



Advancing a Precision Medicine Paradigm in Metastatic Colorectal Cancer:
Systems based patient stratification solutions.

Welcome to the Spring 2020 Newsletter for the COLOSSUS Project

Colorectal cancer is the third most common cancer in Europe. It is approximated that 50-55% of colorectal cancer cases involve RAS mutations (mt). In addition, a sizeable subset of these cases are classified as microsatellite stable, or MSS. Current treatment for metastatic MSS RAS mutated colorectal cancer includes chemotherapy +/- the medicine bevacizumab. However, there are limited treatments options for people with this type of cancer once they develop resistance to this standard treatment. Targeting MSS RAS mutated cancer is clinically challenging and medical advances in this area have not evolved significantly in recent years.

COLOSSUS is a Horizon 2020 funded project that aims to provide new and more effective ways to classify patients with microsatellite stable RAS mutant metastatic colorectal cancer and to develop better treatments for them. The COLOSSUS consortium studies patient blood and biopsy samples and applies advanced multi-omic computational modelling approaches to identify new MSS RAS mt specific subtypes. This strategy is designed to help us predict patient outcomes under standard treatment and to enable the design of more targeted and personalised regimens.

Message from COLOSSUS Coordinator Prof. Annette Byrne, RCSI



Prof Annette Byrne, COLOSSUS Coordinator at the Royal College of Surgeons in Ireland remarks *"The COLOSSUS strategy is based on our ability to integrate systems biomedicine, network analyses and computational modelling approaches to identify new actionable pathways, biomarkers and targets across RAS mutant colorectal cancer. We aim to identify new treatments and develop diagnostic assays for this intractable disease. Metastatic colorectal cancer is a highly prevalent, and complex pathology with a significant economic impact both within a European and global context."*

Prof Byrne continued: *"A centralized data repository and data exchange platform has been established for genomic, proteomic, metabolomics and clinical data; all samples for the retrospective cohort have been identified and the translational study has enrolled its first patients in Germany, Ireland and Spain and is progressing."*



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Partner in the Spotlight: HalioDx

HalioDx (<https://www.haliordx.com/>) is the pioneer of immuno-oncology diagnostic, a transforming approach of cancer care that benefits from novel and deep understanding of the tumor immune microenvironment. The company provides a unique and extensive range of proprietary assays that allow it to extract from the immune contexture of cancer patients the useful information to guide individual treatment strategy and drive the development of new therapies, notably immunotherapies.



HalioDx's Immunoscore® platform aims to improve day-to-day care for patients by providing routine and exploratory diagnostic solutions to clinicians, industrials and academic researchers. The company is based in France (Marseille) and the US (Richmond, Virginia).



The COLOSSUS consortium at their Marseille plenary meeting hosted by HalioDx, October 2019

First Patient recruited to COLOSSUS Translational Trial

University Hospital Mannheim, Germany recruited the first patient to COLOSSUS, an EU funded Horizon 2020 translational trial which could lead to a ground-breaking new way of treating people with advanced metastatic colorectal cancer.

Chief Investigator Prof Matthias Ebert of Heidelberg University and the University Hospital Mannheim, said: *"I am very excited about the potential benefits of this study for people with MSS RAS-mutant metastatic colorectal cancer. Patients and their doctors face special challenges in treatment of the cancer, therefore, COLOSSUS is addressing a key question in colorectal cancer which may hopefully lead to new concepts for the future management of patients in Europe and beyond"*.

Our partners at VHIO have organised a public meeting on the 27th of February 2020. For details see: <http://bit.ly/38Of6Rq>



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COLOSSUS Translational Study Update

The COLOSSUS study will identify new biomarkers and classifiers in blood and/or tissue for microsatellite stable RAS mutated colorectal cancer. Our aim is to develop new diagnostics and therapeutic options for patients bearing this type of cancer after they develop resistance to the current standard of care, and for whom there are no further treatment options currently available.

Thus far, the main focus has been to activate clinical sites and progress recruitment. It is planned to open the study at 10 international sites with a target recruitment of 163 patients. As sponsor, Cancer Trials Ireland manages and oversees the study activities on behalf of Chief Investigators Prof Ray McDermott (Ireland), Prof Matthias Ebert (Germany) and Prof Josep Tabertero (Spain) and COLOSSUS clinicians and scientists.

To date, a total of 7 sites have been activated which include:

Ireland: University Hospital Galway, Bon Secours Hospital Cork, and Tallaght University Hospital

Spain: Hospital Universitari Vall d'Hebron and Institut Catala d'Oncologia at L'Hospitalet de Llobregat. Both sites are in Barcelona

Germany: University Hospital Mannheim and Onkologische Schwerpunktpraxis Speyer



Currently 5 patients are registered to the study. Prof Matthias Ebert and the clinical trials team at University Hospital Mannheim registered the first person to the study in April 2019 and a second was registered in June. The first person in Ireland was registered by Dr Brian Bird and his clinical trials team at Bon Secours Cork in September 2019. In November 2019, Dr Rodrigo Dienstmann and the colorectal cancer clinical research team under the leadership of Dr Elena Elez at Vall d'Hebron Institute of Oncology, registered the first person in Spain and a second was registered by Dr Ramon Salazar and the clinical research team under the leadership of Dr Cristina Santos at Institut Catala d'Oncologia; L'Hospitalet de Llobregat.

An amendment to the protocol addressing challenges to the eligibility criteria for patients is currently under way and it is anticipated that this will improve the accrual rate. The work of all team members at sites is truly appreciated and thank you to all people who are willing to participate in this study.

Further information about the study and the sites can be found at cancertrials.ie, clinicaltrials.gov and https://www.colossusproject.eu/the_project/colossus-translational-study/.



The COLOSSUS team at University Hospital Mannheim



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Dissemination Round-up

Communicating COLOSSUS to the public

- Professor Annette Byrne, Head of the RCSI Precision Cancer Medicine Group and COLOSSUS Coordinator hosted and chaired a Bowel Cancer Awareness Month PPI event at RCSI on the 30th April 2019 in Dublin.
- UCD's David Gomez-Matallanas exhibited COLOSSUS at a public festival in Dublin on 8th June 2019. The UCD festival offered a packed programme of free events. Visitor numbers topped 16,000!

Conference Highlights

- COLOSSUS Coordinator Prof Annette Byrne, RCSI was a distinguished speaker at BIT's 12th annual World Cancer Congress meeting on May 15-17, 2019 in Osaka, Japan. Annette's talk was titled: "*Chromosomal Instability as a Predictive Biomarker in Metastatic Colorectal Cancer*".
- PI Prof Walter Kolch, UCD presented at the "The RAS superfamily and related pathways in health and disease" in Santander, Spain. Walter's talk entitled: "*Computational analysis of RAS signalling networks*" took place on May 16, 2019.
- VHIO PI Dr Rodrigo Dienstmann delivered the plenary talk at ESMO's 21st World Congress on Gastrointestinal Cancer in Barcelona. Rodrigo's talk "*Molecular classification of colon cancer: new insights*" occurred July 5, 2019.
- "*Stratified Treatment of Metastatic Colorectal Cancer (CRC), New Molecular Classification*" was the title of VHIO PI Dr Rodrigo Dienstmann's talk at the ESMO Annual Congress on September 30, 2019 in Barcelona.

Latest COLOSSUS Publications

- R. Dienstmann, K. Connor, A.T. Byrne, the COLOSSUS Consortium, W.H. Fridman, D. Lambrechts, A. Sadanandam, L. Trusolino, J.H.M. Prehn, J. Tabernero, W. Kolch. *Precision therapy in RAS mutant colorectal cancer*. *Gastroenterology*. 2020 Jan 20. pii: S0016-5085(20)30114-1.
- Wolf H. Fridman, Ian Miller, Catherine Sautès-Fridman, Annette T. Byrne, *Therapeutic Targeting of the Colorectal Tumor Stroma*. *Gastroenterology* Vol 158, Issue 2, January 2020.
- Irene Catalano, Elena Grassi, Andrea Bertotti, Livio Trusolino, *Immunogenomics of Colorectal Tumors: Facts and Hypotheses on an Evolving Saga*, *Trends in Cancer*, December 2019, Vol. 5, No. 12.
- M. Russo, G. Crisafulli, A. Sogari, N. Reilly, S. Arena, S. Lamba, A. Bartolini, V. Amodio, A. Magri, L. Novara, I. Sarotto, Z. Nagel, C. Pielt, A. Amatu, A. Sartore-Bianchi, S. Siena, A. Bertotti, L. Trusolino, M. Corigliano, M. Gherardi, M. Lagomarsino, F. D. iNicolantonio, A. Bardelli. *Adaptive mutability of colorectal cancers in response to targeted therapies*. *Science* 2019 Nov 7. pii: eaav4474.
- AC O'Farrell, IS Miller, R. Evans, M. Alamanou, M. Cary, G. Mallya Udupi, A. Lafferty, N. Monsefi, M. Cremona, JHM Prehn, HM Verheul, WM Gallagher, M. Gehrman, AT Byrne. *Implementing Reverse Phase Protein Array Profiling as a Sensitive Method for the Early Pre-Clinical Detection of Off-Target Toxicities Associated with Sunitinib Malate*, *Proteomics Clin Appl*. 2019 Feb 15:e1800159.
- Irene Catalano and Livio Trusolino, *The Stromal and Immune Landscape of Colorectal Cancer Progression during Anti-EGFR Therapy*, *Cancer Cell*, Volume 36, Issue 1, 8 July 2019, Pages 1-3.
- E. Burgermeister, F. Battaglin, F. Eladly, W. Wu, F. Herweck, N. Schulte, J. Betge, N. Härtel, JN Kather, C. Weis, T. Gaiser, A. Marx, C. Weiss, R. Hofheinz, IS Miller, F. Loupakakis, H. Lenz, AT Byrne, MP Ebert. *Aryl hydrocarbon receptor nuclear translocator-like (ARNTL/BMAL1) is associated with bevacizumab resistance in colorectal cancer via regulation of vascular endothelial growth factor A*, *EBioMedicine*. 2019 Jul; 45:139-154.

For more information visit the project website:

www.colossusproject.eu

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