IMI1 Final Project Report Public Summary

Project Acronym: QUIC-CONCEPT

Project Title: QUantitative Imaging in Cancer: CONnecting CEllular Processes with Therapy

Grant Agreement: 115151
Project Duration: 01/09/2011 - 31/12/2017

1. Executive summary

The executive summary will be made publically available, and therefore should not include information deemed as confidential by the consortium. It should be concise (preferably no more than 40 pages), comprehensive and should capture the updates for the last reporting period as well as the overall outputs of the project and its impact. It shall at least cover the following items:

1.1. Project rationale and overall objectives of the project

Imaging measurements (biomarkers) are routinely used in diagnosis, research and treatment in cancer. For the drug developer, a good imaging biomarker shows which drugs are active (and in which dose, schedule and combination, in which patients), before clinical benefit is evident, and which are unlikely to be effective. This allows drug developers to focus their limited resources on the most promising areas of cancer research, and minimises futile exposure of sick patients to ineffective investigational therapies. Unfortunately, available imaging biomarkers illuminate only a small proportion of the tumour pathologies we need to modulate and interrogate. Many investigational therapies seek to reduce tumour cell division and increase tumour cell death, so there is a pressing need to develop measures of proliferation, apoptosis, and necrosis into biomarkers which can reliably support both positive (go) and negative (stop) decisions. Looking further into the future, therapies for, and biomarkers of, the processes of invasion and metastasis will be of increasing importance, because in most cases it is metastasis, not the primary tumour, which kills the patient.

1.2. Overall deliverables of the project

The first objective (approximately 90% of the investment, WP2-5) is to qualify 2-3 specific imaging biomarkers (IBs) of tumour cell proliferation, apoptosis, and necrosis, to allow the drug developer to demonstrate reliably the modulation of these pathologic processes in tumours in patients in future trials. Our vision is that, by the end of the project, drug developers can incorporate these biomarkers for decision-making in Phase I trials of investigational therapies, confident that the biomarkers are technically valid, that a measured change in the biomarker faithfully reflects the desired change in the underlying tumour pathology, and that the IBs can be readily deployed in multiple cancer centres in a robust, consistent, ethical, and cost-effective way that is acceptable to the sick patients who will volunteer for our trials. The second objective (WP6) includes a portfolio of highly innovative, creative and cutting edge approaches to devise, evaluate and introduce IBs of invasion and metastasis.

1.3. Summary of progress versus plan since last period

The project was approved for 22 months of non-cost extension. During this last period:

In WP2, all preclinical studies have been completed. The data generally support our hypothesis that drug-induced changes in imaging biomarkers faithfully reflect drug-induced changes in underlying pathology from multiple tumour models and across modalities, and confounding factors delineated. In this regard we have identified tumour models or drug types that produce confounds in measurement. Regarding assets, in the past year we successfully expanded our imaging repository, XNAT, which now contains over 1200 MRI and over 600 PET images from over 860 tumours. This repository is already providing datasets for new projects in WP2 and WP6 (radiomics) and forms a

key component of the QUIC-CONCEPT sustainability plan. We are also combining data from multiple institutions to objectively assess ADC-histopathology correlates. This work will be summarised and published in due course. We expect that similar initiatives will be undertaken with existing data beyond the current funding period.

In WP3, the two biological validation studies (EORTC 1217 and 1423) have been completed and manuscripts on both studies are underway (1 submitted, 1 draft). The study results were presented at the last consortium general assembly. These ambitious studies were very challenging to recruit for, but in both cases, we accrued sufficient patients to provide a robust test of our hypothesis. More details can be found in the study statistical analysis reports. One abstract on EORTC 1217 was submitted to the European Congress of Radiology 2019.

In WP4, we developed analytical techniques for assessment of underlying image quality magnetic resonance imaging data being used to measure apparent diffusion coefficient (ADC). This included development of a diffusion phantom and automated software for assessment of optimised metrics to identify unexpected deviations from scanner performance. We developed a noise-reduced approach to the calculation of ADC and integrated this software into the Keosys platform. Diffusion weighted imaging from work package 3 was analysed providing results for the two clinical publications. In addition, we developed optimised movement correction techniques to enable routine use of diffusion weighted imaging in the liver during spontaneous respiration and an error modelling technique which allows correction of estimated measurement errors in ADC from individual tumours. The novel techniques provided reduction in the overall limits of agreement for ADC reproducibility to less than 3% from an original value in excess of 20%. This development allows reliable identification of treatment induced changes in ADC and individuals allowing reduction in group sizes for clinical trials from a typical value of 20 to 30 patients.

We also developed analytical techniques to standardise the use of [18 F]-FLT in clinical trials. This included establishing reproducibility in a variety of normal tissues and tumours. Liver and bone marrow identified as optimal normal tissue references with SUVpeak in these tissues showing good reproducibility and not been affected by differences in uptake intervals. We identified use of tissue blood ratio as the optimal assessment metric for [18 F]-FLT uptake in tumours and develop the required analytical software which was then incorporated into the Keosys image analysis platform and validated by analysis of test datasets.

In WP6 we investigated if the Cy5-tagged small immuno protein targeting the catalytic domain of human MMP2 (aMMP2-SIP) detects MMP2 in three tumors non-invasively. We concluded that aMMP2-SIP uptake correlates with MMP2 activity and might therefore be a potential non-invasive imaging biomarker for the evaluation of MMP2 activity in tumors. Furthermore, we validated in several cohorts of patients and murine datasets the concept of Radiomics. Radiomics, the high-throughput mining of quantitative image features from standard-of-care medical imaging that enables data to be extracted and applied within clinical-decision support systems to improve diagnostic, prognostic, and predictive accuracy. Radiomic analysis exploits sophisticated image analysis tools to generate image-based signatures for precision diagnosis and treatment.

1.4. Scientific and technical results/foregrounds of the project

1.4.1. Putative imaging biomarker of cell death and necrosis (MRI ADC)

1.4.2. Putative imaging biomarker of cell proliferation (FLT PET biomarkers)
1.4.3. Putative imaging biomarker of apoptosis (ICMT11 PET biomarkers)
1.4.4. Putative imaging biomarker of propensity to metastasis (CT radiomic signature)
1.4.5. Exploratory programme on imaging biomarkers of invasion (fluorescent MMP probe-based biomarkers)
1.4.6. Internationally-endorsed consensus imaging biomarker roadmap in oncology drug development

1.5. Potential impact and main dissemination activities and exploitation of results

1.5.1. Socioeconomic benefits include the following:

1.5.1.1. Drug developers place their clinical research operations, and in particular advanced pharmacodynamic imaging in early trials of investigational cancer therapies, in European academic centres and hospitals.

1.5.1.2. European imaging businesses, including both SMEs and imaging services provided by hospital/university-associated entities, develop and grow successfully.

1.5.2. Contributions to the health of European Citizens. A good imaging biomarker shows which drugs are active (and in which dose, schedule and combination, in which patients), before clinical benefit is evident, and which are unlikely to be effective. This allows drug developers to focus their limited resources on the most promising areas of cancer research.

1.5.2.1 Good validated imaging biomarkers hasten the introduction of safer and more effective treatments for European cancer patients

1.5.2.2 Good validated imaging biomarkers minimise futile exposure of sick patients to ineffective investigational therapies.

1.5.3. Increasing the competitiveness of Europe and helping to establish Europe as the most attractive place for biopharmaceutical research and development.

1.5.3.1 EORTC has established a network of universities and hospitals equipped to measure validated imaging biomarkers in a standardised way.

1.5.3.2 The EU-led international consensus imaging biomarker roadmap in oncology drug development equips European imaging companies to develop and validate their imaging biomarkers in the most effective and efficient way.

1.5.3.3 QuIC-ConCePT has established a network of universities equipped to measure validated imaging biomarkers in preclinical models in a standardised way.

QuIC-ConCePT has a strong publication policy, and the publications are listed on www.quic-concept.eu. Of particular note, the following QuIC-ConCePT publications have already received more than 50 citations.

title	journal	year	citations
Decoding tumour phenotype by n…	Nature Communications	2014	793
Radiomics: Extracting more inf…	European Journal of Cancer	2012	621
Predicting outcomes in radiati…	Nature Reviews Clinical Oncolo	2013	206
CT-based radiomic signature pr…	Radiotherapy and Oncology	2015	165
Stability of FDG-PET Radiomics…	Acta Oncologica	2013	139
Imaging biomarker roadmap for …	Nat Rev Clin Oncol	2017	134

Robust Radiomics feature quant…	PlosOne	2015	129
'Rapid Learning health care in…	Radiotherapy and Oncology	2013	106
Quantifying heterogeneity in h…	European Journal of Cancer	2012	98
Functional MRI for radiotherap…	Magnetic Resonance Imaging	2012	88
Quantitative computed tomograp…	PlosOne	2015	73
Volumetric CT-based segmentat…	Scientific Reports	2013	63
Qualification of imaging bioma…	European Journal of Cancer	2012	59
Apparent diffusion coefficient…	European Journal of Cancer	2012	57
[18F]FLT: An imaging biomarker…	European Journal of Cancer	2012	55

(Please note that citations are a lagging indicator in that there is a delay between performing the work, submitting for publication, appearing in the journal and getting cited)

1.6. Lessons learned and further opportunities for research

IMI provides a unique opportunity for academic, EFPIA and SME scientists to form deep pre-competitive collaborations to address major challenges. Our experience in QuIC-ConCePT at the outset was that all participants approached the project with an open and collegial attitude. EFPIA participation was valued for the in-kind contribution and for the expertise, perspective and enthusiasm of its scientists. However over the time-scale of an IMI project, EFPIA companies' priorities may change, and key scientists move on. Withdrawal of funding and in-kind has been a challenge for the project, particularly in the early stages, which preceded adoption of EFPIA's policy on "Continued Commitment to IMI projects". While we welcome EFPIA's commitment to attempt to mitigate the financial consequences, we would also urge EFPIA to do more to mitigate the intellectual consequences when EFPIA scientists move on, particularly in the case of EPFIA scientists with a significant role in setting the scientific direction for the project.

In view of the project achievements, our views on potential new research to further advance the field could be:

- Artificial intelligence (continuity plan of QuIC-ConCePT WP6-radiomics): collecting and re-analysing clinically imaging data from pharma's phase III oncological trials. Machine deep learning to explore, develop, and validate new imaging features.
- Integration of imaging biomarkers and fluid based biomarkers in monitoring cancer treatment (continuity plan of WP3). Both biomarkers are non-invasive and need to be validated. The combination of imaging and liquid biopsy assay will detect response or relapse at an earlier time point; therefore patients can benefit the next line anti-cancer therapy in case of emergence of tumour resistance.