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Sharing experiences and best practices in running clinical trials in Horizon 2020

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DISCLOSURES



- Personal financial interests, honoraria for advisory role, travel grants, research grants (past 5 years): Hoffman La-Roche, Sanofi Aventis, Amgen, Merck Serono, Servier, MSD
- Institutional financial interests, my institution received honoraria due to my investigator contribution in clinical trials from (past 5 years): Hoffman La-Roche, Sanofi Aventis, Amgen, Merck Serono, MSD, Boehringer Ingelheim, AbbVie, Array Pharmaceuticals, Pierre-Fabre, Novartis





• I'm a clinician







THE MOTRICOLOR PARADIGM



<u>Mo</u>lecularly guided <u>Tri</u>als with treatment strategies in patients with advanced newly molecular defined subtypes of <u>Color</u>ectal cancer



CRC SCENARIO

The evolution of biomarkers for matched targeted therapies has been restrictive (until recently) in mCRC.



HYPOTHESIS AND PERSPECTIVE

Intrinsic gene expression subtyping MAY increase the biological understanding of the disease and optimize patient stratification based on differences in outcome and response patterns to targeted agents.

PUBLISHED CASSIFIERS



Colorectal cancer intrinsic subtypes



Budinska, 2013; Marisa, 2013; Roepman, 2013; Sadanandam, 2013; De Sousa e Melo, 2013; Schlicker, 2012; TCGA, 2012





The consensus molecular subtypes of colorectal cancer

medicine



CMS1 MSI immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		KRAS mutations	n de ferenzen en en en ferenziet
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis

Guinney et al. Nat Med 2015

MOTRICOLOR AIM



- To stratify CRC patients based on molecular signatures and match them to specific therapies
 - ✓ TGFβ gene signature
 - ✓ BRAFm gene signature
 - ✓ MSI gene signature



PROOF OF CONCEPT



Proof-of-concept: Three matched therapies for the three specific populations?





PHC-13-2014

New Therapies For Chronic Non-communicable Diseases

- Previous collaboration: successful COLTHERES Consortium
- No direct results from the project could be translated into the clinical setting
- However, Agendia (SME participating in COLTHERES) had identified three molecular profiles of Colorectal Cancer patients with specific gene expression "signatures"
- Idea pre-PoC: These specific populations might be treatable with therapies matching to their gene expression profiles

Proof-of-concept: Three matched therapies for the three specific populations – preclinical validation



THE CONSORTIUM



The consensus molecular subtypes of colorectal cancer

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THE CONSORTIUM









TOPIC ADAPTATION



First idea



Topic Description

Scope

tenting date:

273 Exception and Description achiev Dealfine **Jud stage Deadline**

TOPIC: New therapies for chronic non-communicable diseases

PHC 12-2004

from other two

11-03-2014 17:00:00 18-08-0018 (1):00:00

Tane Zone ((Brussels time)

Call Instant row

Specific challenge: Chronic opo-car and healthcare systems. Invocative, and effective them

best quality of care often prevention fails. While a considerable amount of anowledge has bee generated by humedical research in recent years, the development of new therapies is stagnating, in part due to a lack of clinical validation.

Tagic identifier: Passen of actions

Deselling the dat:

Scope, Clinical trial(s) supporting priorf of concept in humans to essent the potential strictal efficacy of the novel therapeutic concept(s) and / or optimization of evaluatile therapies (e.g. drug repurposing). The application may build on pre-existing pre-clinical research and adultional results from large scale databases. A concise feasibility essenseent sutified by available published and preliminary results and supporting data should also be provided. Considerations of effectiveness and potential clinical benefit (possibly including real world data) should be integrated in the application if relevant.

The Commission considers that proposals requesting a contribution from the EU of between EUR 4 and 6 million would allow this specific challenge to be addressed appropriately. Renetheless, this does not preclude submission and selection of proposals requesting other amounts.

Expected inpact: This should provide:

New therapeutic strategies, adapted where relevant to the differing needs of men and women, with the highest potential to generate advances in clinical practice for theorie diseases, including multi- or comorbidity, ready for further development.

Early eachiners of cardidate strategies univery to succeed.

Contribute to the improvement of the therapeutic outcome of major chronic health issues with significant impact on burtlen of diseases both for individual patients and for health care systems.

Type of action: Research and innovation actions

Strengths: Repurposing strategies, letter of intent for CT1 and CT3

TOPIC ADAPTATION: KEY ELEMENTS

- Strategies aimed at patient stratification depending on each individual molecular profile were based on tumour mutations. MoTriColor goes one step further for the first time patients will be stratified based on their gene expression profiles and then matched to a particular clinical trial
- Patient's specific response and resistance to specific therapies will be monitored by liquid biopsies
- It is estimated that CRC is currently third in the list of incurable cancers in terms of lives lost. Because early detection is difficult, patients often go undiagnosed until the cancer is at an advanced stage, leading to particularly poor prognosis.
- The objective is to improve both prognosis and treatment outcome for patients suffering from metastatic CRC who have not responded to standard therapies. It is estimated that **up to 30% of these unresponsive patients** present one of the disease profiles MoTriColor is addressing.







NOVELTY



TOPIC ADAPTATION: "MUST HAVEs"



1.2. RELATION TO THE WORK PROGRAMME

It is therefore clear proposal has a solid foundation on the basic pre-clinical research h, the current proposa **fits the scope** 13-2014 call in that *"The application may build on pre-existing pre-clinical research"*.

In the current application we propose three clinical trials, each based on molecular stratification of mCRC patients.
 our program is a perfect fit erapies

is stagnating, in part due to a lack of clinical validation". MoTri(**Will do exactly that** lecular insights into the biology of CRC to the clinic through molecular stratification of tumours.

• A second important aim of PHC13-2014 is "Clinical trial(s) supporting proof of concept in humans to assess the potential clinical efficacy of the novel therapeutic concept(s) (optimisation of available therapies (e.g. drug repurposing)". All three of the trials we propos **fit the general goal of** is a cy of novel therapeutic concepts. One of our studies specific whether an established (off patent) BC and NSCLC drug, vinorelbine, has clinical utility for the treatment of a subgroup of mCRC patients that have a "BRAFm-like" phenotype, as identified by gene expression analysis (see below).

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TOPIC ADAPTATION: "MUST HAVES"



In summary, ation for t (clinical impact) bridge the result for t (value creation). (the contract of the patient (clinical impact) bridge the result of the result of the patient (clinical impact) bridge the result of the result of the patient (clinical impact) bridge the result of the result of

(...) our three clinical trials rep three great opportunities improve the therapeutic outcome of a major chronic health issue with significant impact on the burgen of useases, both for individual patients and for health care systems", which is one of the maje expected impacts of PHC13-2014.

The impact and benefit for individual patients is clear: getting the right drug early on to patients with molecularly matched therapies should be far superior to the "one size fits all" approach that we currently use for treatment of CRC. The benefit for the health care systems itment of patients with ineffective drugs is costly and ready to dealer and cost domisticant much a patient progresses on a given first line therapy. As such, molecular stratification has the promise of improved health outcomes at manageable cost to the health care system.



Someone must take care of (almost) everything... ¿Who leads?

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¿WHO LEADS?



Previous consortium leaded by Translational PI (successful case: publications, results)

Our team is leaded by key opinion leader Clinical PI (topic is clinical)

From the clinical partners, others did not count with SUPPORT for writing/ coordinating proposal

VHIO leads

MOTRICOLOR

<u>Mo</u>lecularly guided <u>Tri</u>als with treatment strategies in patients with advanced newly molecular defined subtypes of <u>Color</u>ectal cancer

MOTRICOLOR





MOTRICOLOR





VHIO's management team

ORGANIZATION OF IDEA AND WORK





ORGANIZATION OF IDEA AND WORK





TRANSLATIONAL NEEDS





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MOTRICOLOR/INTRACOLOR FINAL PROPOSAL





TRANSLATIONAL OPPORTUNITIES





SOME LESSONS LEARNED (APPLICATION)



- Dependency of many occupied people: will be a handicap
- Prepare to take decisions out of your expertise: no fear
- People will assume that you are reviewing everything... most will only review their parts (if)
- When working with consultancy groups, tasks must be clearly defined (overlap may jeopardize logistics)

Better to address potential risks than hiding them: Evaluators should be bloodhounds!



THE MOTRICOLOR KICK OFF



<u>Mo</u>lecularly guided <u>Tri</u>als with treatment strategies in patients with advances newly molecular defined subtypes of <u>Color</u>ectal cancer

MOTRICOLOR WORK PACKAGES





BASIC: CONSORTIUM COMMUNICATION



Barcelona Kick off 2015

Valencia General Assembly 2017

MOTRICOLOR

General Assembly Meeting 4 November 20-30 2018, Naples, ITALY

General Assembly: One per year Executive Board: Four per year Clinical Stearing Committe Meeting: Q21D

Welcome!

GENERAL TIMELINES



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SCIENTIFIC COORDINATION & PROJECT MANAGEMENT



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BUILDING A GOOD NETWORK IS CRUCIAL

Referrals 2018 (incl+SF+Pre-SF)





send shipment

WP1 KICK OFF

potentially eligible patient

→ check eligibility criteria → intranet > useful documents > project documents > incl&excl criteria

→ submit sample to intranet → intranet > sample tracking > sample tracking > screening ID

prepare shipment

- → complete signature request form per sample → intranet > sample track
- → write MTC number on each FFPE slide → 10 slides of 5 micron thick
- ightarrow do not include a copy of the PA report
- → announce shipment per email → mireille.snel@agendia.com
- → update intranet → intranet > sample tracking > sample tracking > sample sent

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WP1 IMPACTS ON WP2, WP3, WP4... WP5, WP6, WP7



VALL D'HEBRON

An screening strategy must be agreed by all partners: resources are limited

PRE-SCREENING AND CT CRONOGRAMA



	1st Batch screened	Screening stopped	Screening activate (RESTRICTED)	Status
Date	23/01/2017	14/06/2018	20/09/2018	09/05/2019
Slots	23/575	458/575	476/575	548/575*
% eligible to CTs	55%	59%	59%	59%

Site	CT1 Site Activation date	CT2 Site Activation date	CT3 Site Activation date
VHIO	×	17/04/2018	02/11/2017
ICO	×	03/04/2014	09/11/2017
INCLIVA	×	03/04/2018	13/11/2017
NKI	30/03/2018	31/01/2018	14/12/2017
GOMN	×	21/12/2018	04/05/2018
UNINA2	×	21/12/2018	23/11/2017
KUL	x	23/01/2019	08/01/2018



RISK MANAGEMENT

- Risks can be positive (opportunities) or negative (threats).
- Risk identification is expected to be bottom-up.
- Each risk has two basic variables: probability (P) and impact (I). Both 1-Low to 3-High. A risk index is calculated as r = P * I.
- Mitigation plans will be defined: actions to be undertaken to affect probability and/or impact *before the risk happens*.
- Contingency plans will be defined: actions to be undertaken if the risk happens.
- The risk management procedure will be included in the Project Handbook. Templates to be made available.



RISK MANAGEMENT

- Failure of reproducibility of signatures in FFPE samples
- Not availability of drugs if strategic interests change for the Pharmaceutical companies that support the consecution of clinical trials 1 and 3
- Loss of recruited patients follow-up
 - Administrative work/ethics approvals in some sites may delay the recruitment of patients
- Difficulty in identifying patients complying with inclusion criteria
- Problems in the samples' circuits/management
- No detection of T cell responses against neoepitopes in PBMCs. NOT YET
- We expect to find more responding T cells in tumour-infiltrating lymphocytes (TILs) than in PBMCs, but detecting responses in PBMCs would represent a less invasive procedure for the prediction of responses.
- No identification of genetic variants by the designed panel

HAPPENED

NOT YET

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PRE-SCREENING AND CT CRONOGRAMA



	1st Batch screened	Screening stopped	Screening activate (RESTRICTED)	Status
Date	23/01/2017	14/06/2018	20/09/2018	09/05/2019
Slots	23/575	458/575	476/575	548/575*
% eligible to CTs	55%	59%	59%	59%

MITIGATION PLANS:

- 1. Speed up screening in order to include patients ready to start (some emergent slots)
- 2. Restrict screening to certain (90% sure) molecularly selected population
- 3. Create additional slots (provided by WP1 coordinators): 200 extra slots

Site	CT1 Site Activation date	CT2 Site Activation date	CT3 Site Activation date
VHIO	x	17/04/2018	02/11/2017
ICO	x	03/04/2014	09/11/2017
INCLIVA	x	03/04/2018	13/11/2017
NKI	30/03/2018	31/01/2018	14/12/2017
GOMN	x	21/12/2018	04/05/2018
UNINA2	×	21/12/2018	23/11/2017
KUL	x	23/01/2019	08/01/2018

CONTINGENCY PLANS:

- Replace the drug: New generation drug (added value)
- Consider alternative hypothesis based on preclinics





H2020 IS A TEAM-WORK

Mind meld

Interdisciplinary science must break down barriers between fields to build common ground.

- ✓ Clinicians
- ✓ Biologists
- ✓ Bioinformatics
- ✓ Statiticians
- ✓ Engineers

✓ And FUNDAMENTAL: *PROJECT MANAGEMENT*







Yes Hope so Sharing experiences and best practices in running clinical trials in Horizon 2020 Try to

*Thank you to the scientific committee for giving us the opportunity to present here our work (and help us with one of our deliverables (WP 9 dissemination and exploitation)

AKNOWLEDGEMENTS

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Raquel Comas (Data Curator, VHIO)

All the researchers, clinicians, coworkers involved in the study

Patients and their families without whom anything would be possible









BEORTC

The future of cancer therapy





Thank you

Elena Elez MD PhD

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