VALL D'HEBRON Institute of Oncology

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

Elena Elez MD PhD (Colon Cancer Program)

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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

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DISCLOSURES

- I’m a clinician

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KEY ELEMENTS

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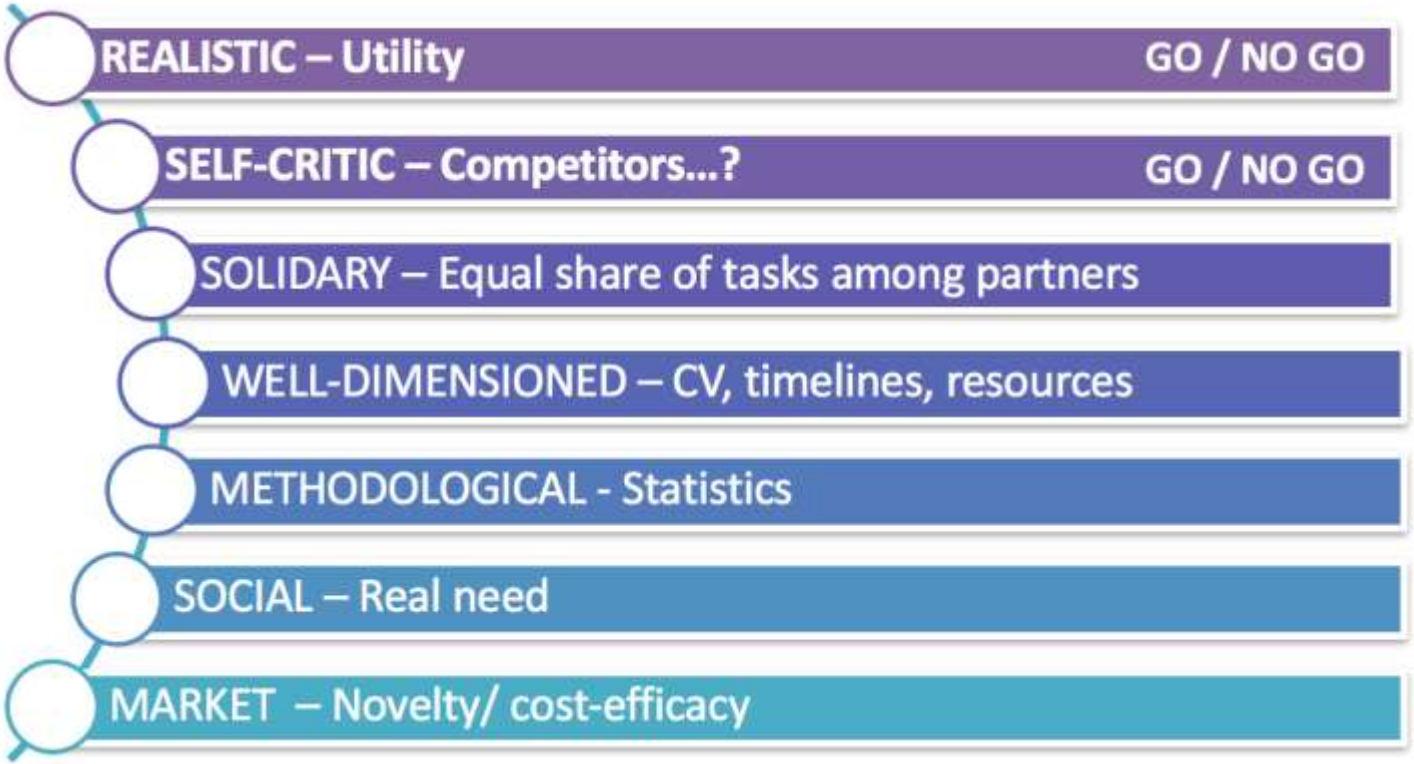
VISION



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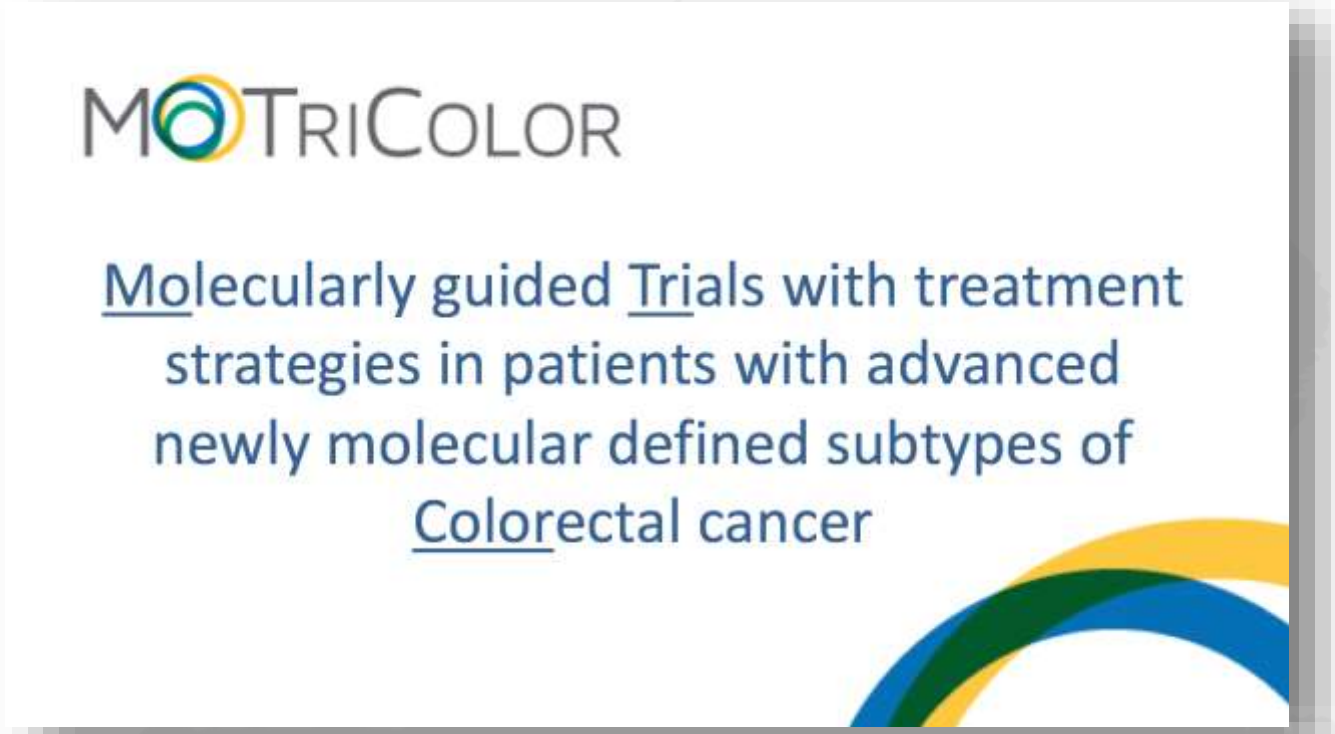
THE MOTRICOLOR PARADIGM



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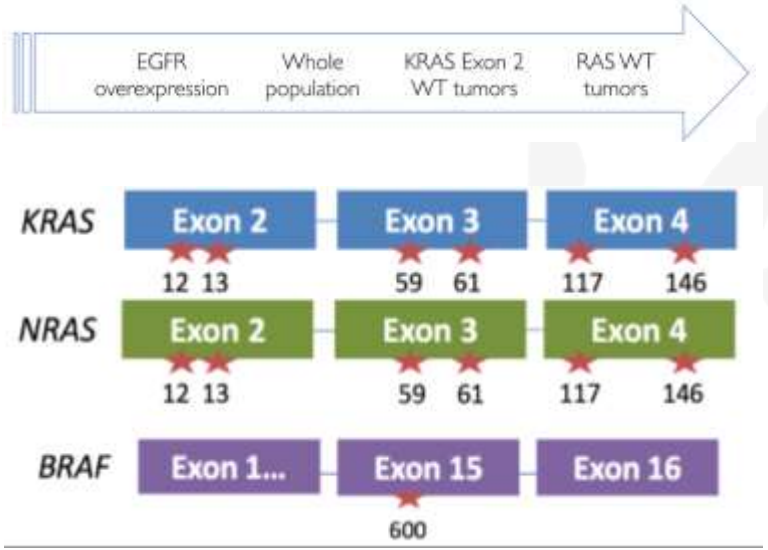
CRC SCENARIO

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.

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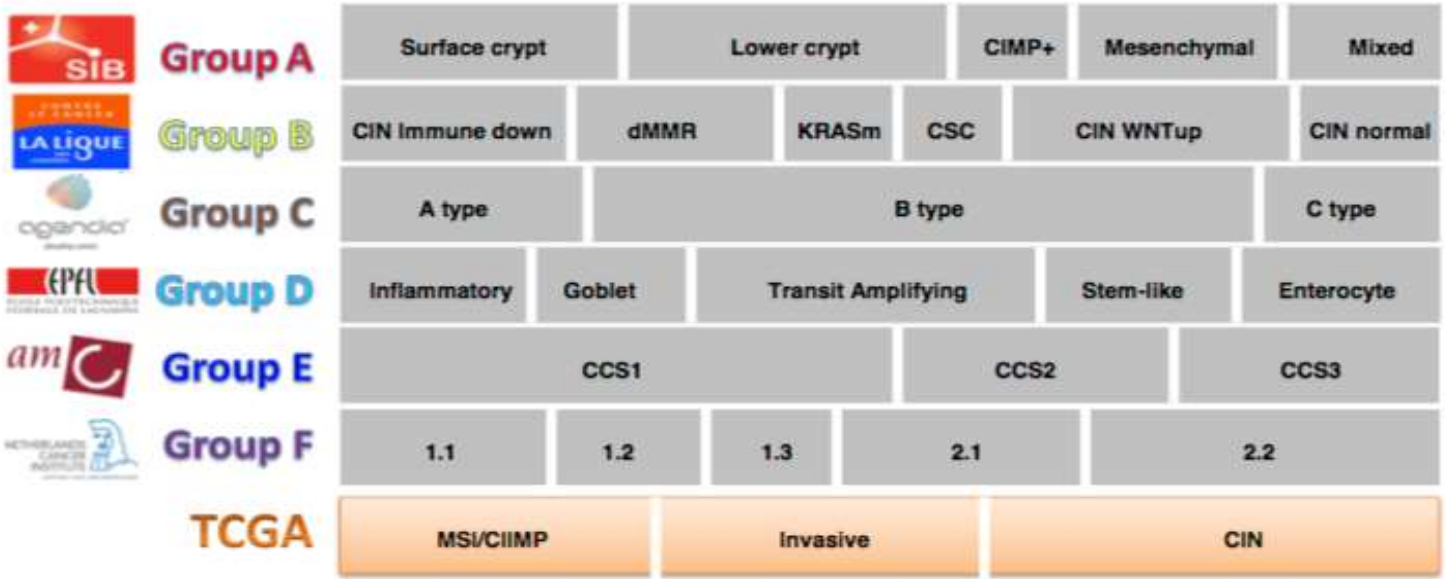
Van Cutsem E, *et al.* J Clin Oncol. 2015 Mar 1;33(7):692-700. 2. Douillard JY, *et al.* N Engl J Med. 2013 Sep 12;369(11):1023-34.

PUBLISHED CASSIFIERS

Colorectal cancer intrinsic subtypes



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

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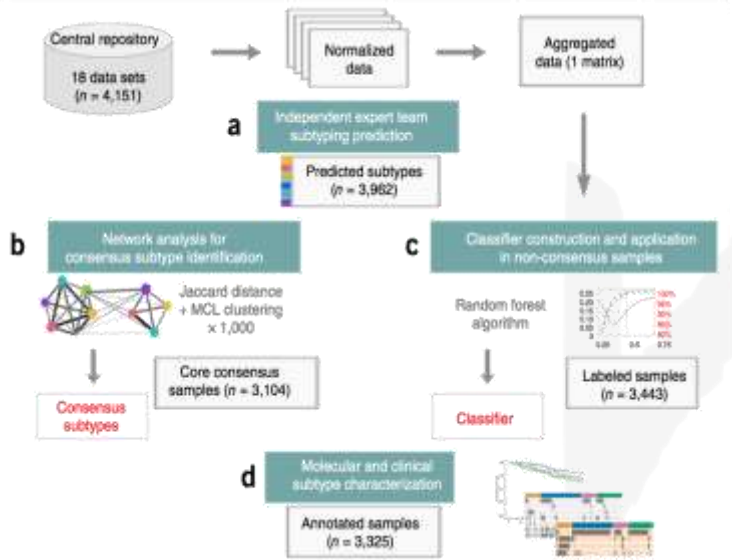
THE CONSENSUS MOLECULAR SUBTYPES

The consensus molecular subtypes of colorectal cancer

nature 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	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGF-β activation, angiogenesis

Guinney et al. Nat Med 2015

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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

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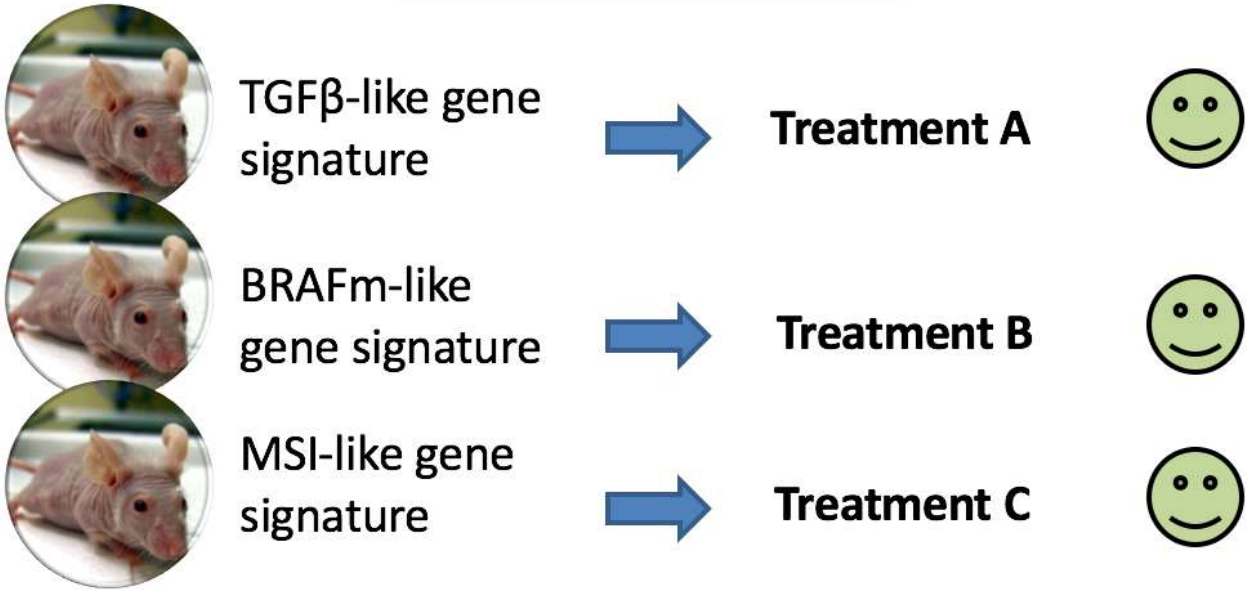
PROOF OF CONCEPT

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



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¿WHY DECIDING TO APPLY FOR THE SPECIFIC TOPIC?

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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

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THE CONSORTIUM

The consensus molecular subtypes of colorectal cancer

Justin Guinney[1,21], Rodrigo Dienstmann[1,2,21], Xin Wang[3,4,21], Aurélien de Reyniès[5,21], Andreas Schlicker[6,21], Charlotte Soneson[7,21], Laetitia Marisa[5,21], Paul Roepman[8,21], Gift Nyamundanda[9,21], Paolo Angelino[7], Brian M Bot[1], Jeffrey S Morris[10], Iris M Simon[8], Sarah Gerster[7], Evelyn Fessler[3], Felipe De Sousa E Melo[3], Edoardo Missiaglia[7], Hena Ramay[7], David Barras[7], Krisztian Homicsko[11], Dipen Maru[10], Ganiraju C Manyam[10], Bradley Broom[10], Valerie Boige[12], Beatriz Perez-Villamil[13], Ted Laderas[1], Ramon Salazar[14], Joe W Gray[15], Douglas Hanahan[11], Josep Tabernero[2], Rene Bernards[6], Stephen H Friend[1], Pierre Laurent-Puig[16,17,22], Jan Paul Medema[3,22], Anguraj Sadanandam[9,22], Lodewyk Wessels[6,22], Mauro Delorenzi[7,18,19,22], Scott Kopetz[10,22], Louis Vermeulen[3,22] & Sabine Tejpar[20,22]

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THE CONSORTIUM

COLTHERES
colon therapy research consortium

Predicting individual response and resistance of CRC patients to targeted therapies

Patient Samples + clinical response data

Molecular analysis using multiple omics' technologies

Assays to detect mutated DNA in serum from CRC patient

Mutational, expression epi-genomic and proteomic profiles

Cellular/*Xenopatients* modelling of biomarkers for targeted agents

Reverse genetic screens to identify genes affecting resistance and sensitivity to targeted agents

Forward genetic screens to identify genes affecting resistance and sensitivity to targeted agents

Design of hypothesis driven biomarkers-based phase 1/2a clinical trials

New algorithms for tumor-patients risk stratification
Dissemination of project data

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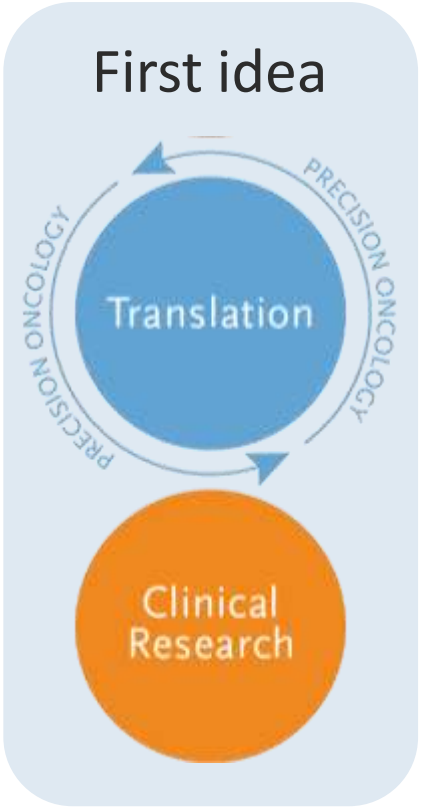
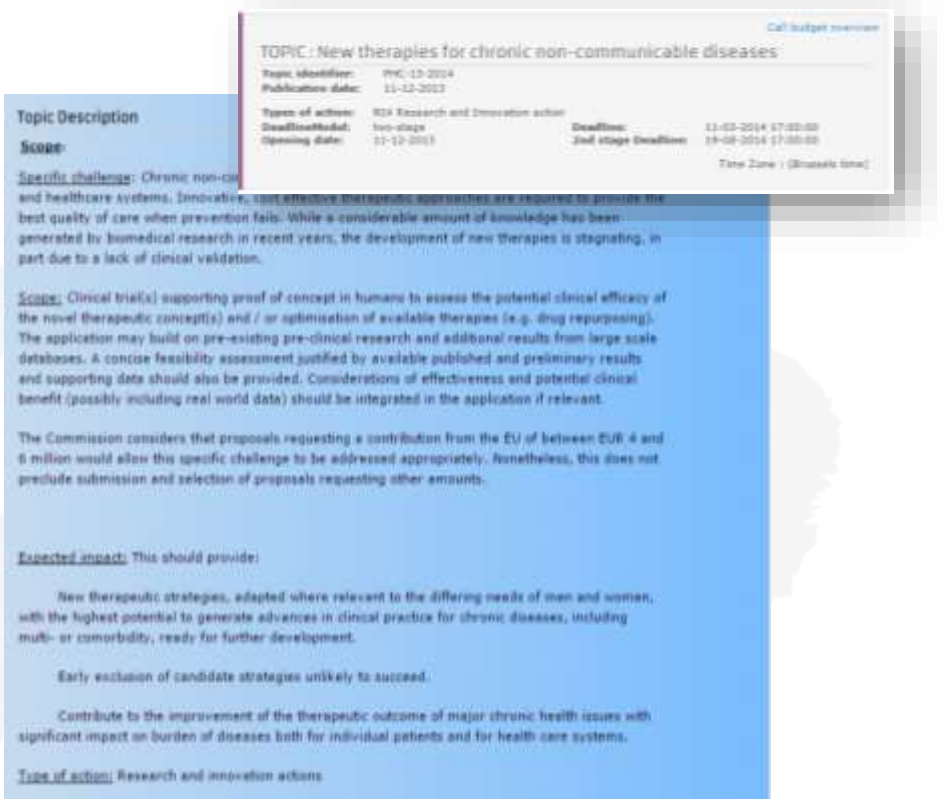
TOPIC ADAPTATION





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

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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

NOVELTY

- Patient's specific response and resistance to specific therapies will be monitored by **liquid biopsies**

NOVELTY

- 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.**

SOCIAL IMPACT

- 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.

MARKET

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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 enge of PHC13-2014: "*Nevertheless, while a considerable esearch i erapies is stagnating, in part due to a lack of clinical validation*". MoTriC 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 acy of novel therapeutic concepts. One of our studies specifi e aim to test 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 bridge the resu h (the COLTHERES project) to the patient European marke **(clinical impact)** **(value creation)**.

(…) our three clinical trials rep *improve the therapeutic outcome of a major chronic health issue with significant impact on the burden of diseases, both for individual patients and for health care systems*", which is one of the maj **three great opportunities** **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 tment of patients with ineffective drugs is costly and leads to additional cost downstream when 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. **benefit for the health care systems**

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

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¿WHO LEADS?

MOTRICOLOR

Molecularly guided Trials with treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer

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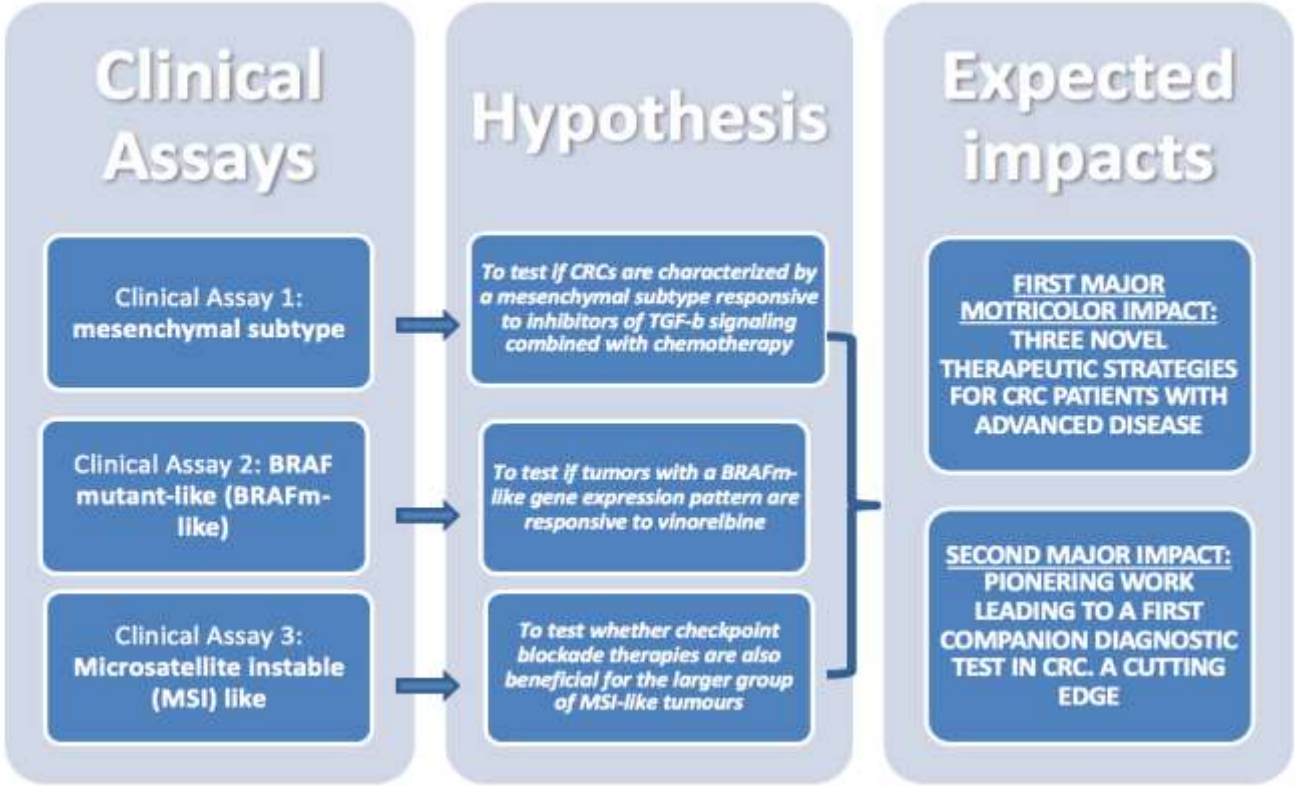
MOTRICOLOR



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MOTRICOLOR

Principal Investigator

Writing

Partners

Budget and Coordination

VHIO's management team

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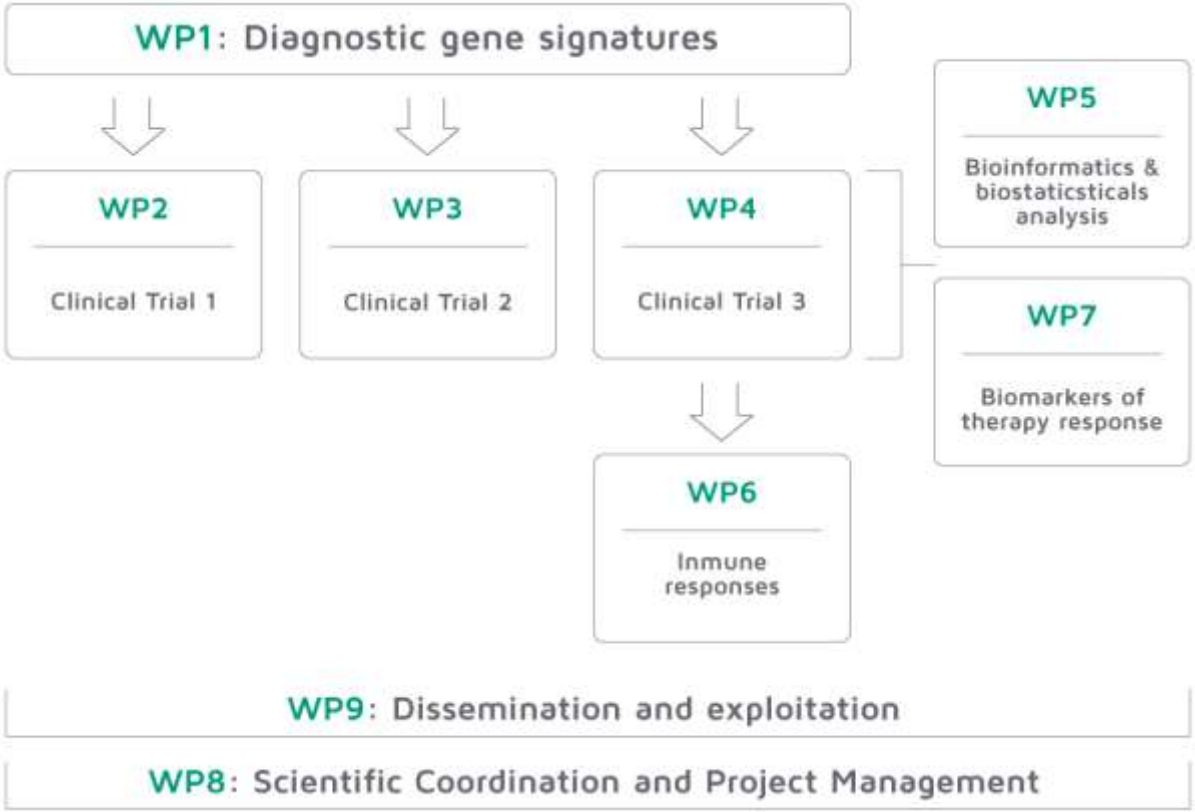
ORGANIZATION OF IDEA AND WORK



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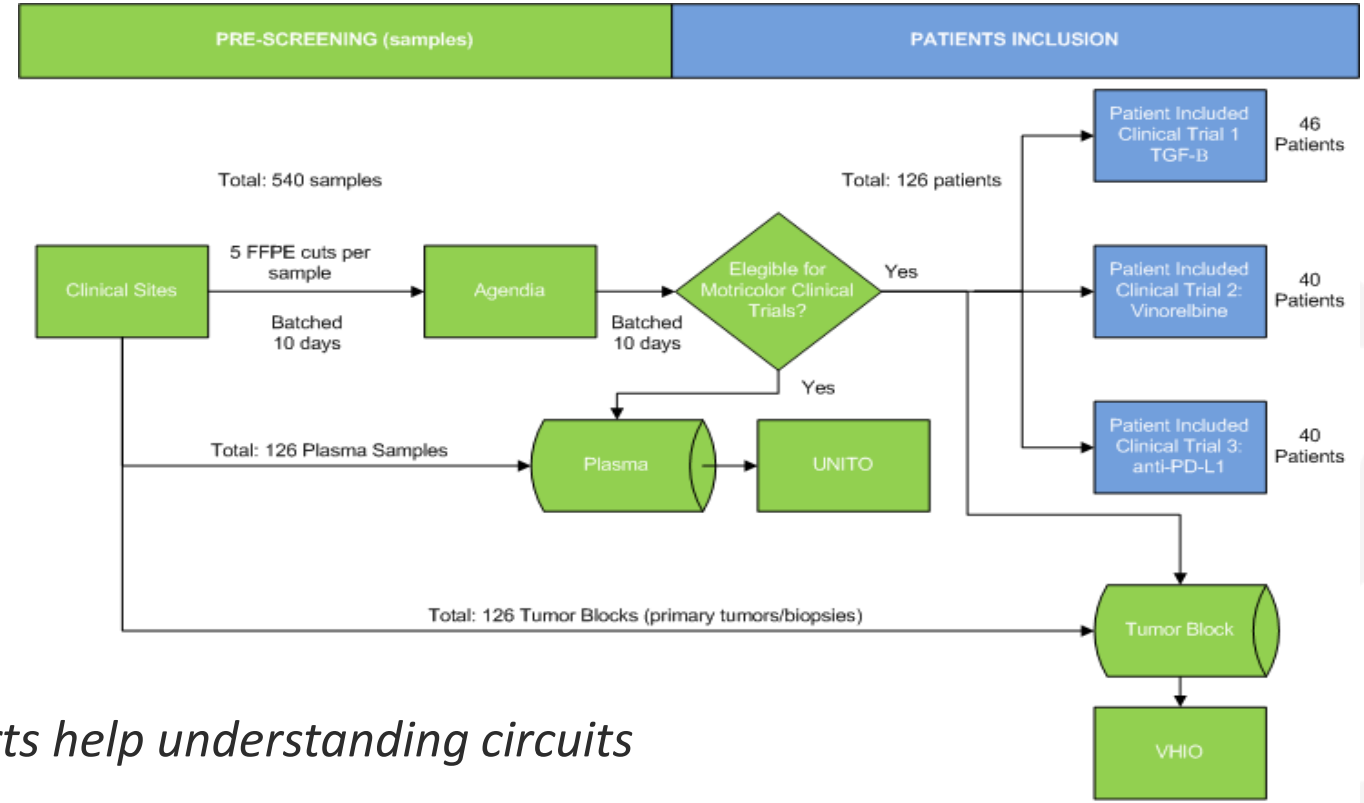
ORGANIZATION OF IDEA AND WORK



Flowcharts help understanding circuits

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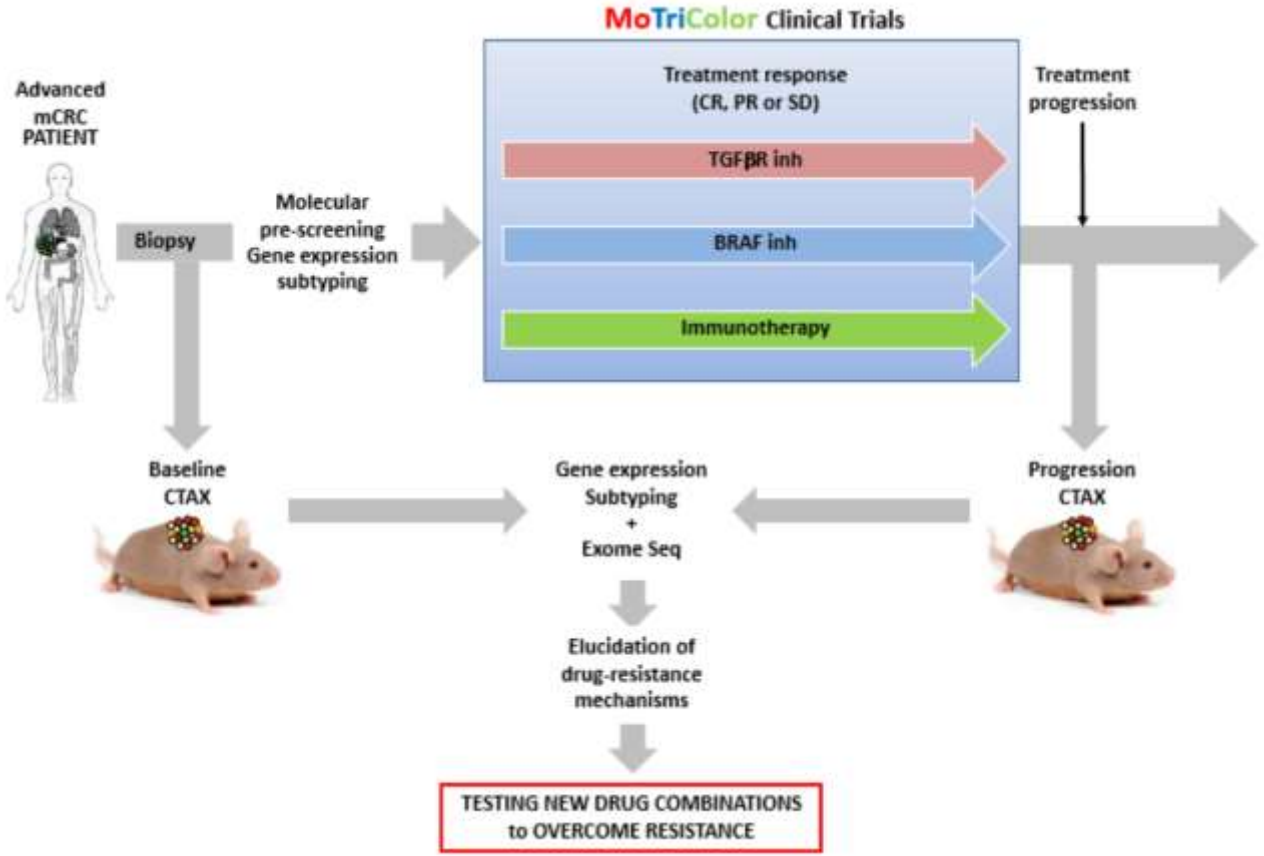
TRANSLATIONAL NEEDS



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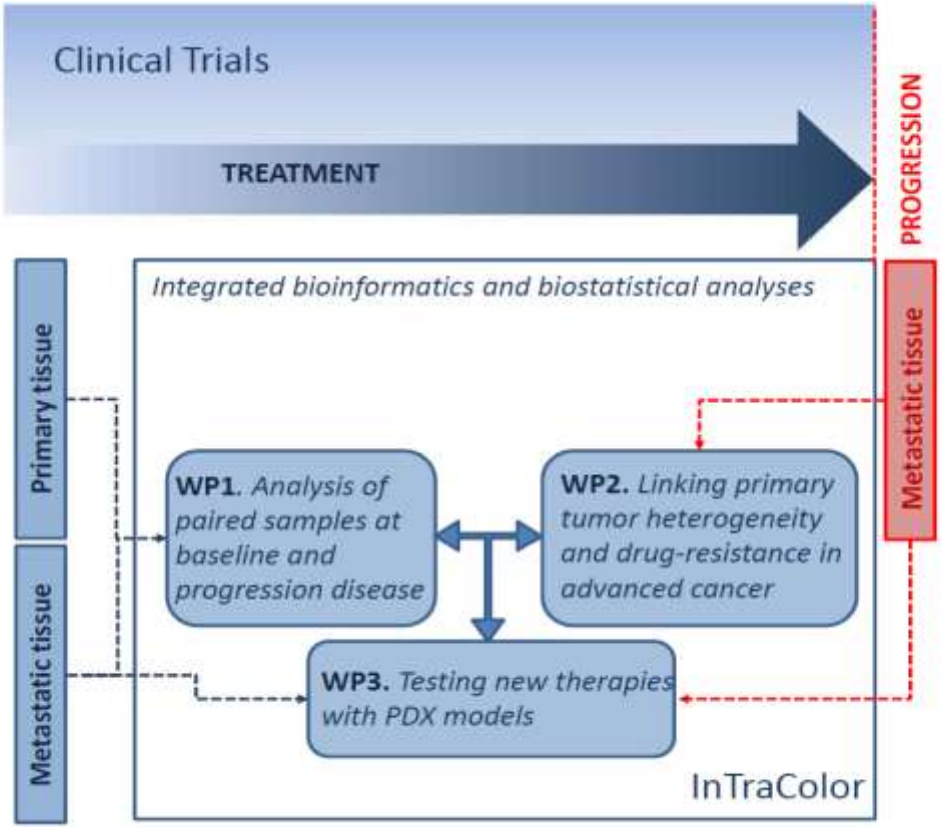
MOTRICOLOR/INTRACOLOR FINAL PROPOSAL



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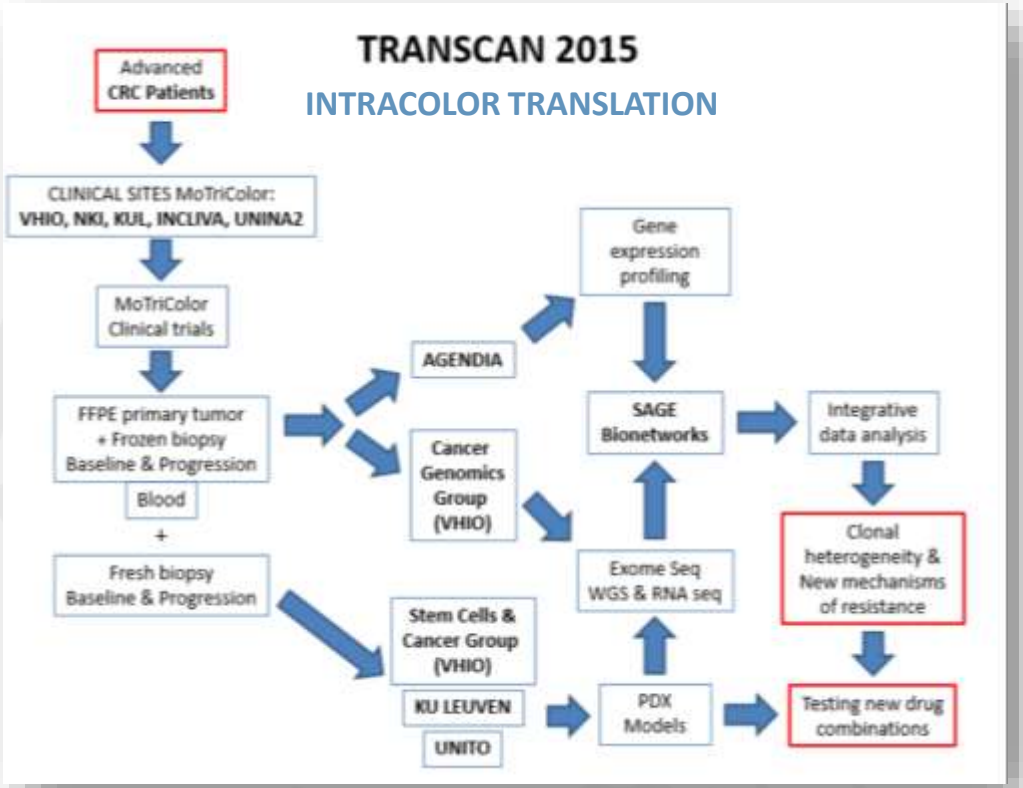
TRANSLATIONAL OPPORTUNITIES

TRANSCAN
ERA NET on Translational Cancer Research

HORIZON 2020



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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!

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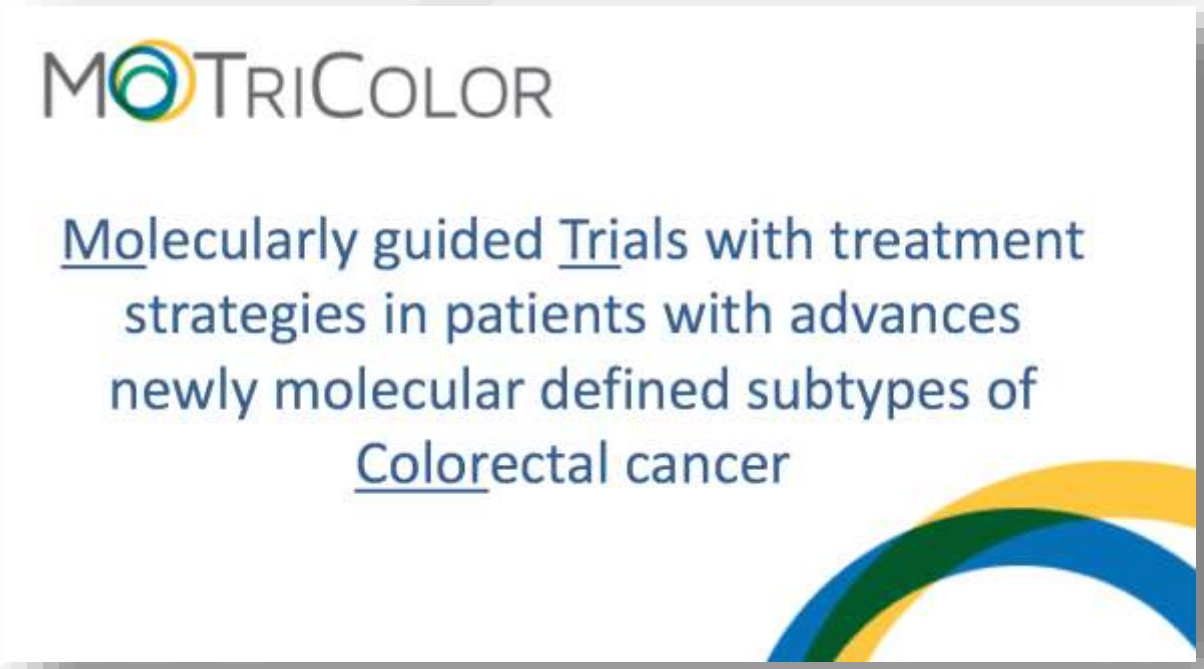
THE MOTRICOLOR KICK OFF



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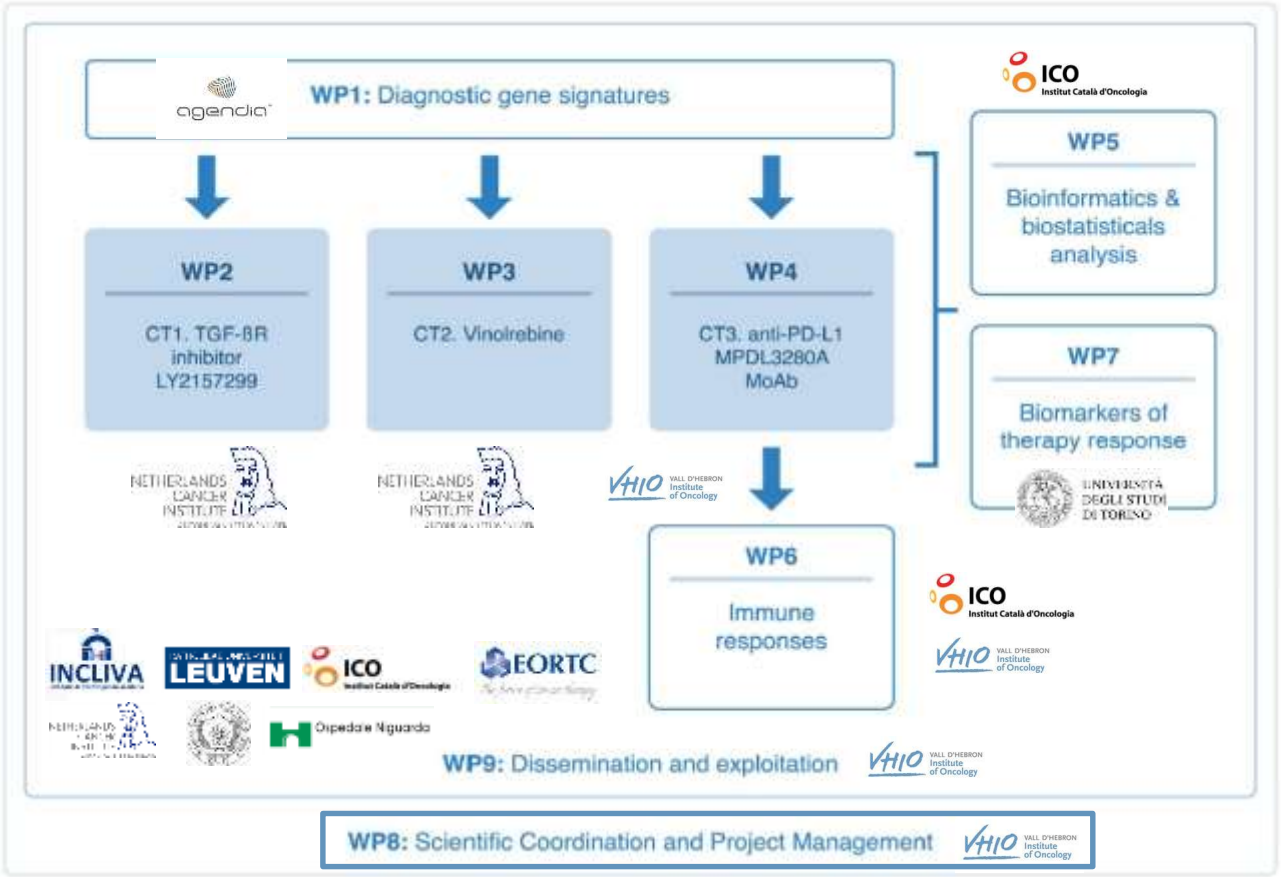
MOTRICOLOR WORK PACKAGES



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BASIC: CONSORTIUM COMMUNICATION


Barcelona Kick off 2015


Valencia General Assembly 2017

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

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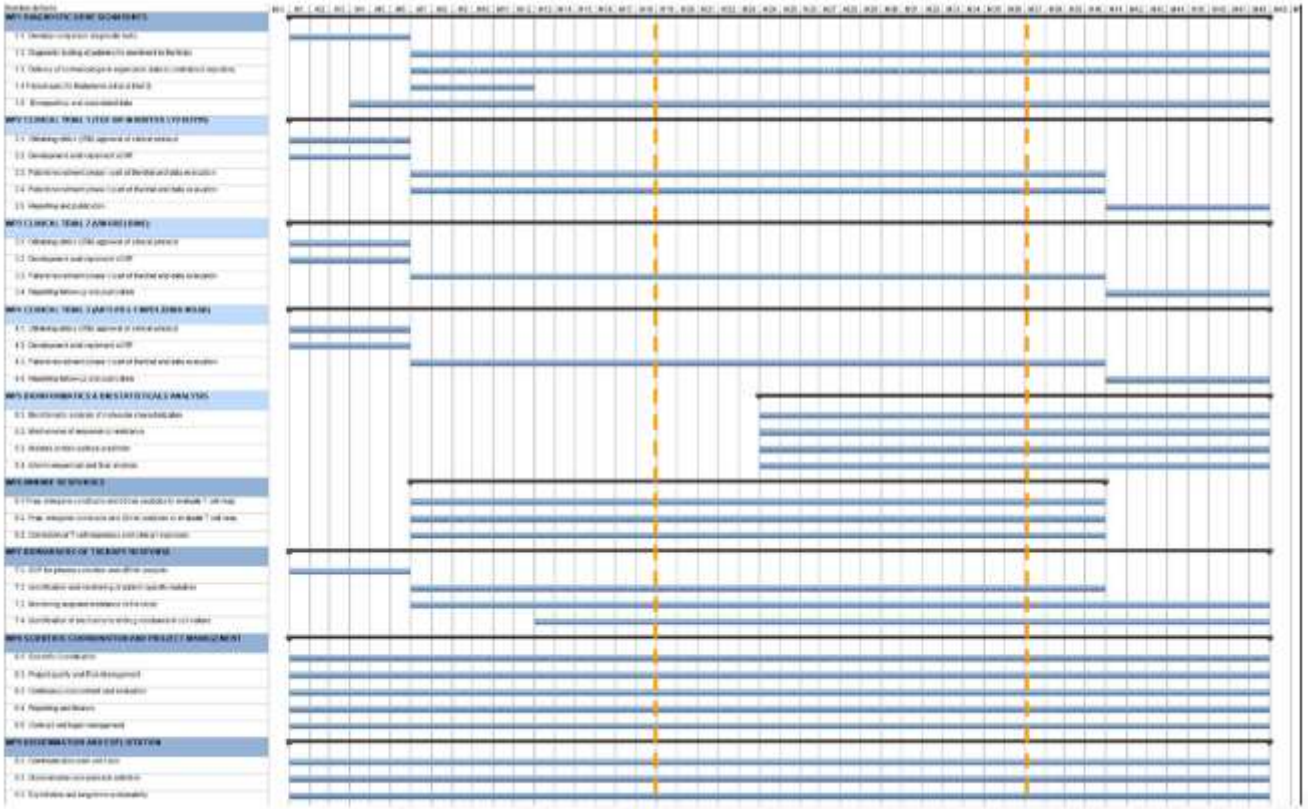
GENERAL TIMELINES



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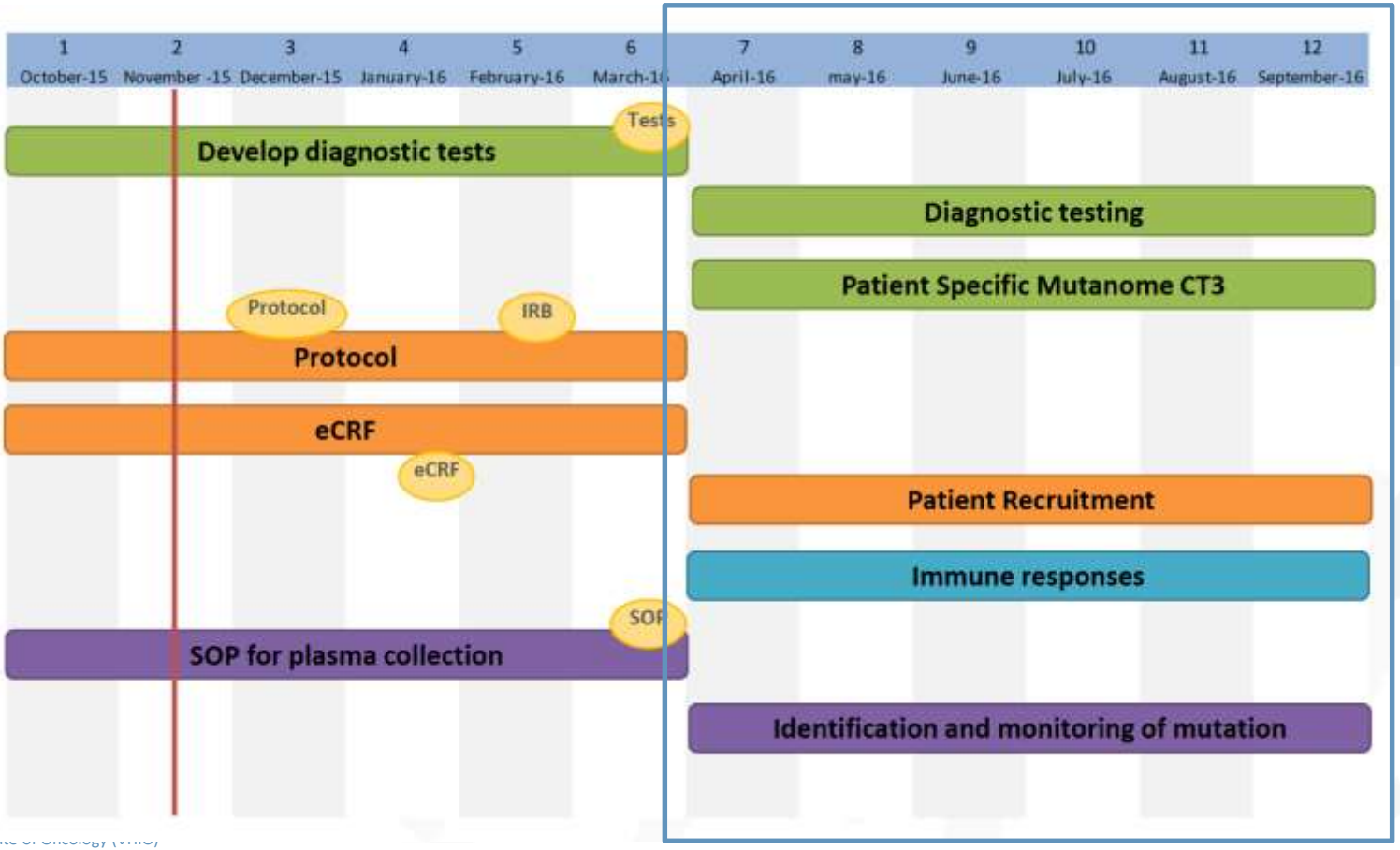
SCIENTIFIC COORDINATION & PROJECT MANAGEMENT



2016

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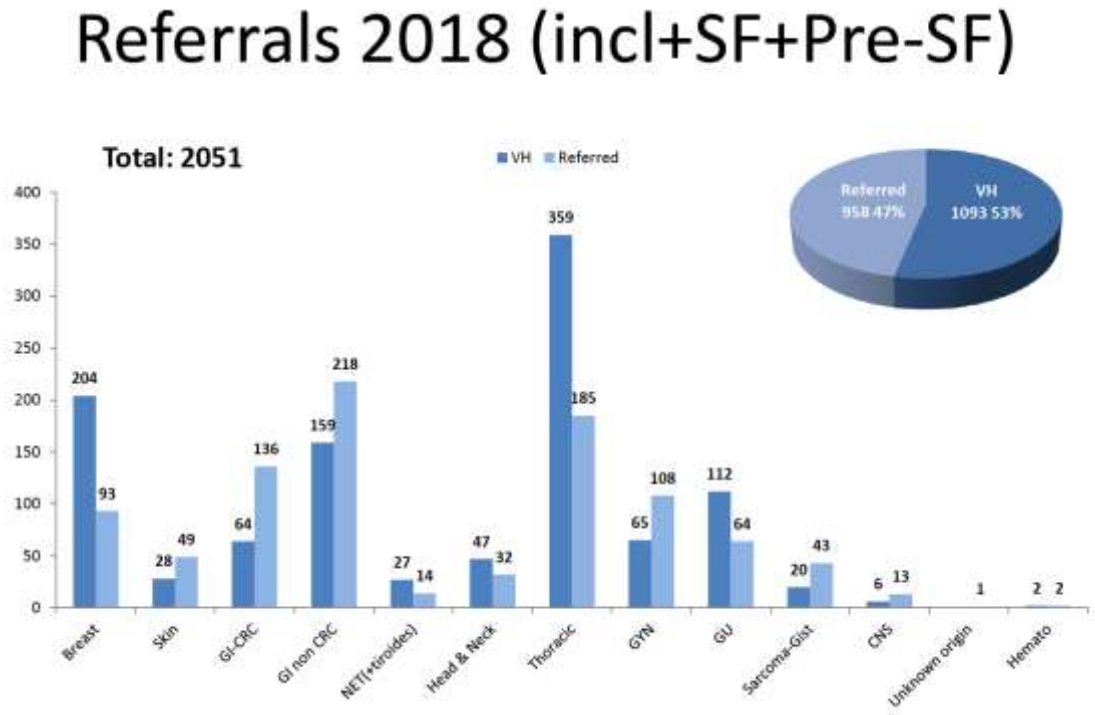
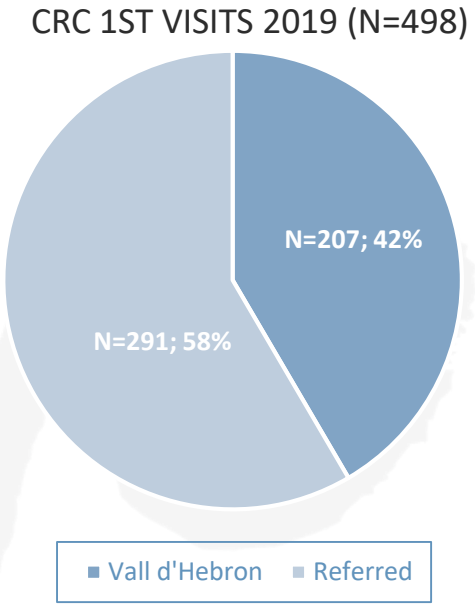
BUILDING A GOOD NETWORK IS CRUCIAL





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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
- → 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

send shipment

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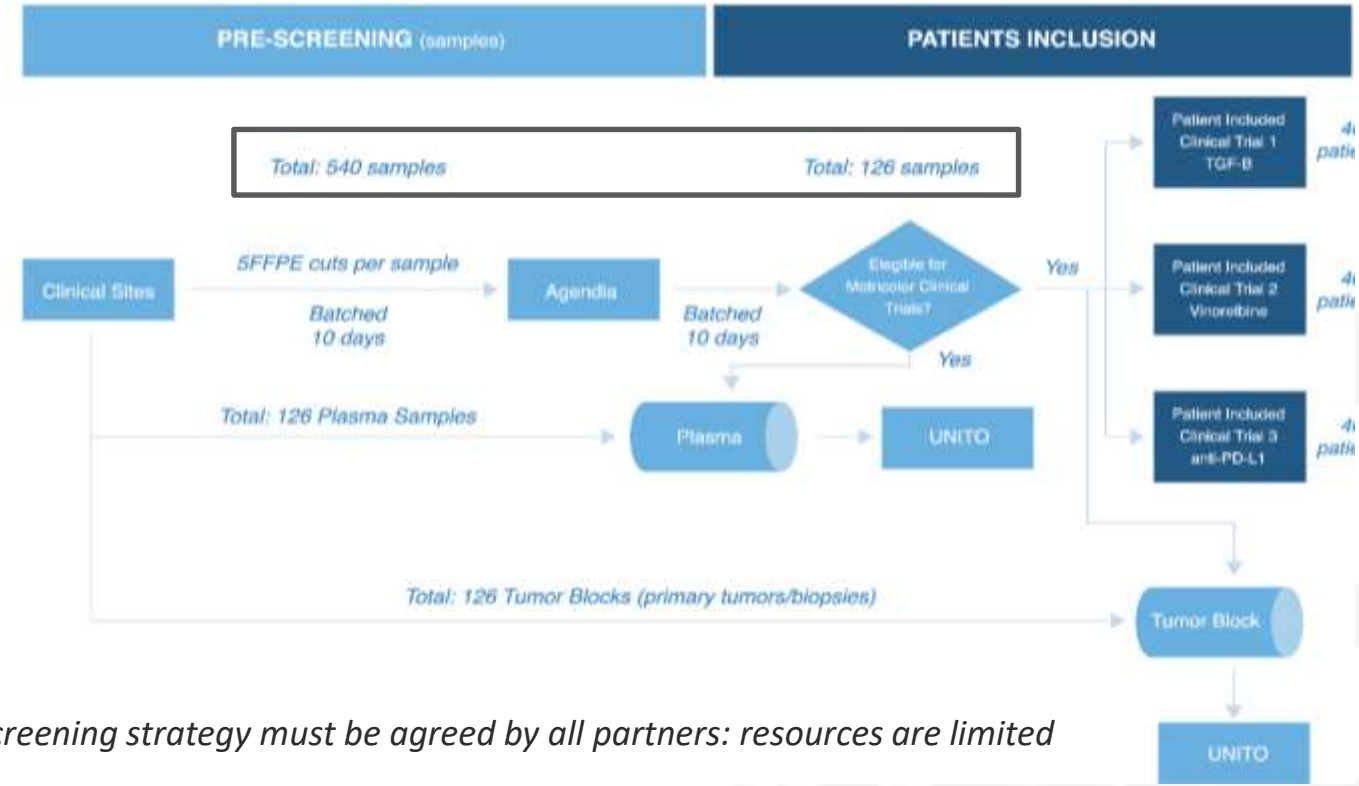
WP1 IMPACTS ON WP2, WP3, WP4… WP5, WP6, WP7



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

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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%

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	×	23/01/2019	08/01/2018

* 200 extra slots ready to be used

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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.

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RISK MANAGEMENT

- Failure of reproducibility of signatures in FFPE samples — NOT YET
- 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 — HAPPENED
- 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

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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	x	21/12/2018	23/11/2017
KUL	x	23/01/2019	08/01/2018

CONTINGENCY PLANS:

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

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KEY ELEMENTS

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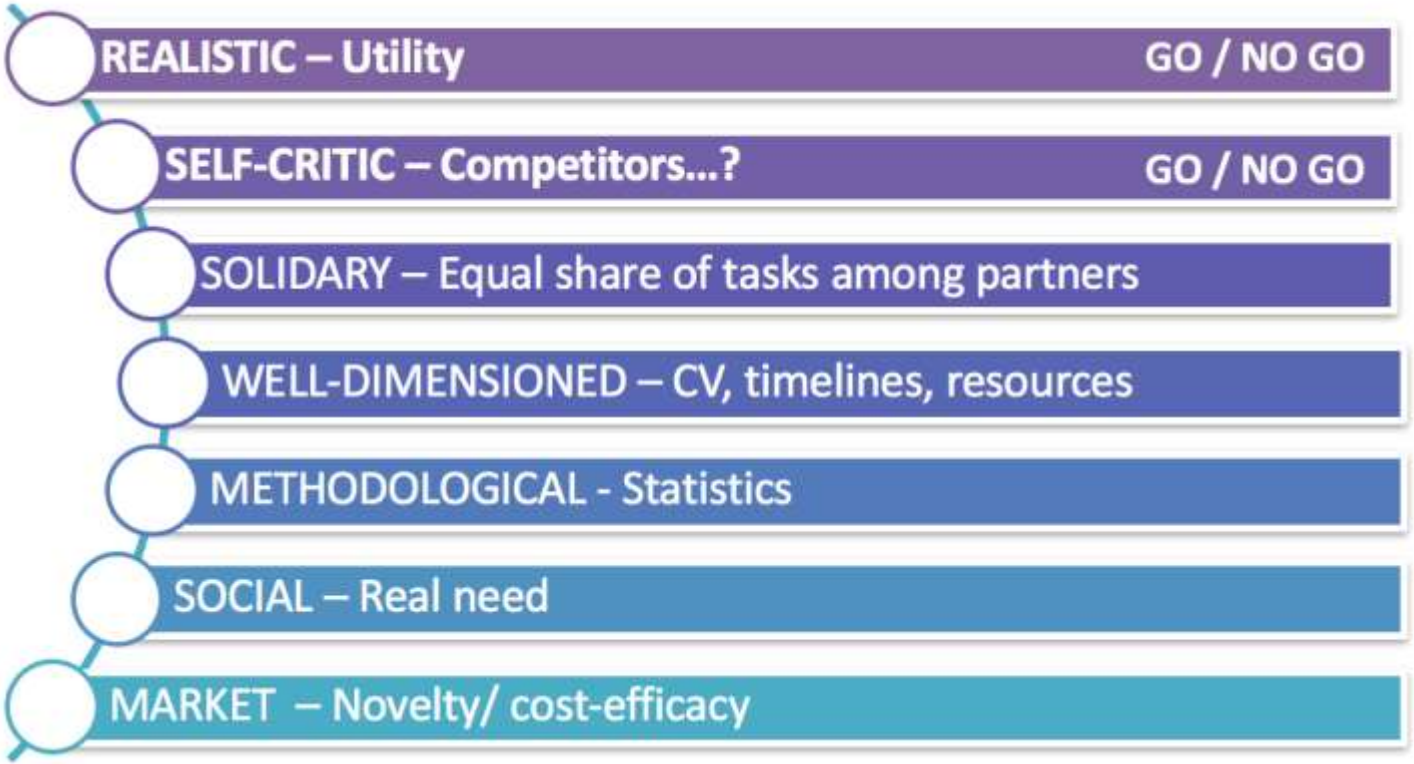

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H2020 IS A TEAM-WORK

Mind meld

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

- ✓ Clinicians
- ✓ Biologists
- ✓ Bioinformatics
- ✓ Statiticians
- ✓ Engineers
- ✓ And FUNDAMENTAL: *PROJECT MANAGEMENT*

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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)*

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AKNOWLEDGEMENTS

Josep Tabernero MD PhD, Head Medical Oncology Department; VHIO

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Javier Gonzalo (PhD, Project Manager, VHIO)

Ariadna Garcia (Research Nurse, VHIO)

Raquel Comas (Data Curator, VHIO)

All the researchers, clinicians, coworkers involved in the study

Patients and their families without whom anything would be possible

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Thank you

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