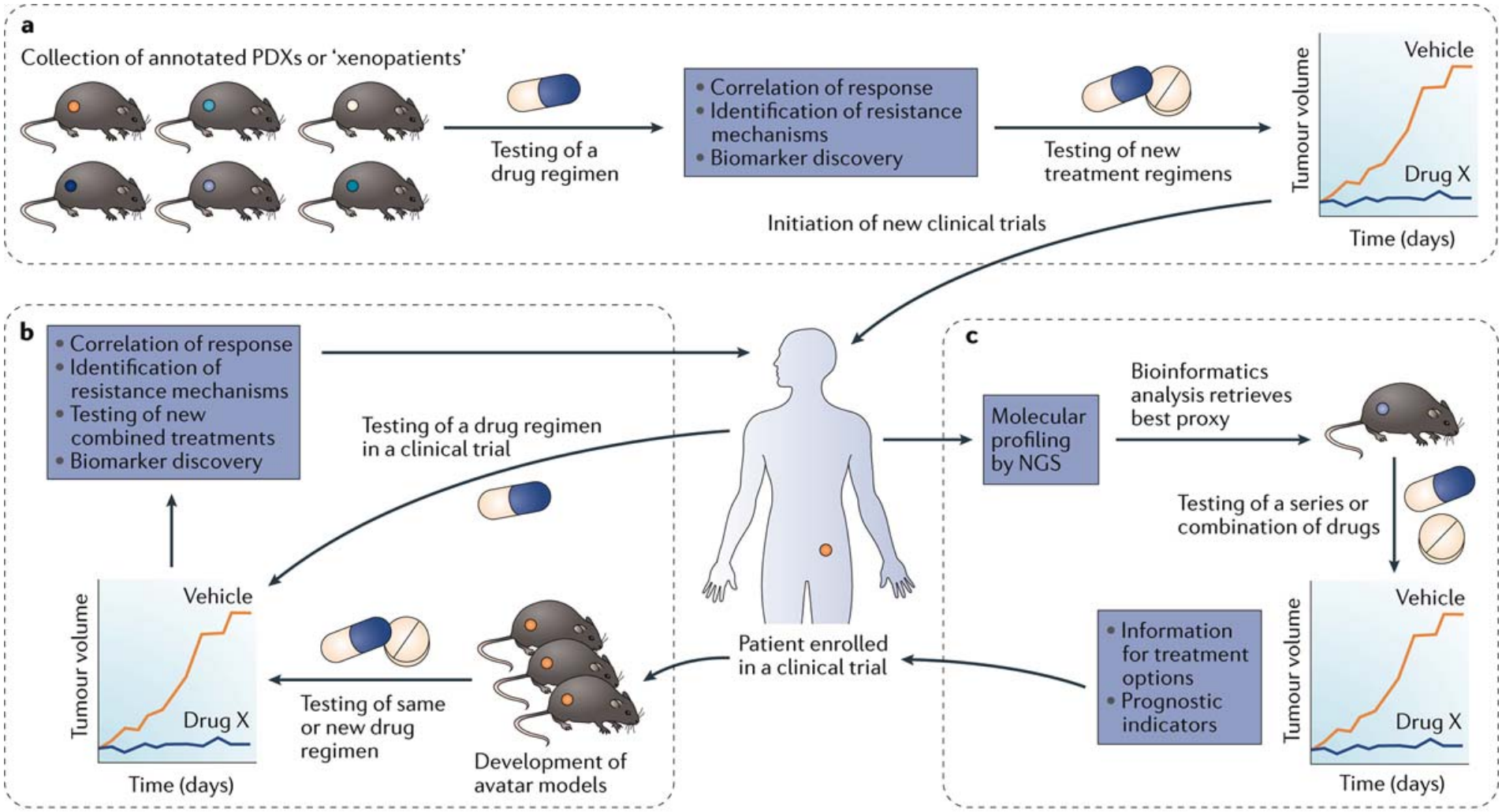
Nature Reviews | Cancer

PDX preclinical study designs



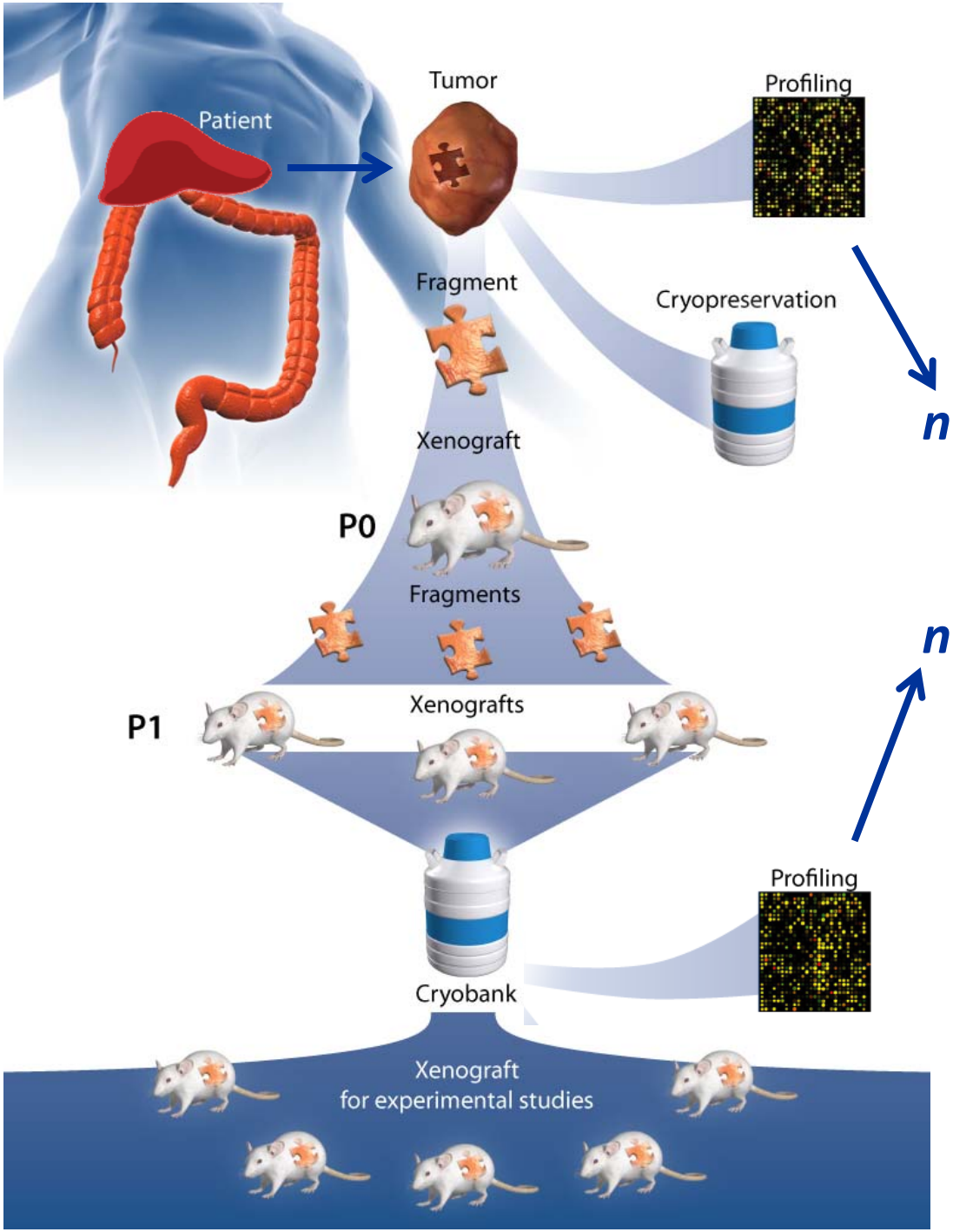
Nature Reviews | Cancer

PDX preclinical study designs



Nature Reviews | Cancer

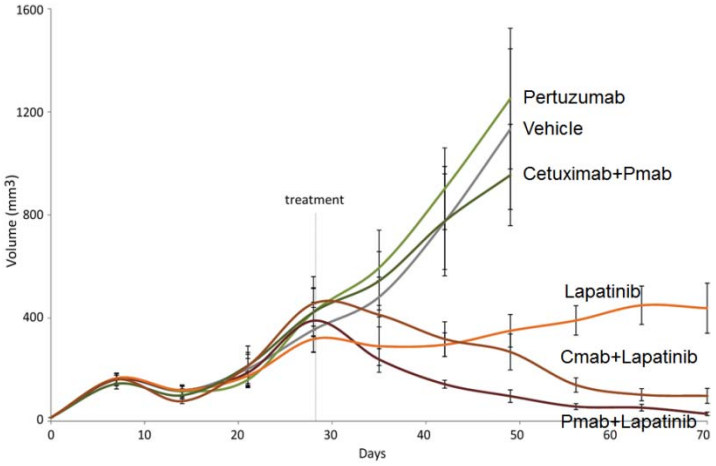
CRC PDXs at Candiolo



n = 180

n = 110

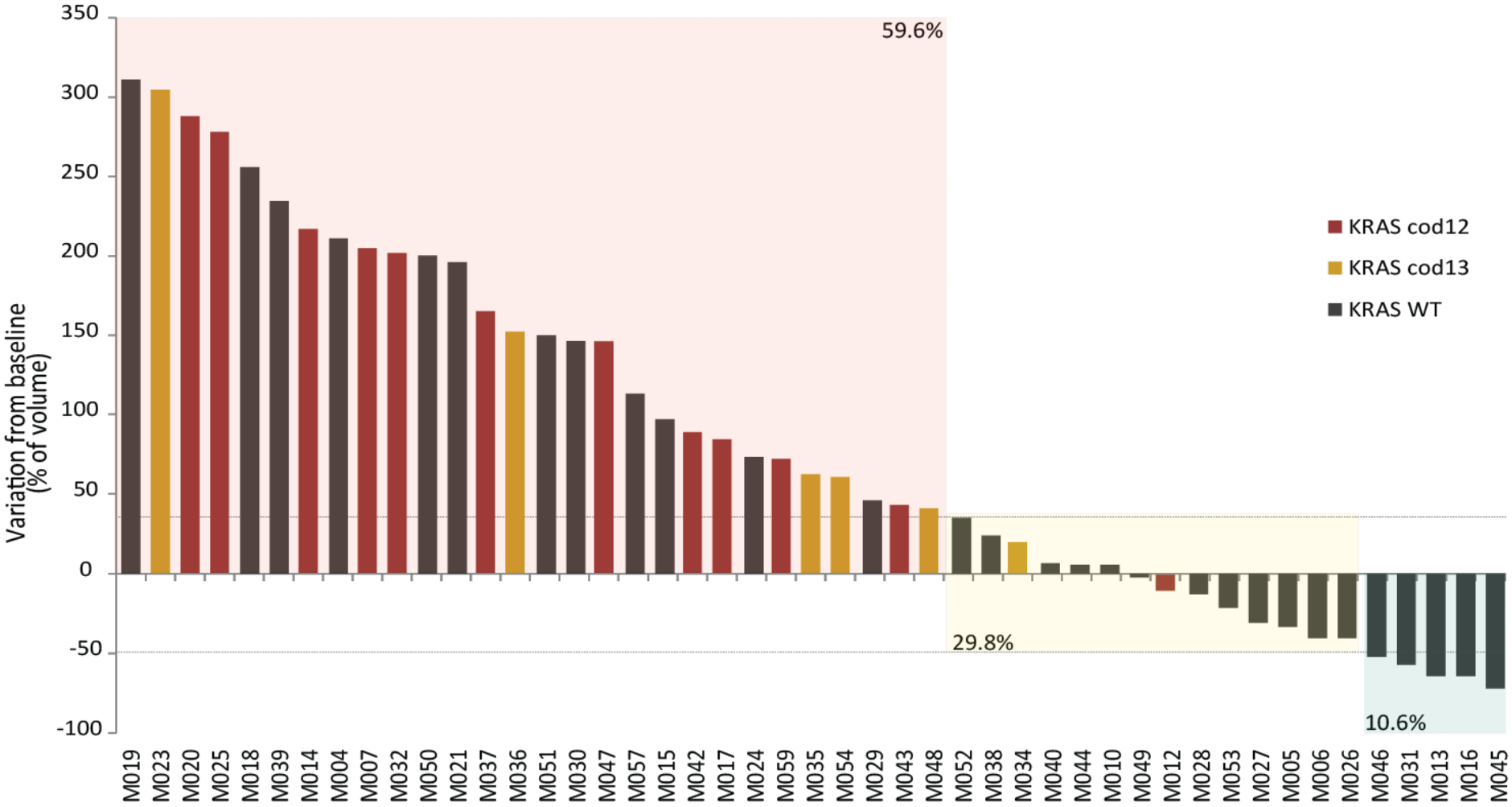
n = 515



Bertotti et al, Cancer Discovery 2011

Predictive biomarkers of response to cetuximab

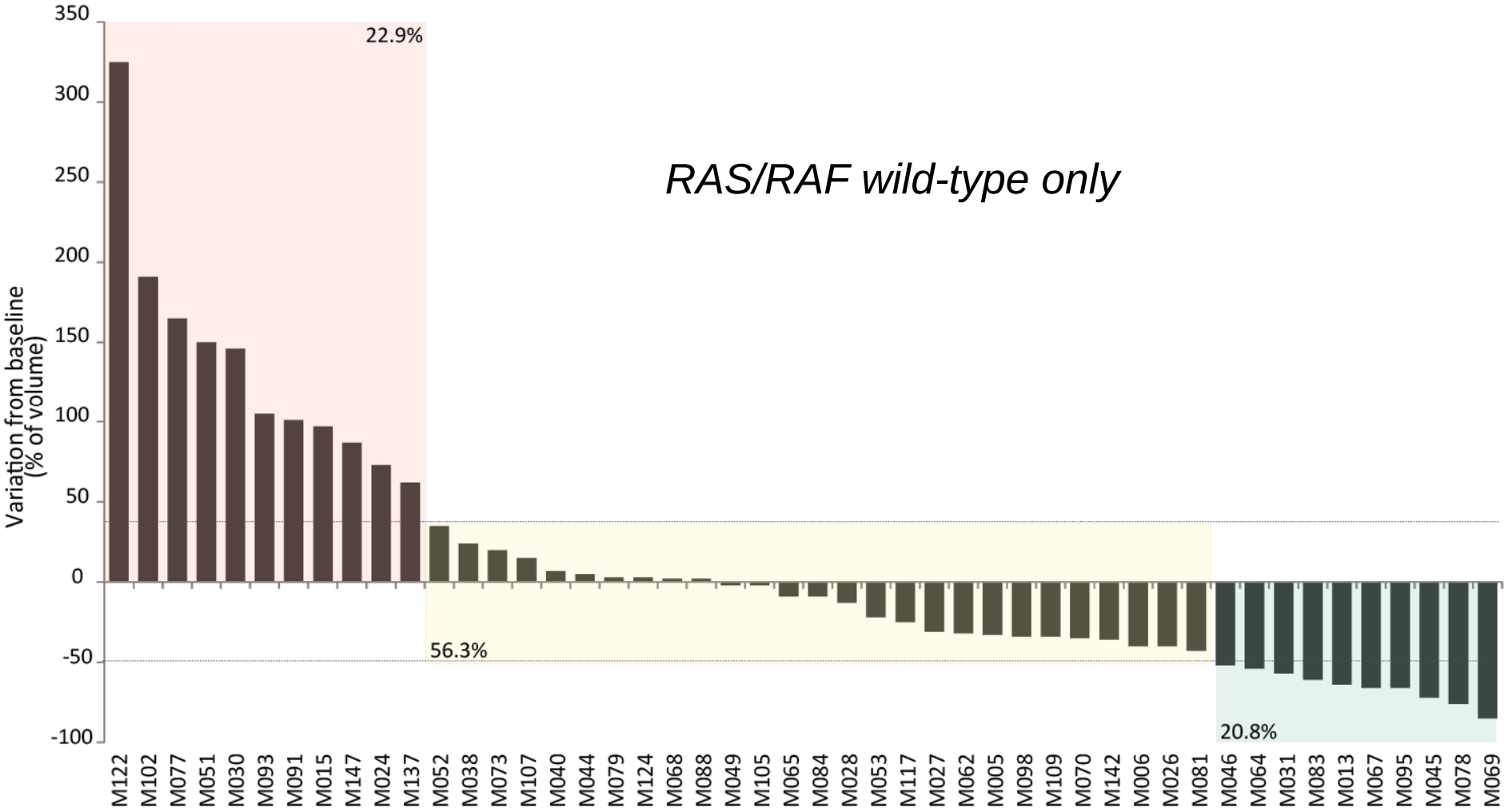
Genetic status affects PDX response like in patients



Bertotti et al, Cancer Discovery 2011

Predictive biomarkers of response to cetuximab

Genetic selection affects response rate

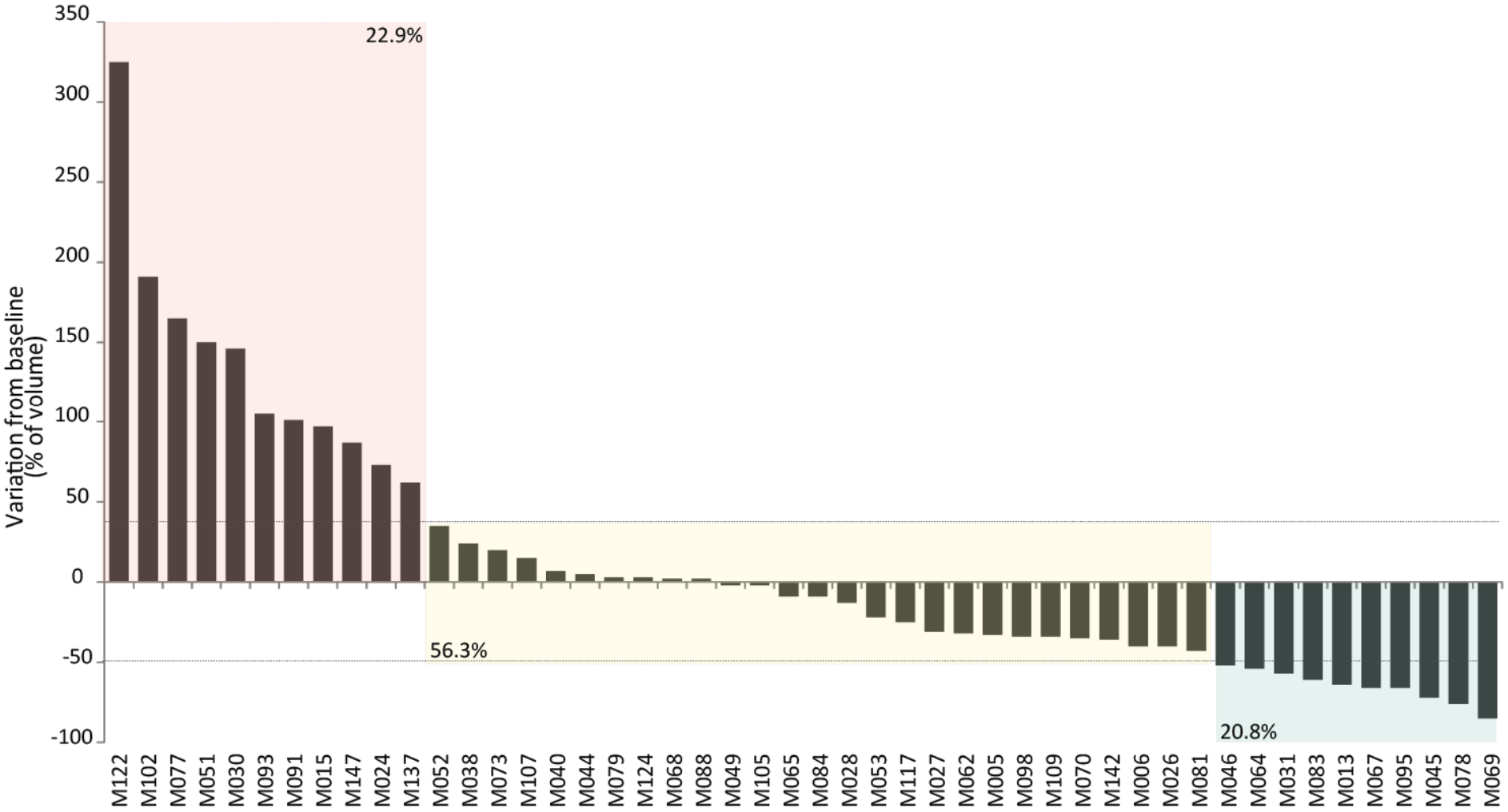


RAS/RAF wild-type only

Bertotti et al, Cancer Discovery 2011

Predictive biomarkers of response to cetuximab

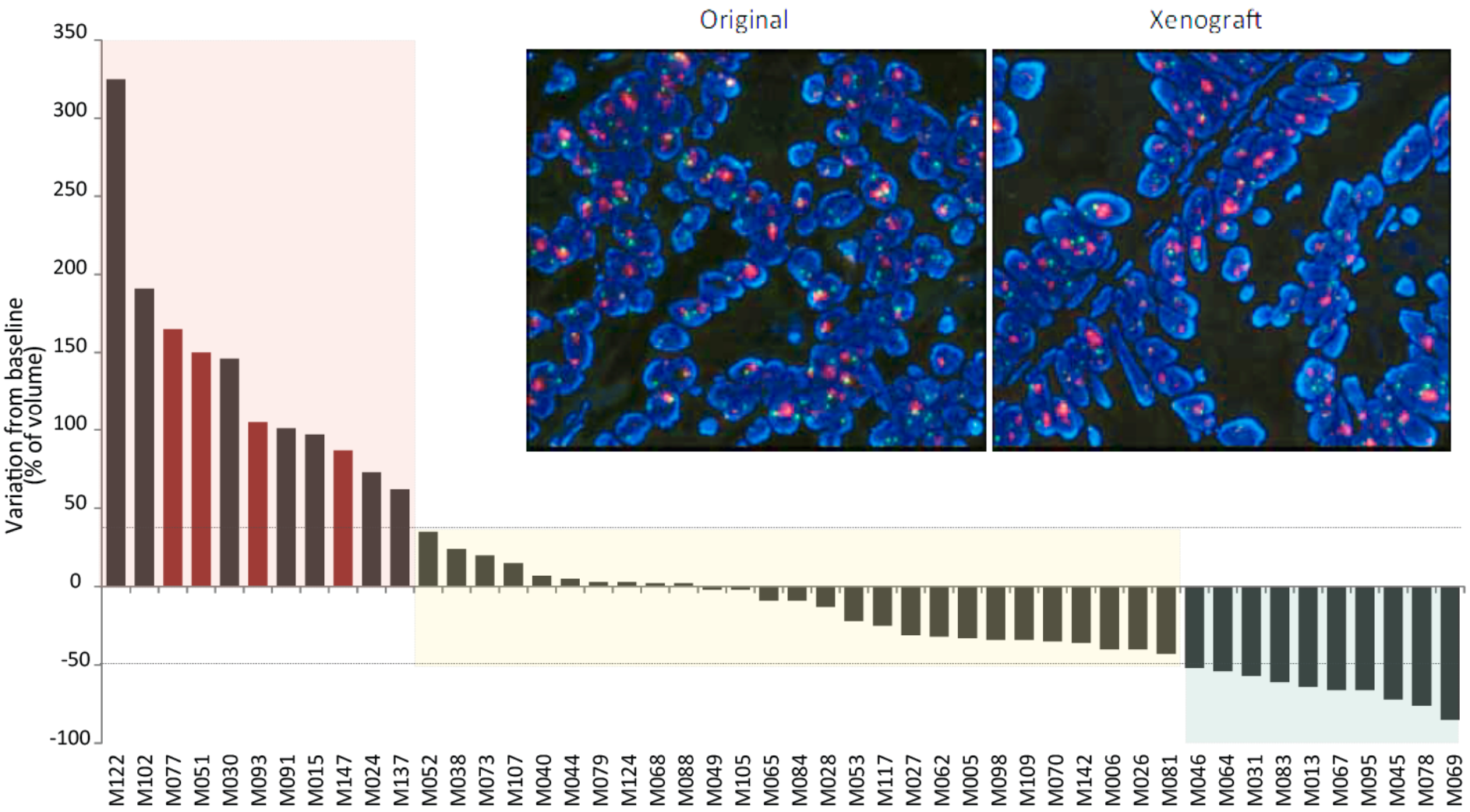
Other genetic biomarkers of resistance?



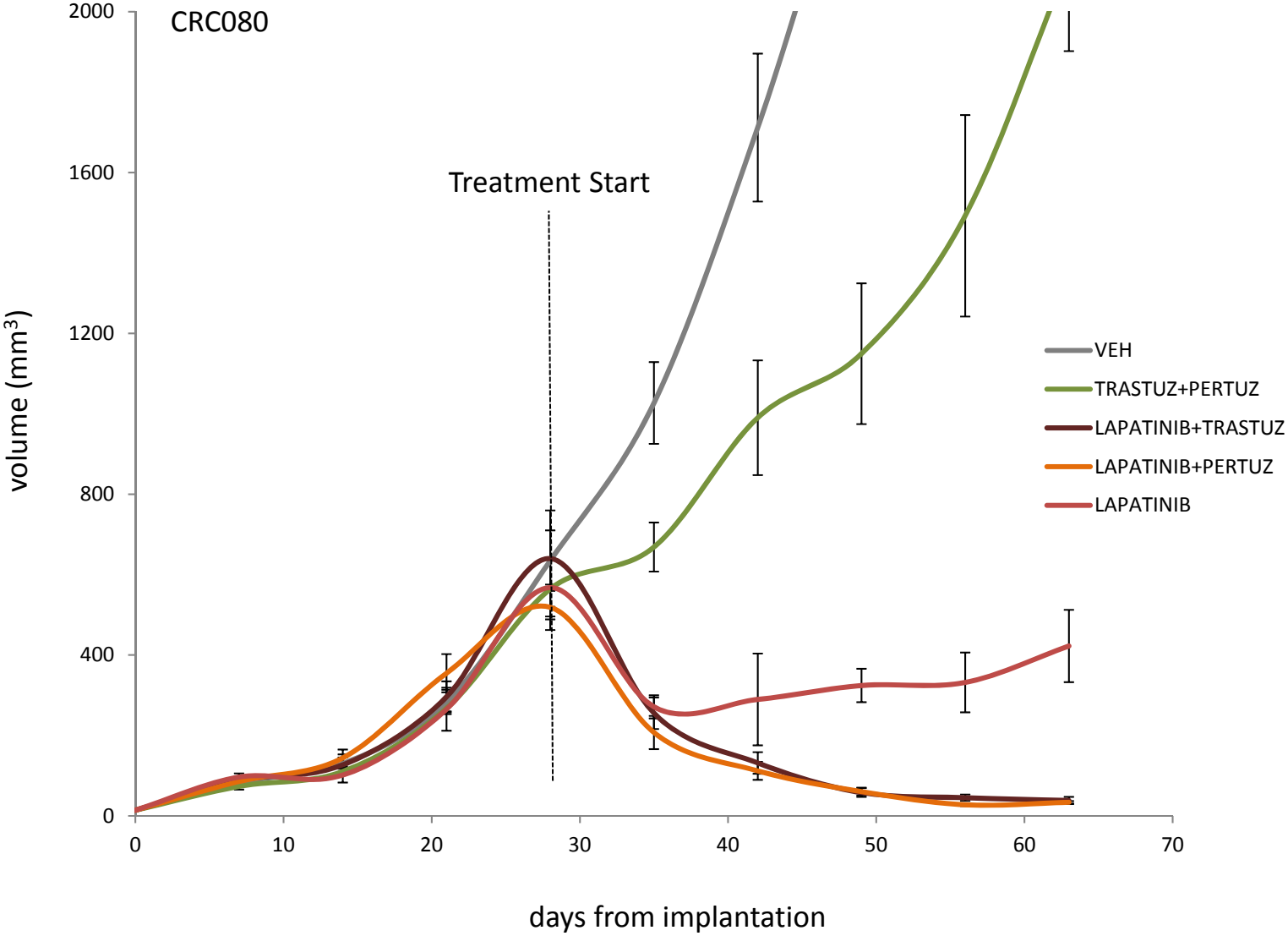
Bertotti et al, Cancer Discovery 2011

Predictive biomarkers of response to cetuximab

HER2 amplification is enriched in cetuximab-resistant PDXs



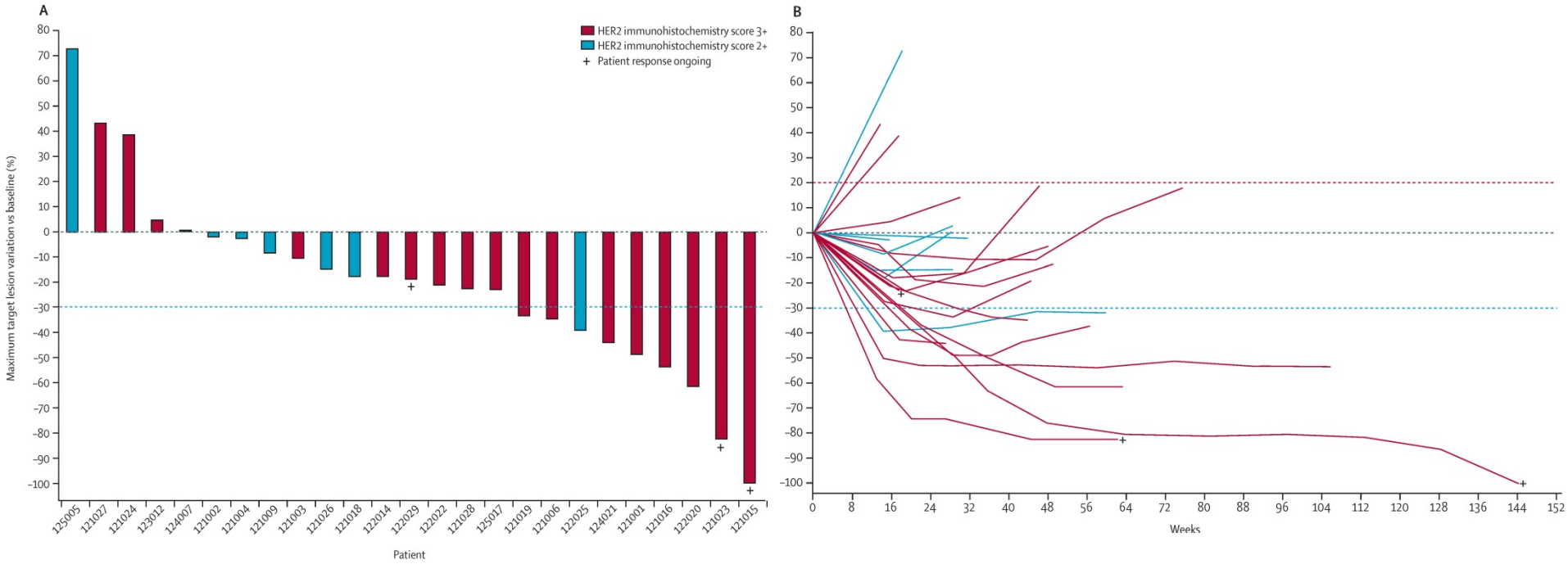
Only certain anti-EGFR + anti-HER2 combinations induce tumour shrinkage in HER2-amplified CRCs



The HERACLES trial: Targeting HER2 in KRAS WT, cetuximab-resistant mCRC

Heracles and the Hydra (Early Hellenistic Period), Musei Capitolini, Rome

The HERACLES Trial: from “Xenopatients” to patients



Sartore-Bianchi et al., *Lancet Oncology* 2016

Opportunities arising from a European PDX community

- **Recapitulate inter-tumor heterogeneity** through assembly of large collections
- **“Pan-cancer” preclinical approaches** may become feasible
- **Standardization and benchmarking** of pharmacological and molecular profiling
- **Wider range of expertise** in technological platforms applied to PDX

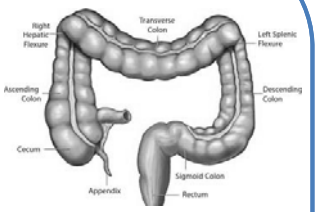
EurOPDX Consortium at a glance

- **Launched in 2013**
- **19 academic institutions** in Europe and the US, among which **6 Comprehensive Cancer Centres**
- Each institution is part of an hospital or is collaborating with a neighbouring one.
- **Expertise in basic, preclinical, translational and clinical oncology**

EurOPDX

Details of the collection for some pathologies

Colorectal cancer (754)



- 291 primary tumors
- 444 liver mets
- 4 lung mets
- 15 other mets

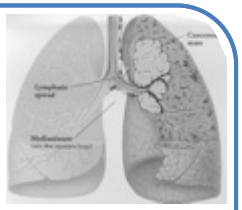
Characterization: 400 + already characterized by transcriptome arrays and targeted sequencing, but also 140+ by WES and 250+ drug monitoring

Pancreatic cancer (235)

Characterization: 120+ transcriptomic, 100+ CGH, 120+ WES, 20+ WGS, 70+ RNAseq, 70+ MiR

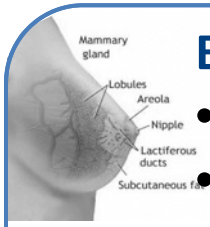
1500+ subcutaneous and orthotopic models - 30+ different pathologies

Lung cancer (71)



- 59 NSCLC
- 12 SCLC

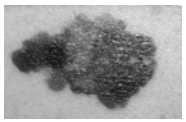
Characterization: targeted seq, 20+ transcriptomic



Breast cancer (161)

- 54 luminal
- 89 triple negative
- 18 HER2+

Characterization: 40+ CGH, 90+ transcriptomic, 40+ WES, 55+ drug monitoring



Skin melanoma (136)

20+ WES, 40+ gene panel, drug monitoring

More info on www.europdx.eu

Standards

- **minimal information on the models**: workshop in Nov. 2014 + development of global standards in collaboration with EBI-EMBL (Terry Meehan) > Article Meehan TF et al., published in a special informatics issue of Cancer Research on November 1st

Focus on Computer Resources

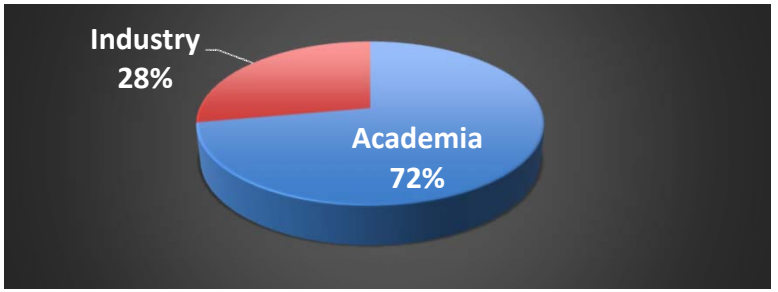
Cancer Research

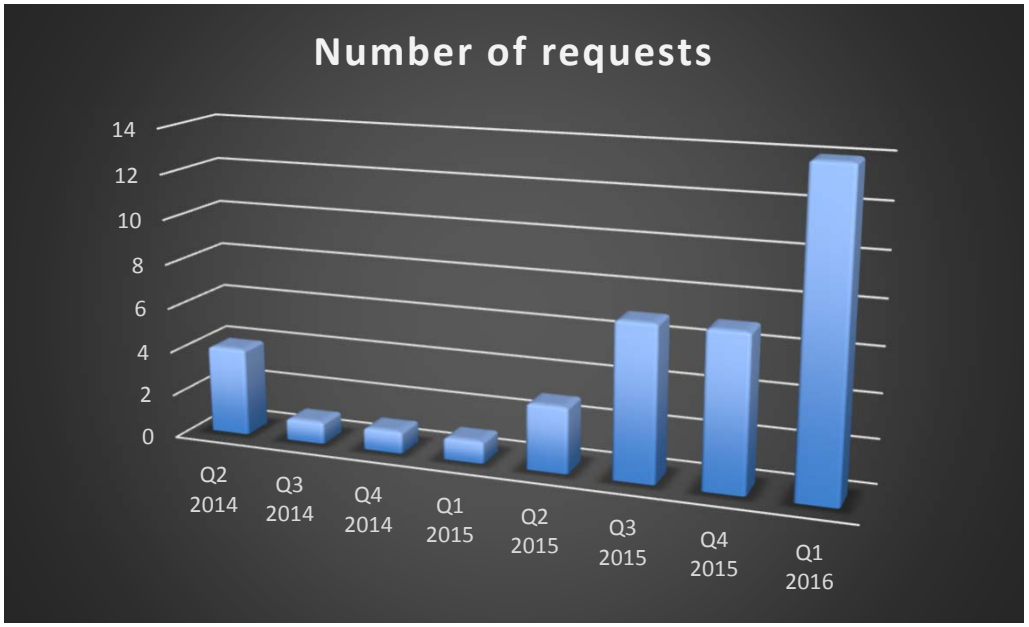
PDX-MI: Minimal Information for Patient-Derived Tumor Xenograft Models

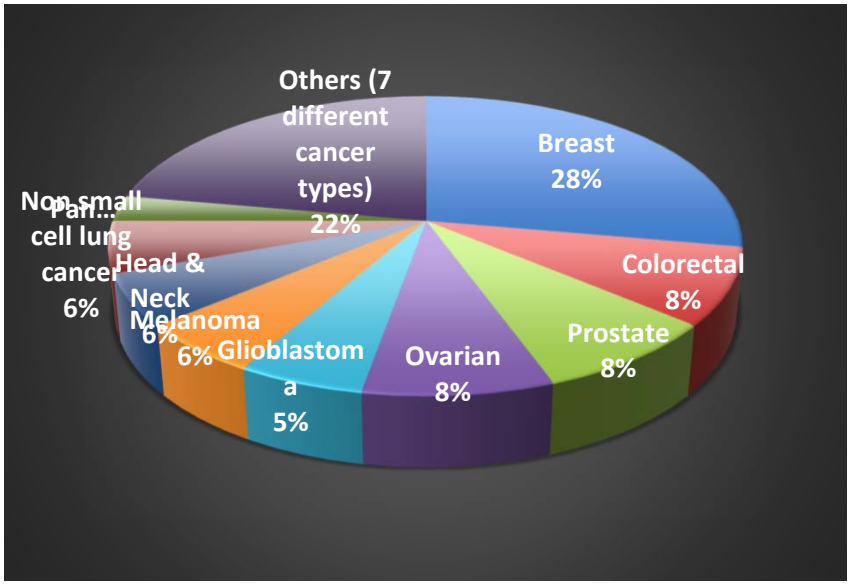
Terrence F. Meehan[1], Nathalie Conte[1], Theodore Goldstein[2], Giorgio Inghirami[3], Mark A. Murakami[4], Sebastian Brabetz[5,6], Zhiping Gu[7], Jeffrey A. Wiser[7], Patrick Dunn[7], Dale A. Begley[8], Debra M. Krupke[8], Andrea Bertotti[9], Alejandra Bruna[10], Matthew H. Brush[11], Annette T. Byrne[12], Carlos Caldas[10], Amanda L. Christie[4], Dominic A. Clark[1], Heidi Dowst[13], Jonathan R. Dry[14], James H. Doroshow[15], Olivier Duchamp[16], Yvonne A. Evrard[17], Stephane Ferretti[18], Kristopher K. Frese[19], Neal C. Goodwin[20], Danielle Greenawalt[21], Melissa A. Haendel[11], Els Hermans[22], Peter J. Houghton[23], Jos Jonkers[24], Kristel Kemper[24], Tin O. Khor[25], Michael T. Lewis[26], K.C. Kent Lloyd[27], Jeremy Mason[1], Enzo Medico[9], Steven B. Neuhauser[8], James M. Olson[28], Daniel S. Peeper[24], Oscar M. Rueda[10], Je Kyung Seong[29], Livio Trusolino[9], Emilie Vinolo[30], Robert J. Wechsler-Reya[31], David M. Weinstock[4], Alana Welm[32], S. John Weroha[33], Frédéric Amant[24,34], Stefan M. Pfister[5,6,35], Marcel Kool[5,6], Helen Parkinson[1], Atul J. Butte[2], and Carol J. Bult[8]

EDIReX: EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts

- Successful Proposal to call INFRAIA-2-2017 “Integrating Activities for Starting Communities” – Activities start in 2018
- To fulfill a clear need for access to PDX models from the scientific community:
  - **Model delivery/deposit**
  - **Drug efficacy studies**







The EDIReX partnership

#			Name	Country
EurOPDX members	1	N	IT	Università Di Torino	Italy
	2	N		Katholieke Universiteit Leuven	Belgium
	3	N		CRUK - University Of Cambridge	UK
	4	N		Institut Curie	France
	5	N		Institut D'investigacio Oncologica De Vall-hebron	Spain
	6	N		Centro Nacional De Investigaciones Oncologicas	Spain
	7		IT	Masarykova Univerzita	Czech Rep
	8			Royal College Of Surgeons In Ireland	Ireland
	9			Institut Catala D'oncologia	Spain
	10			University Of Manchester	UK
	11			Academisch Ziekenhuis Groningen	Netherlands
	12			Oslo Universitetssykehus Hf	Norway
	13			Istituto Europeo Di Oncologia	Italy
	14			University Of Glasgow	UK
	15	N		Nederlands Kanker Instituut	Netherlands
	16		IT	EMBL-EBI	Germany-UK
SMEs	17		IT	Kairos3d Srl	Italy
	18			Ocello Bv	Netherlands
	19			Seeding Science	France

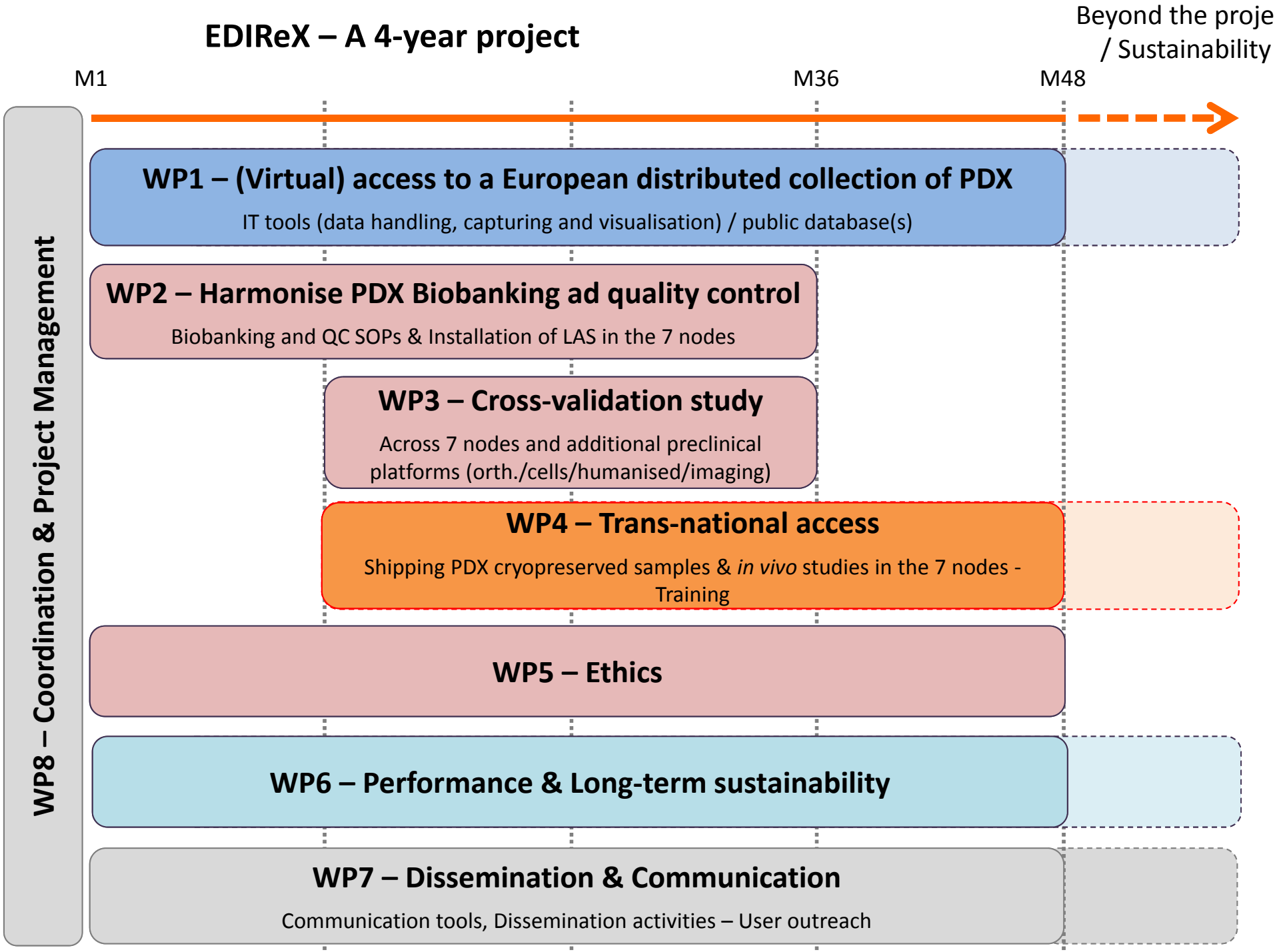
BBMRI gateway for health

National Cancer Institute

3D data view

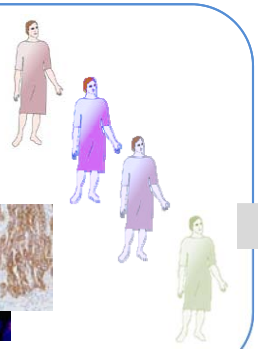
***Ex vivo* cells**

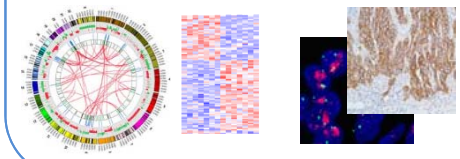
Project MGT


EDIReX – A 4-year project
Beyond the proje
/ Sustainability
M1
M36
M48
WP8 – Coordination & Project Management
WP1 – (Virtual) access to a European distributed collection of PDX
IT tools (data handling, capturing and visualisation) / public database(s)
WP2 – Harmonise PDX Biobanking ad quality control
Biobanking and QC SOPs & Installation of LAS in the 7 nodes
WP3 – Cross-validation study
Across 7 nodes and additional preclinical platforms (orth./cells/humanised/imaging)
WP4 – Trans-national access
Shipping PDX cryopreserved samples & *in vivo* studies in the 7 nodes - Training
WP5 – Ethics
WP6 – Performance & Long-term sustainability
WP7 – Dissemination & Communication
Communication tools, Dissemination activities – User outreach

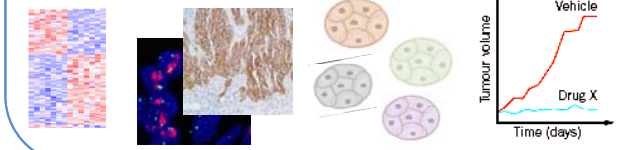
A precision oncology perspective

Patients
- Clinical data
- Histology
- Molecular profiles

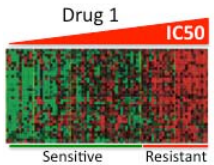




Patient-derived models (xenografts, cell cultures)
- Histology
- Molecular profiles
- Pharmacology



Public data
- Molecular datasets
- Pharmacogenomics
- Biomarker signatures

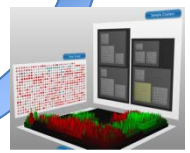


Capture, Storage, Standardisation

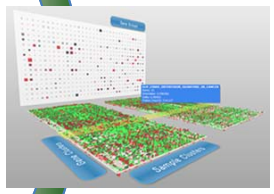
Data integration, analysis and visualisation

Individual patient

Diagnosis, prognosis and therapeutic decision.



Integrative visual reports



Data mining

Bioinformatician/ Translational researcher

New biomarker / stratification hypotheses

Possible interactions with INFRAFRONTIER

- Phenotyping/imaging capabilities
  - Drug efficacy studies
  - Modeling metastasis
  - Monitoring side effects of drug combinations
- Genetic engineering to improve PDX models
  - Facilitating tumour engraftment
  - Facilitating reconstitution of a human immune system
  - "Humanizing" mouse MHC
- Integrating PDX and mouse tumorigenesis models
- "Health passport", QC etc.
- Biobanking

EurOPDX

Translating Knowledge in Oncology

Visit www.europdx.eu for the latest news about the Consortium

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Enzo Medico, EDIReX Coordinator (enzo.medico@ircc.it)

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SAVE THE DATE