SESSION INAUGURALE

Phases Précoces en cancérologie : Vision 2030 !

Modérateur : Fabrice Barlesi

Avec la participation de : Jean-Yves Blay, Olivier Rixe

La prochaine decade en Recherche Clinique Precoce

PHASES PRECOCES EN CANCEROLOGIE

Novembre 2024

Olivier Rixe, MD, PhD

Conflict of Interest

- I am French!

Next generation of… study sites

1990

2024

Next generation of…investigators

CPT-11

The European Experience

J. P. ARMAND,[a] C. TERRET, C. COUTEAU, AND O. RIXE

Institut Gustave Roussy
39 rue Camille Desmoulins
94805 Villejuif Cedex, France

INTRODUCTION

CPT-11 (irinotecan) is a semi-synthetic agent derived from camptothecin, an alkaloid isolated from the Chinese tree, *Camptotheca acuminata*. It differs from camptothecin by virtue of the substitution of a piperidine lateral chain, which makes it more water-soluble.

CPT-11 has an original and unique mechanism of action. Its anti-tumor activity is due to its inhibition of DNA topoisomerase I, the enzyme which is responsible for controlling the topology of DNA during the replication phase. The enzyme induces transient breaks in single DNA strands which potentiate the action of polymerases and replication of the DNA double helix. CPT-11 stabilizes the cleavable complex formed at numerous sites on the double helix by topoisomerase I and DNA. This stabilized cleavage complex causes the arrest of the replication fork which, in turn, results in the inhibition of DNA synthesis, and ultimately cell death.[1,2]

In preclinical trials, CPT-11 showed cytotoxic activity against colony-forming units (CFUs) obtained from non-small cell, colorectal, ovarian, breast and lung tumors, as well as mesotheliomas.[3] CPT-11 has also demonstrated excellent activity against xenografted human tumors in nude mice, including colonic and bronchial epidermoid cancer.[4] Tumoral cell lines showing pleïotropic resistance have also been shown to be sensitive to CPT-11.[5] Finally, CPT-11 has no cross-resistance with topotecan, another topoisomerase I inhibitor.[6]

In vivo, CPT-11 is converted into an active metabolite, SN-38 (7-ethyl-10-hydroxy-camptothecin) in the liver. Preclinical trials suggest that CPT-11 acts as a 'pro-drug' and that its anti-tumor activity is due to SN-38. *In vitro*, SN-38 inhibits topoisomerase I activity with a potency that is 250- to 1,000-fold greater than that of CPT-11.[7,8] It has been shown that the lactone form of SN-38 predominates in plasma[9] and it is the lactone form that is capable of anti-tumor activity.[10] A reversible hydrolytic and pH-dependent reaction converts the closed lactone form of both CPT-11 and SN-38 into an open carboxylate form.

Promising pre-clinical results have resulted in the implementation of clinical trials, with phase I trials beginning in Europe in 1990.[11–13] The aim of these studies was to determine the best administration schedule and an optimum dose for subsequent phase II trials. The efficacy of CPT-11 has thus been tested against different

1996

ANNALS NEW YORK ACADEMY OF SCIENCES

Impossible equation

Investigational New Drugs (2019) 37:519–523
https://doi.org/10.1007/s10637-018-0699-1

SHORT REPORT

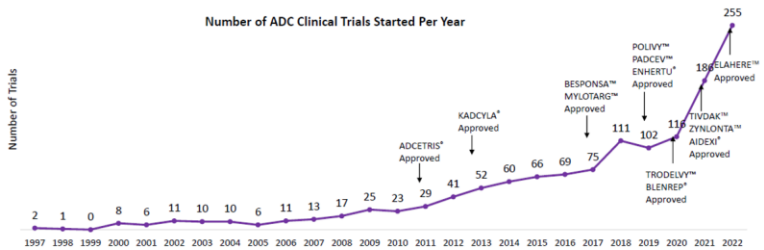
Increasing complexity in oncology phase I clinical trials

Laeeq Malik [1,2] · David Lu [1]

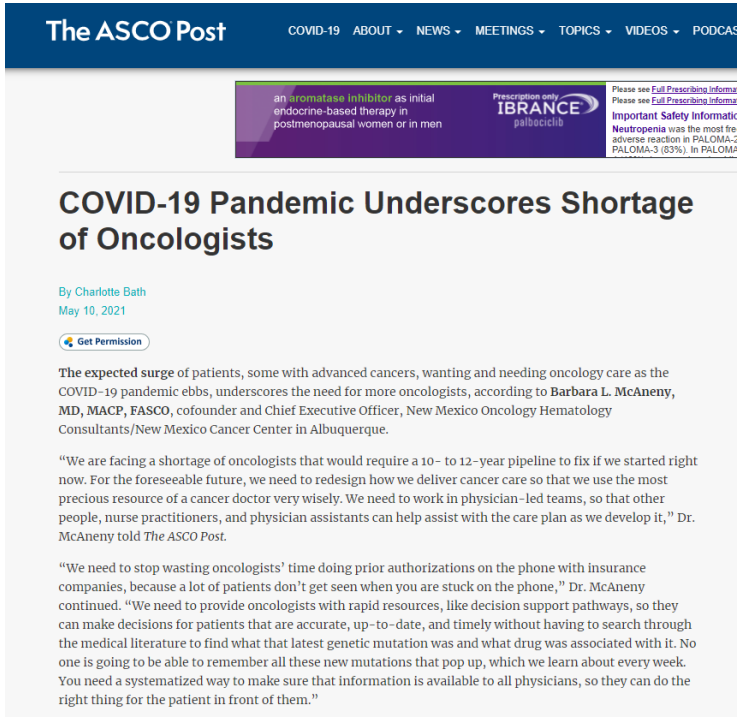
Received: 4 October 2018 / Accepted: 12 November 2018 / Published online: 16 November 2018

Summary
Clinical trials in oncology have become increasingly complex because of incorporation of predictive biomarkers and patient selection based on molecular profiling of tumors. We have examined the change in procedures and work intensity in phase 1 oncology trials over the years with several parameters used as surrogates of complexity. Categories that were included as events were clinical evaluations, pharmacokinetic (PK) laboratory tests, non-PK laboratory tests, specific molecular or histological characteristics, questionnaires and subjective assessments, routine clinical and physical examinations, imaging, invasive procedures and others. The information was extracted using a standardized form including study type, tumor type, information on agent, participant characteristics and study mandated events during the first 3 cycles of each protocol. A total of 102 phase I oncology and hematology study protocols that were active at a single institution in 1996, 2006 and 2016 were evaluated. In 2016, there were significantly more ($P < 0.05$) median number of procedures, outpatient tests, subjective assessments, PK's, molecular profiling, biopsies and medication dispensing times. There were higher median numbers of procedures in studies in hematologic malignancies, testing immunotherapies and those with over 15 inclusion or exclusion criteria. These values also differed significantly ($P < .005$) when the median values were compared in nonparametric tests. Our results suggest that study related procedures in cancer phase I trials have substantially increased over the last two decades. The successful conduct of early-phase oncology clinical trials in future will require additional research resources.

Keywords Trials · Complexity · Phase I



40% are phase 1 studies!



The ASCO Post

COVID-19 ABOUT NEWS MEETINGS TOPICS VIDEOS PODCAS

COVID-19 Pandemic Underscores Shortage of Oncologists

By Charlotte Bath
May 10, 2021

Get Permission

The expected surge of patients, some with advanced cancers, wanting and needing oncology care as the COVID-19 pandemic ebbs, underscores the need for more oncologists, according to **Barbara L. McAneny, MD, MACP, FASCO**, cofounder and Chief Executive Officer, New Mexico Oncology Hematology Consultants/New Mexico Cancer Center in Albuquerque.

"We are facing a shortage of oncologists that would require a 10- to 12-year pipeline to fix if we started right now. For the foreseeable future, we need to redesign how we deliver cancer care so that we use the most precious resource of a cancer doctor very wisely. We need to work in physician-led teams, so that other people, nurse practitioners, and physician assistants can help assist with the care plan as we develop it," Dr. McAneny told *The ASCO Post*.

"We need to stop wasting oncologists' time doing prior authorizations on the phone with insurance companies, because a lot of patients don't get seen when you are stuck on the phone," Dr. McAneny continued. "We need to provide oncologists with rapid resources, like decision support pathways, so they can make decisions for patients that are accurate, up-to-date, and timely without having to search through the medical literature to find what that latest genetic mutation was and what drug was associated with it. No one is going to be able to remember all these new mutations that pop up, which we learn about every week. You need a systematized way to make sure that information is available to all physicians, so they can do the right thing for the patient in front of them."

US, ASIA, AUS: my personal observation

US

- Crisis in PI leadership
- Concerns about operational model (start up, staffing)
- Limited IR resources
- Data quality
- Academic/Private
- Strong scientific platforms (still)

Japan, Korea, AUS

- Short start-up time
- Data quality
- Excellent operational models
- High prioritization
- Strong PI expertise
- Translational capabilities?

BARCELONA 2024 ESMO congress

Preliminary results from a Phase 1, first-in-human study of DS-9606, a Claudin 6 (CLDN6)-directed antibody–drug conjugate, in patients with tumor types known to express CLDN6

Manish R. Patel,[1,2] Erika Hamilton,[2] Sarina Anne Piha-Paul,[3] Jason Henry,[4] Udai Banerji,[5] Mohammed Najeeb Al Hallak,[6] Hiroyuki Okada,[7] Meng Qian,[7] Xinyuan Zhang,[7] Nabil Said,[7] Valery Chatikhine,[7] Elisa Fontana[8]

[1]Florida Cancer Specialists, Sarasota, FL, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Sarah Cannon Research Institute, Denver, CO, USA; [5]Institute of Cancer Research and the Royal Marsden Hospital, London, UK; [6]Karmanos Cancer Institute, Detroit, MI, USA; [7]Daiichi Sankyo Inc., Basking Ridge, NJ, USA; [8]Sarah Cannon Research Institute, London, UK.

Manish R. Patel

#610O

FRANCE: My personal observation

- Strong PI leadership
- Exceptional transitional/science capabilities
- IR resources
- UNICANCER

- Long start-up time
- Data quality
- Operational models
- Low prioritization
- Molecular screening (routine)
- And, IVDR…

EU IVDR Regulation

EFPIA 22OCT2024

60,000 fewer clinical trial places for Europeans

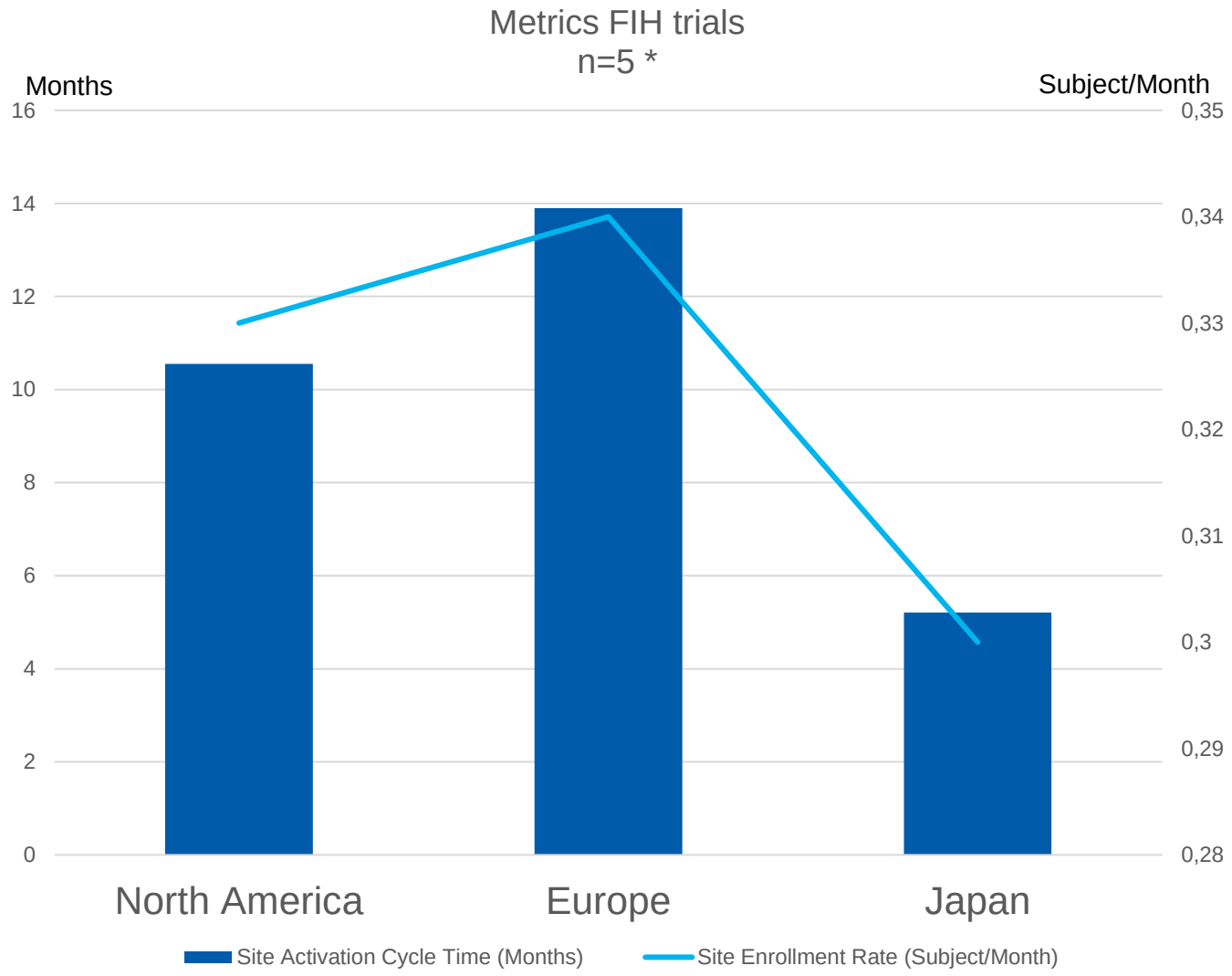
Phase 1 trial : despite increased phase one trials over the past 10 years - 32% to 41% - the **EEA has seen a gradual decline from 19% to 14%**

Fall in the EEA may be driven by the In-vitro Diagnostic Regulation (IVDR), which poses operational challenges for multi-country trials in **oncology and trials which are dependent on in-vitro testing.**

https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/60-000-fewer-clinical-trial-places-for-europeans-despite-global-surge-in-research-projects/

…without simplification in IVDR regulation, we may skip EU/France for FIH as a prioritized region…

FIH most recent internal data



Median
* No Companion Diagnostic studies

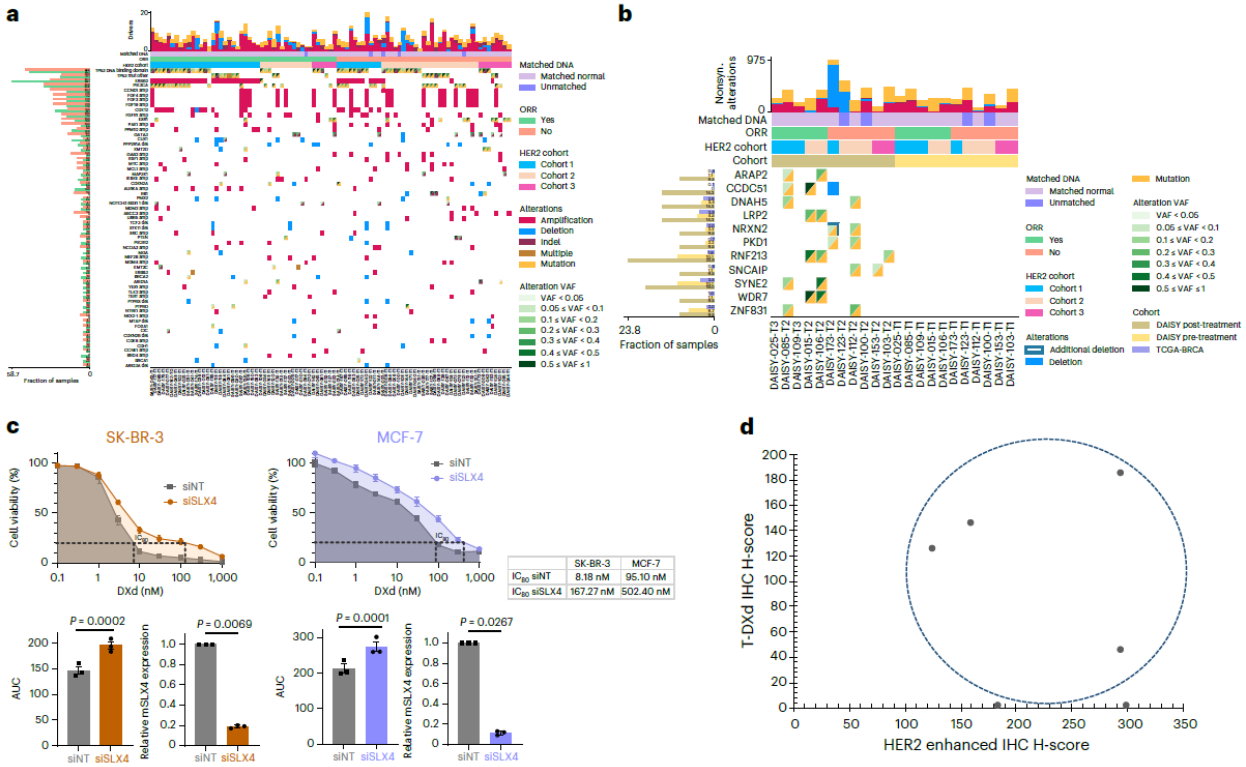
The Daisy trial- GRCC 2022

nature medicine

Article https://doi.org/10.1038/s41591-023-02478-2

Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial

1. Although HER2 expression substantially decreased at the time of resistance to T-DXd, there **is no robust evidence that a reduction of T-DXd uptake is the dominant mechanism of resistance**
2. **Identified mutations of *SLX4*** at resistance in three of 21 (14%) patients. *SLX4* encodes a DNA repair protein that regulates structure-specific endonucleases and might have a role in resistance to TOP1 inhibition.
3. In contrast to previous data, **no *TOP1* mutations** at the time of resistance



Phase 1 site selection: criteria

1. PI
2. PI
3. PI
4. PI
5. PI

1. A real PI
2. Operational/staffing model (data quality/enrolment rate/ start up time)
3. Prioritization
4. Translational science
5. Global footprint
6. Innovative systems (ePRO, radiomics)
7. Molecular screening (routine)
8. Patient diversity

…2030

Simplicity is the ultimate sophistication

Viewpoint

The need for pragmatic, affordable, and practice-changing real-life clinical trials in oncology

Alexandra Leary, Benjamin Besse, Fabrice André

Thanks to technological advances and improved understanding of cancer biology, clinical research in oncology has become increasingly complex. Trials testing novel interventions are subject to restrictive inclusion criteria, growing infrastructure required for molecular testing or safe delivery of complex biotherapeutics and administrative burden of regulatory requirements for approval of novel therapeutics, and prohibitive costs. Many trials test strategies that cannot be optimally implemented in diverse real-world settings due to technological or funding issues. Testing is also done in idealised populations, which limits the generalisability of trial results to the intended patients. Although complex oncology trials remain a priority, there is also room for other types of clinical research. Simple practice-changing

meet eligibility requirements for randomised clinical trials with novel drugs.[2] Trials strive to recruit young, fit patients, yet most cancers affect older patients with comorbidities. Results of trials done in idealised settings are unlikely to be transferable to a general population of patients with cancer. Several biological parameters are frequently included as trial selection criteria without solid clinical justification. Using a data-driven approach to broaden restrictive criteria, including laboratory values, to real-life populations of patients with cancer, investigators have shown that relaxing criteria doubled the number of eligible patients with a minimal effect on the hazard ratio for overall survival.[3]

The magnitude of benefit from novel drugs is also a concern. In a review of 92 novel cancer therapies approved

Published Online
December 8, 2023
https://doi.org/10.1016/
S0140-6736(23)02199-2

Department of Medicine (A Leary MD, Prof F André MD) **and Department of Clinical Research** (Prof B Besse MD), **Gustave Roussy, Université Paris-Saclay, Villejuif, France**

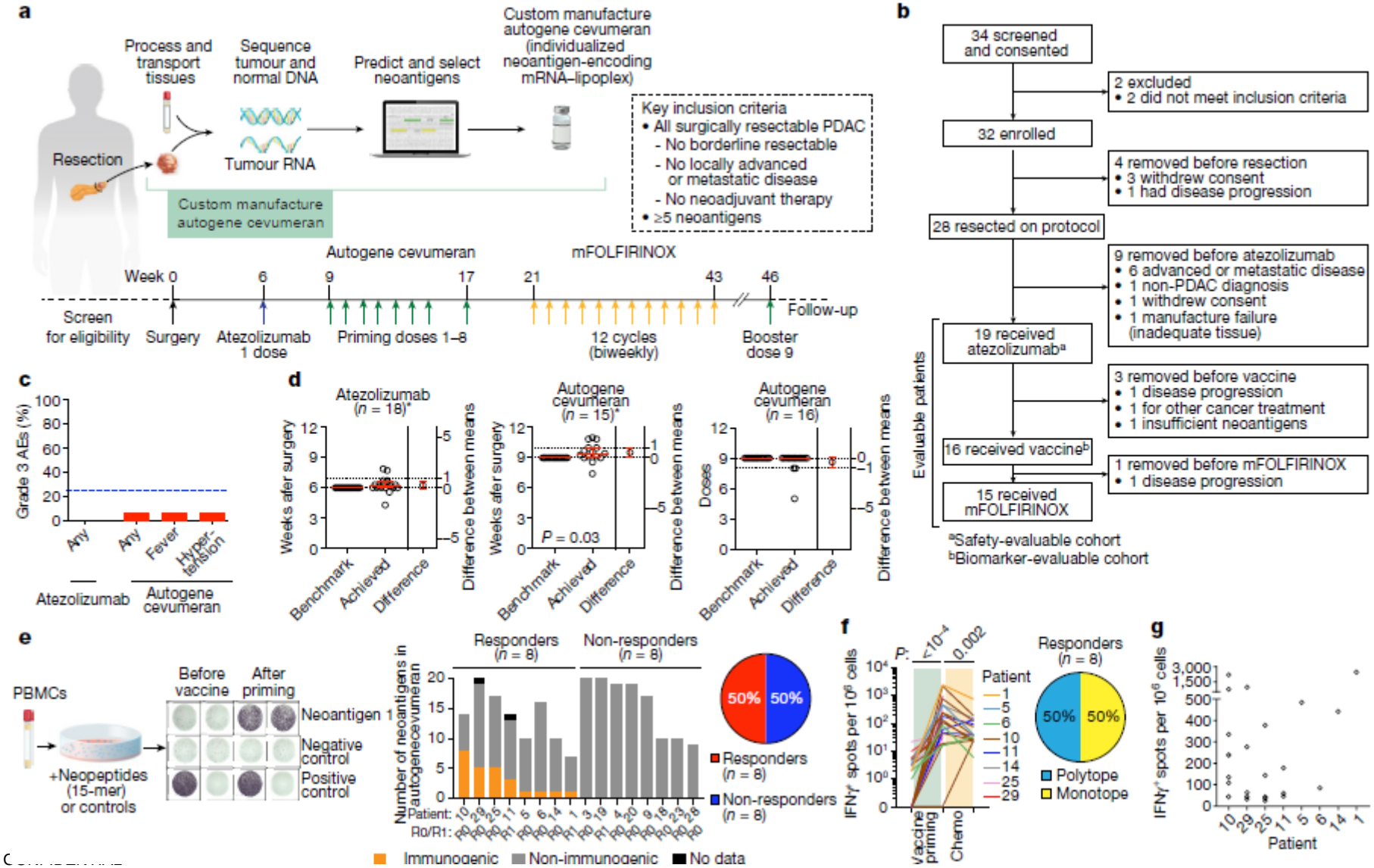
Correspondence to:
Dr Alexandra Leary, Department of Medicine, Gustave Roussy, Université Paris-Saclay, Villejuif 94805, France
alexandra.leary@gustaveroussy.fr

Article

Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer

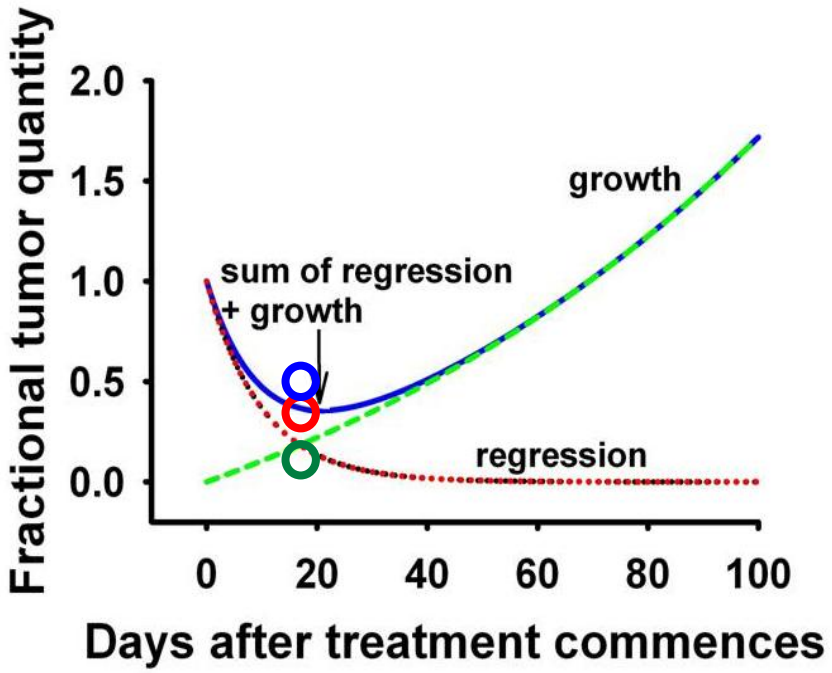
https://doi.org/10.1038/s41586-023-06063-y
Received: 10 January 2023
Accepted: 6 April 2023
Published online: 10 May 2023
Open access
Check for updates

Luis A. Rojas[1,2,10], Zachary Sethna[1,2,10], Kevin C. Soares[2,3], Cristina Olcese[2], Nan Pang[2], Erin Patterson[2], Jayon Lihm[4], Nicholas Ceglia[4], Pablo Guasp[1,2], Alexander Chu[4], Rebecca Yu[1,2], Adrienne Kaya Chandra[1,2], Theresa Waters[1,2], Jennifer Ruan[1,2], Masataka Amisaki[1,2,3], Abderezak Zebboudj[1,2], Zagaa Odgerel[1,2], George Payne[1,2], Evelyna Derhovanessian[5], Felicitas Müller[5], Ina Rhee[5], Mahesh Yadav[5], Anton Dobrin[1,2], Michel Sadelain[1,2], Marta Luksza[6], Noah Cohen[1,2], Laura Tang[1], Olca Basturk[1], Mithat Gönen[1], Seth Katz[1], Richard Kinh Do[1], Andrew S. Epstein[1], Parisa Momtaz[1,2], Wungki Park[1,2,6], Ryan Sugarman[1,2], Anna M. Varghese[1,2], Elizabeth Won[1,2], Avni Desai[1,2], Alice C. Wei[1,2], Michael I. D'Angelica[1,2], T. Peter Kingham[1,2], Ira Mellman[5], Taha Merghoub[1,6], Jedd D. Wolchok[1,6], Ugur Sahin[7], Özlem Türeci[7,8], Benjamin D. Greenbaum[4,11,12], William R. Jarnagin[1,2], Jeffrey Drebin[1,2], Eileen M. O'Reilly[1,2,9] & Vinod P. Balachandran[1,2,9,13]

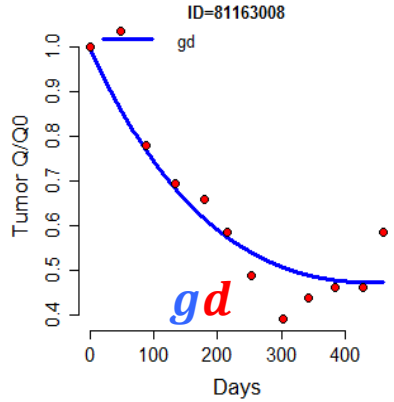


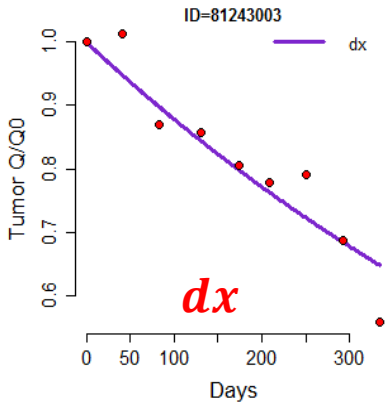
G-score: Patients Classified by 4 Models (dx, gx, gd, $gd\Phi$)

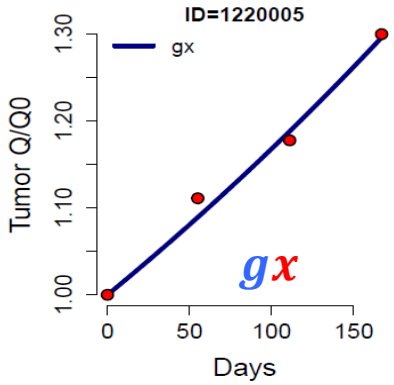
g = growth; d = decay.
dx = decay only; gx = growth only; gd = equal growth and decay; gd-phi = weighted growth and decay

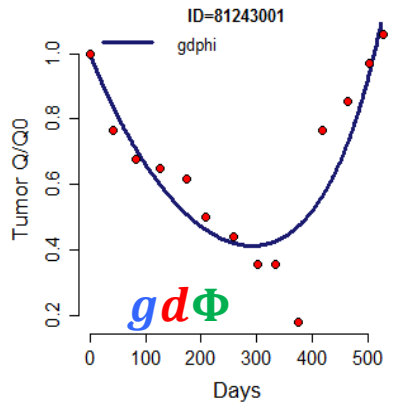


$f(t) = e^{-d \cdot t}$	dx
$f(t) = e^{g \cdot t}$	gx
$f(t) = e^{g \cdot t} + e^{-d \cdot t} - 1$	gd
$f(t) = (1 - \Phi)e^{g \cdot t} + \Phi e^{-d \cdot t}$	$gd\Phi$









G-SCORE- UNICANCER-PDAC

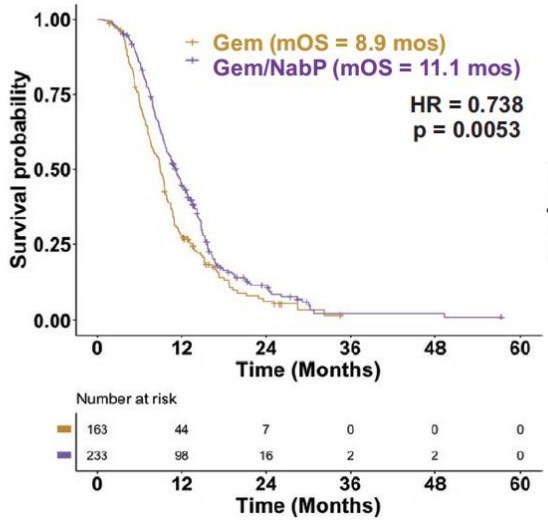
The Oncologist, 2022, **XX**, 1–10
https://doi.org/10.1093/oncolo/oyac217
Advance access publication XX XX XXXX
Original Article

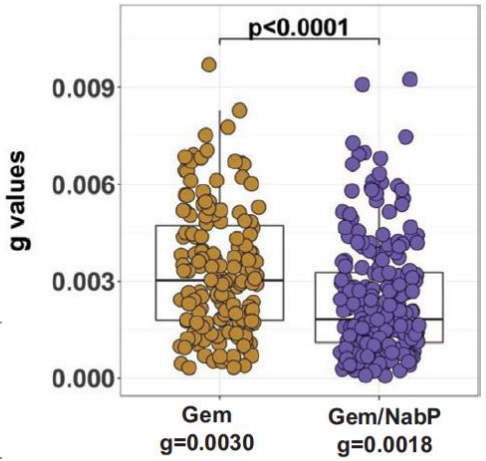
OXFORD

Tumor Growth Rate Informs Treatment Efficacy in Metastatic Pancreatic Adenocarcinoma: Application of a Growth and Regression Model to Pivotal Trial and Real-World Data

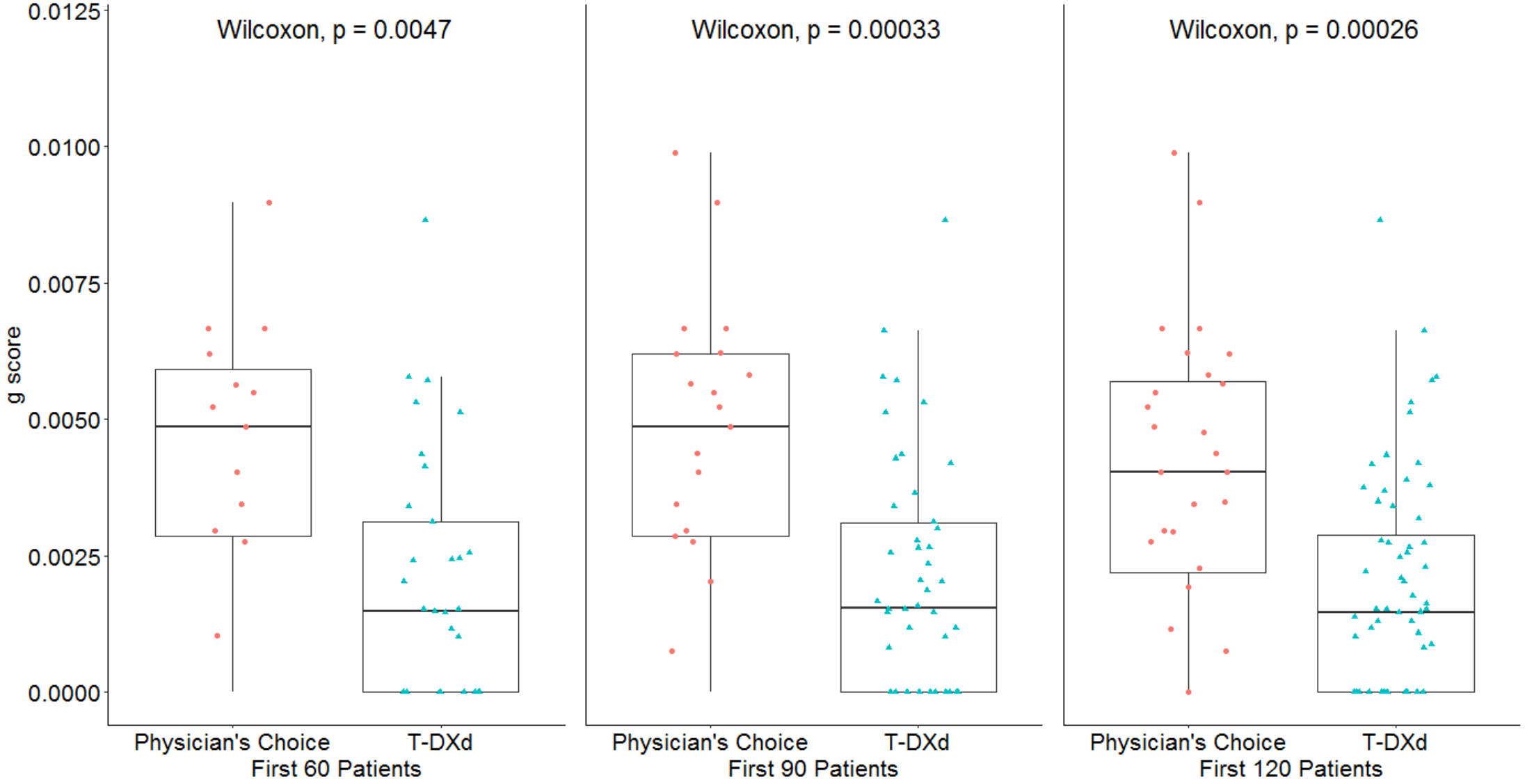
Celine Yeh[1], Mengxi Zhou[2], Keith Sigel[3], Gayle Jameson[4], Ruth White[2], Rachael Safyan[2], Yvonne Saenger[2], Elizabeth Hecht[5], John Chabot[2], Stephen Schreibman[2], Béata Juzyna[6], Marc Ychou[7], Thierry Conroy[8], Tito Fojo[2,9], Gulam A. Manji[2], Daniel Von Hoff[10,11], Susan E. Bates[*,2,9]

[1]Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA
[2]Department of Medicine, Division of Hematology/Oncology, Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA
[3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[4]Department of Medical Oncology/Hematology, HonorHealth Research Institute, Scottsdale, AZ, USA





Timing of g score analysis for meaningful IA [TAT-ESMO meeting 2024]



A new phase 1 methodology

2030 and early development

1. Next gen ADC
   - new payloads (new cytotoxic and beyond)
   - new moa (masked ADC)
2. TPD
3. Next gen IO
4. Evolution in cancer statistics (aging +metabolic syndrome) → HCC, PDAC
5. Biomarker discovery
6. New methodology (study designs/endpoints)

About TPD…

Global Players	MGD Startups	Disease	Deal Stage	Upfront ($M)	Total ($M)	Source
Novartis	Monte Rosa	Immunology	Phase I	$150	$2,100	2024-10
Roche	Monte Rosa	Oncology, CNS	Discovery	$50	$2,000	2023-10
Pfizer	Triana	Oncology, other disease areas	Discovery	$49	$1,549	2024-10
Biogen	Neomorph	CNS, Immunology Rare disease	Discovery	Not Disclosed	$1,450	2024-10
Takeda	Degron	Oncology, CNS, Immunology	Discovery	Not Disclosed	$1,200	2024-05
Vertex	Orum Thx	Oncology	Discovery	$15	$945	2024-07
BMS	VantAI	Not Disclosed	Discovery	Not Disclosed	$674	2024-02

MERCI !!!!!

(BTW, you are baking a very, very good bread!)

SESSION INAUGURALE

Phases Précoces en cancérologie : Vision 2030 !

Modérateur : Fabrice Barlesi

Avec la participation de : Jean-Yves Blay, Olivier Rixe

2024

Introduction
le point de vue académique

J-Y Blay

SCOPP : phases précoces en cancérologie

Six ans

Forum de dialogue, multipartenaires

Préoccupations : délai accès recherche, délais accès remboursement

Des progrès sensibles : Délai/métriques, AP…

De nouveaux goulots d’étranglement

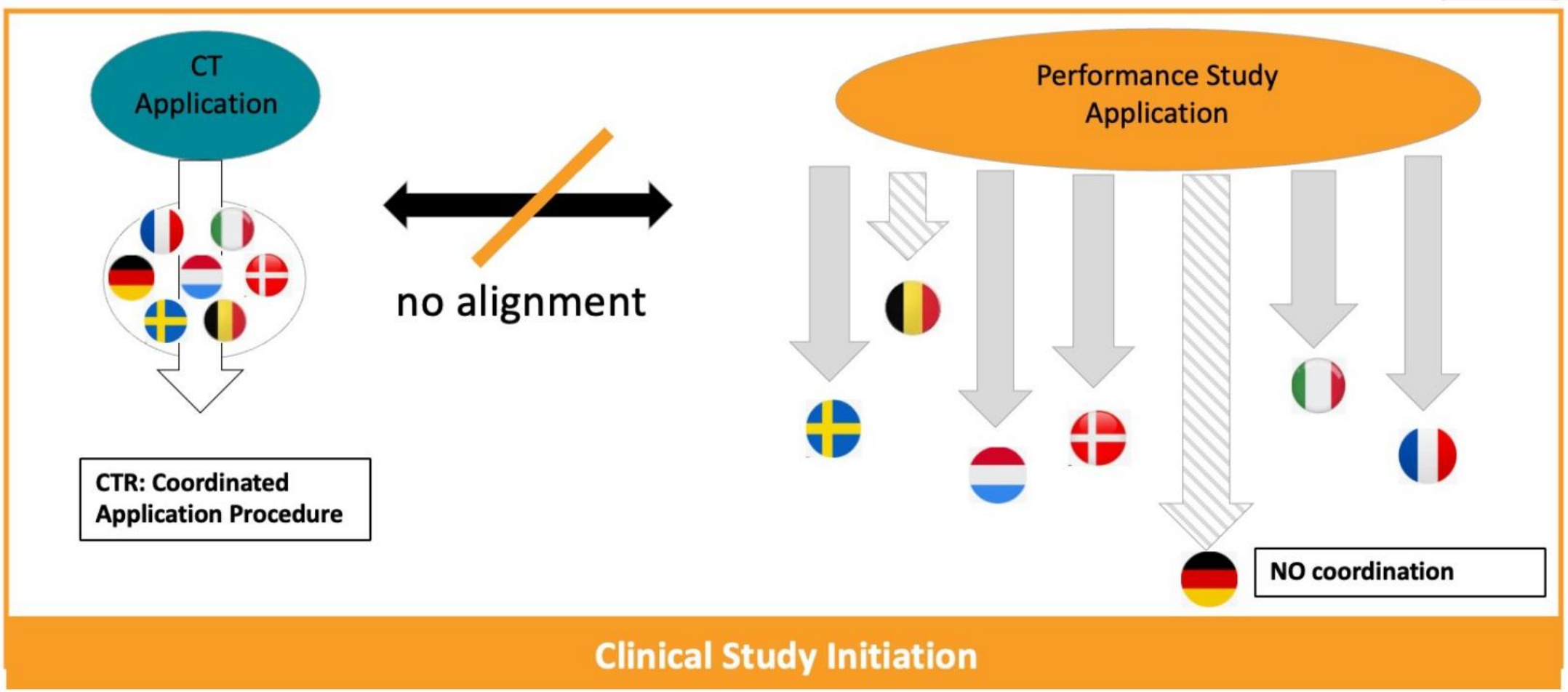
INTRODUCTION EU-IVDR

- The EU recently revised the laws governing **medical devices and in vitro diagnostics** to align with the developments of the sector over the last 20 years.
- The priority was to ensure a **robust, transparent and sustainable regulatory framework** and maintain a **high level of safety**, while **supporting innovation**.
- This included **Regulation (EU) 2017/746 on in vitro diagnostic medical device (IVDR)** which came into effect on **26th May 2022** and aims to ensure patients' safety, provide a more transparent framework for IVDs and deliver access to innovative medical technologies.
- The implementation of the IVDR has been **challenged** by a lack of infrastructure, guidance, and coordination, triggering a series of unintended consequences.

IVDR - OPERATIONAL CHALLENGE

- **Expected performance study authorisation** prior to use of a diagnostic in a clinical study, in addition to other requirements, such as authorisation of a clinical trial application for the medicinal product study and ethics committee approval.
- **Protocol submission into EUDAMED** without any coordinated process in place, infrastructure or necessary guidance.
- As a result, the study sponsor must **submit an application to every Member State** involved in the clinical trial independently.
- **Lack of harmonised rules** for performance studies resulting in divergent interpretations across Member States, clinical trial sponsors and diagnostics manufacturers.
- Some Member States might also have **different timing requirements** for submitting the performance study application, or **unclear processes** about where and how to submit a performance study application.

Negative impact of IVDR on clinical trials using an IVD: Lack of coordinated process & clarity for Performance Studies



Ability to initiate clinical trials in Europe is severely impacted!

- Delayed access to novel therapies for European patients
- Reduced access to clinical trials for European citizens
- Adverse impact on other initiatives e.g. European Beating Cancer Plan, Act EU

IVDR Related Roadblocks Delaying Start of Clinical Trials

SPONSORS assessing need for PSA

Roadblocks

e.g.: no published PSA-IVDR submission guidance, test awaiting CE Marking may require PSA

SPONSORS preparing PSA

Roadblocks

e.g.:no feedback from Ethic Com; high variability of docs required

SUBMISSION of PSA to NCAs

Roadblocks

e.g.:unstable submission portal; request for certified translations; EthC specific local forms

Rodblocks in review of PSA

Roadblocks

e.g.:delays due to EthC review; request PSA for left-over samples

Start of Clinical Trial

Roadblocks legend:

Orange = **Infrastructure** challenge

Blue = **Lack of clear guidance**

Yellow = **Lack of alignment/harmonized** approach

EFPIA Survey Results - March 2023

Between **82 and 160 trials** are currently being delayed in Europe, with an expected **238 to 420 trials*** to be delayed over the **next 3 years**.

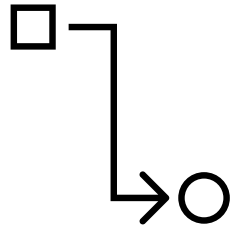
These delays mean that between **33,815 to 42,200 patients*** in Europe are expected to have delayed access to clinical trials over the **next 3 years**, around half of them (**up to 27,400**) being cancer patients.

The launch of **89 therapies** could be delayed because of this legislation, in innovative therapeutic areas such as oncology and rare diseases.

Up to 400 trials are expected to enroll fewer patients, meaning some people missing out on innovative new treatments.

43% of companies surveyed said they expect delays of **6 to 12 months** to current clinical trials, with **48%** expecting **6 to 12 months** delays over the next three years.

67% of companies would consider reducing the number of EU trial sites if IVDR requirements remain the same, noting these trials would move to the US, Canada, UK, and Asia, among other locations.



‘COMBINE’ project

- analysing the regulatory landscape for combined studies on the IVDR/MDR/CTR interface

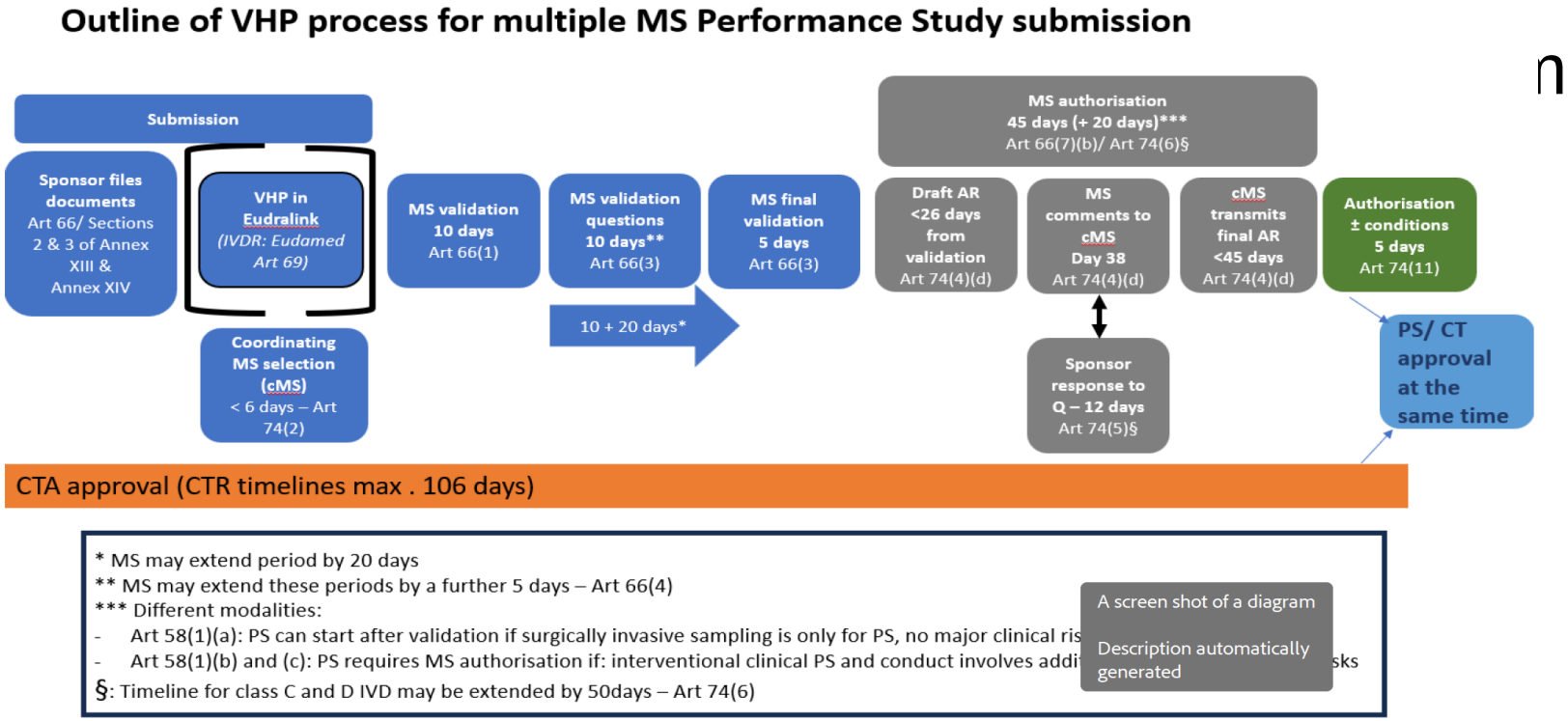
Kick-off meeting - joined project board and group meeting

Please note: The meeting is being recorded - for internal briefing only

Oct 31st 2023

SCOPE OF VHP

- Multinational (both industry and academic-sponsored) clinical trials in the EU involving an IMP requiring CTA submission and an IVD requiring a PSA.
- Inclusion of Ethics Committees, to be considered.
- Nationa nonised require



A screen shot of a diagram

Description automatically generated

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

EU HEALTH TECHNOLOGY ASSESSMENT (HTA) REGULATION

EU HTA REGULATION

- Adopted by the EU institutions in December 2021 - Applicable in January 2025.
- Establishes a **permanent EU framework for joint work & collaboration** (replacing project-based cooperation).
- Aims to improve access to innovative medicines by:
  - establishing EU-wide processes for assessing new medicines (scientific/clinical aspects)

Joint Clinical Assessments (JCAs)

Joint Scientific Consultations (JSCs)

Identification of emerging health technologies

Voluntary cooperation in other areas

Four main areas of joint work:

EU HTA REGULATION

New concept of **Joint Clinical Assessments (JCAs)**

Assessments of new health technologies conducted at the EU level

Key aspects of JCAs

- JCA reports can be considered at the Member States level, though there is no hard obligation to use them.
- JCAs will only cover clinical domains (i.e. currently used technologies, description, relative clinical effectiveness, etc.).
- Non-clinical domains (i.e. economic evaluation, ethical aspects, etc.) will not be assessed through JCAs.

Benefits of JCAs

- Lower unnecessary duplication of work for HTA bodies.
- Improved patient access to innovative medicines, including cancer medicines.
- High-quality assessment reports available for use in all EU Member States (including those with limited HTA capacity).

HTA STAKEHOLDER NETWORK

Advisory body consisting of stakeholders with an interest in HTA, including representatives of HCP. Part of the governing structure of the HTA Regulation.

Aims to facilitate dialogue between stakeholder organisations and the Member State HTA Coordination Group (HTACG):

- *Involvement in HTACG's annual Work Programmes;*
- *Meetings with the HTACG at least once a year.*

First open call for applications held from December 2022 - February 2023.

New future call for applications under consideration.

Conclusions

L’Europe décroche

Les efforts en France doivent se poursuivre

… et se complète d’une action politique forte en UE

Ensemble pour faire bouger cette situation