A novel artificial intelligence (AI) imaging biomarker of tumor vascularity and heterogeneity radiomics to predict survival benefit of fruquintinib vs placebo in metastatic colorectal cancer (mCRC)

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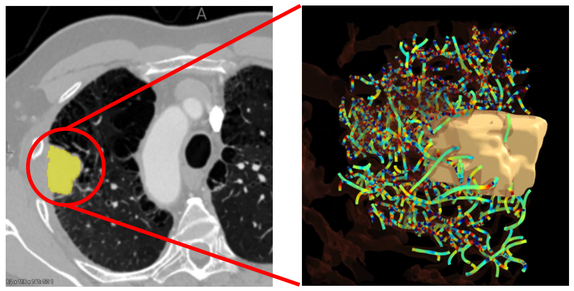
Background

- At initial diagnosis of colorectal cancer (CRC), approximately 15–30% of patients present with metastatic CRC (mCRC). Additionally, 20–50% of patients diagnosed with Stage I–III CRC eventually develop mCRC[1-3]
- Despite progress in systemic chemotherapy and targeted treatments, the five-year survival rate for patients with distant mCRC is 16.2%[2]
- Fruquintinib, a highly selective oral inhibitor of all three vascular endothelial growth factor receptors (VEGFRs -1, -2, and -3), suppresses tumor angiogenesis and is approved (including in the United States and the European Union) for previously treated mCRC[4-6]
- Traditional imaging methods do not fully capture the dynamic changes that occur within the tumor vasculature and tumor microenvironment, making it difficult to accurately evaluate the extent and impact of fruquintinib's anti-angiogenic mechanism[7]
- To date, some of the methods to demonstrate the anti-angiogenic effects of a drug are either invasive (angiogram or biopsy) or specialized imaging procedures like contrast enhanced perfusion computed tomography (CT) or magnetic resonance imaging (MRI) scans
- Quantitative Vessel Tortuosity (QVT), an advanced radiomic analysis of peritumoral vasculature, can quantify vessel branching and tortuosity on standard CT, enabling a non-invasive biomarker of anti-angiogenic response **(Figure 1)**[7]
- The objective of this analysis was to develop and validate an AI-based imaging biomarker to predict long-term survival benefit of fruquintinib versus placebo in mCRC using standard-of-care CT scans

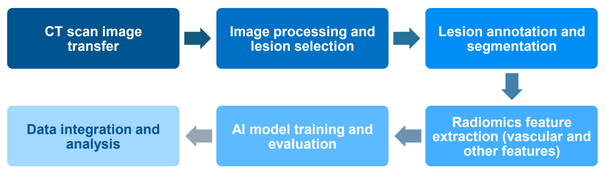
Figure 1: QVT visualization showing the curvature and twistedness of blood vessels



Methods

- A retrospective analysis was conducted using images from 221 patients enrolled in the phase 3 FRESCO-2 trial (NCT04322539)
- Metastatic lung lesions were annotated in 3D on CT scans from screening and Cycle 3, Day 1 (C3D1; first-on-treatment visit)
  - In the fruquintinib arm, 162 patients (422 lesions) were analyzed, and in the placebo arm, 59 patients (167 lesions) were analyzed
  - Lung metastases were chosen due to both their frequency and clinical importance in mCRC
  - Primary colorectal lesions were not analyzed due to the high rate of resection prior to the screening exam/fruquintinib administration, which yielded insufficient data quantity for analysis
- Annotations were performed using manual segmentation of metastatic lesions of the lung using a cloud-based annotation platform **(Figure 2)**
  - Final annotations were reviewed and approved by a practicing senior radiologist
  - Up to 5 lesions were manually annotated per scan; lesions were visible and measurable on both the screening and C3D1 visit scans for consistent tracking of treatment effect

Figure 2: Flow diagram demonstrating the workflow of the analysis



Aim

To develop and validate an AI and radiomics-based imaging biomarker to predict survival benefit of fruquintinib versus placebo in mCRC using standard-of-care CT scans

Methods

FRESCO-2:
Patients with mCRC from North America, Europe, Japan, and Australia (**N=691**)

R 2:1

Fruquintinib (n=461)
5 mg PO, QD + BSC, 28-day cycle
(3 weeks on, 1 week off)

Placebo (n=230)
5 mg PO, QD + BSC, 28-day cycle
(3 weeks on, 1 week off)

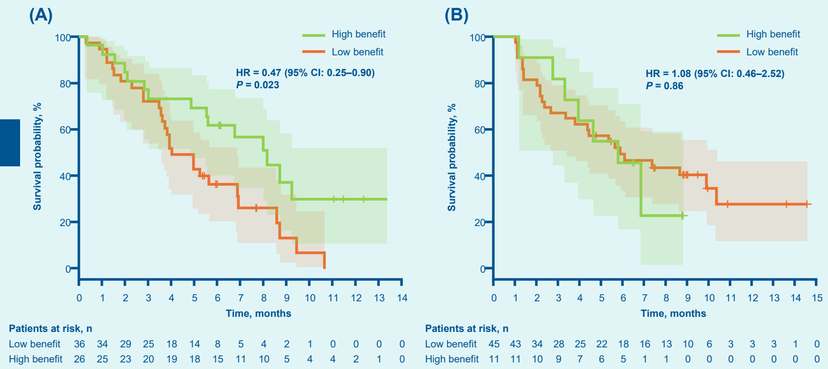
Treatment until progressive disease or unacceptable toxicity

Post-hoc QVT analysis (N=221):

- CT scans showing lung lesions from patients in the fruquintinib and placebo arms were analyzed for QVT features, quantifying peritumoral vascularity, textural heterogeneity, and shape categories at baseline and first-on-treatment follow-up
- An AI-based radiomics signature was developed predicting low versus high survival benefit as a continuous variable selected by the model, which was then evaluated on a held-out test dataset

Results

Figure 5: Kaplan–Meier curves of custom radiomic benefit groups, associated with improved survival in a held-out test set of the fruquintinib arm (A) but not the placebo arm (B)



- The final 12-feature radiomic signature (7 QVT, 4 texture, 1 shape) stratified patients with high versus low survival benefit with fruquintinib but not with placebo
- Fruquintinib patients with a high survival benefit exhibited decreased vascular branching patterns and fewer vessel twists versus patients with a low survival benefit, who exhibited elevated vascular tortuosity

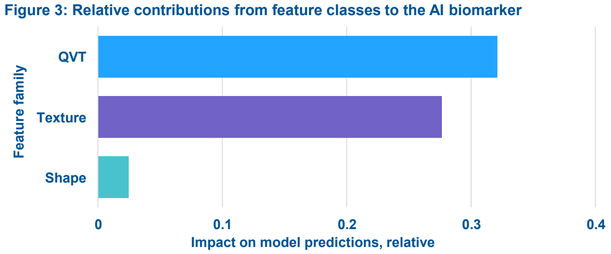
Key takeaways

This novel, non-invasive, imaging biomarker demonstrated its potential use as a response biomarker for fruquintinib and other anti-angiogenic therapies

This analysis highlights the use of AI imaging biomarkers of tumor angiogenesis and tumor heterogeneity in advancing precision medicine

- Twelve features were selected in the final model (based on the stability and predictive power of the features): 7 QVT features, 4 texture features, and 1 shape feature
- The AI biomarker cutoff for dividing patients into low and high benefit groups was set according to the threshold value, 0.384, which yielded the most significant overall survival (OS) stratification within the training set via Wald test for both fruquintinib and placebo arms
  - Of the 12 features, the 7 QVT features collectively contributed the most to the AI imaging biomarker **(Figure 3)**

Figure 3: Relative contributions from feature classes to the AI biomarker



Model training

- The lung lesion dataset from the fruquintinib treatment arm (n=159) was partitioned into a training set (60%, n=97) and a held-out test set (40%, n=62) using stratified random sampling
- The AI biomarker was tuned using 5-fold cross-validation. Each fold was repeated 25 times with different random initialization
- The hyper-parameters (including the number of features, stability thresholds, and feature selection criteria) were systematically optimized
  - In addition to QVT features, radiomic texture and shape features were extracted to capture a broad spectrum of tumor phenotypic information and dynamics of treatment response
  - Only features demonstrating high stability across diverse perturbations were included. Features underwent preprocessing steps including imputation and standardization

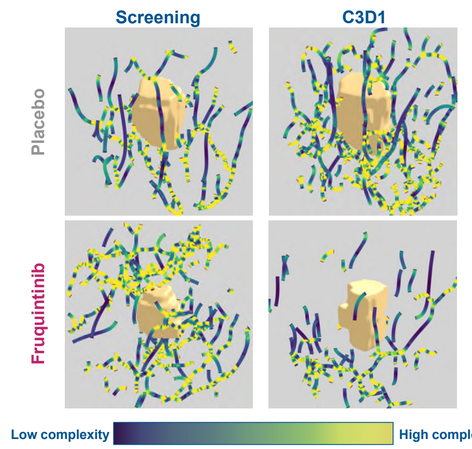
Evaluation

- Cox proportional hazards models were used to assess the model's association with OS
- The biomarker's association with OS was independently evaluated in the fruquintinib arm and the placebo arm to distinguish between predictive and general prognostic value
- Shapley additive explanation (SHAP) analysis was applied to interpret the contributions of individual features to the AI biomarker, quantifying the relative contribution of each included feature to the model's output

Results

- The final 12-feature radiomic signature (7 QVT, 4 texture, 1 shape) stratified patients with high versus low survival benefit with fruquintinib but not with placebo
- Fruquintinib patients with a high survival benefit exhibited decreased vascular branching patterns and fewer vessel twists, versus patients with a low survival benefit who exhibited elevated vascular tortuosity
  - Additionally, placebo-treated tumors showed an increase (complexity) in vessel curve intensity, while fruquintinib-treated tumors showed a reduction (normalization) in vessel curve intensity at C3D1 when compared with baseline **(Figure 4)**

Figure 4: Tumor visualization of change in vessel curve intensity



- The AI biomarker demonstrated strong predictive performance in the held-out test set of fruquintinib-treated patients, indicating statistically significant stratification of patients by OS **(Summary Panel, Figure 5)**
- The hazard ratio (HR) of 0.47 for fruquintinib suggests that patients classified as "high benefit" by the AI biomarker had over 50% reduced risk of death as compared to radiomic low benefit patients **(Table 1)**
- Importantly, when the same AI biomarker was applied to the placebo arm, it did not significantly stratify patients by OS. This indicates that the AI biomarker's predictive ability is specific to fruquintinib treatment benefit and not a general prognostic indicator

Table 1: Performance of AI biomarker benefit groups in held-out test dataset

	HR	95% CI	*P*-value
Treatment arm	0.47	0.25–0.90	0.023
Placebo arm	1.08	0.46–2.52	0.86

CI, confidence interval.

Conclusions

- Overall, QVT as a novel, AI-based, non-invasive, imaging biomarker demonstrated its potential use as a response biomarker for fruquintinib and other anti-angiogenic therapies
- The biomarker's ability to stratify patients as early as first-on-treatment follow-up into distinct survival groups provides critical information early in the treatment course
  - The demonstrated specificity of the biomarker to the fruquintinib treatment arm, rather than being a general prognostic indicator, underscores its value in personalized medicine within the anti-angiogenesis context
- This early prediction of benefit may inform clinical decision-making, allowing for the prompt identification of patients benefiting from fruquintinib
- The biomarker's robust performance is supported by the diversity of its training data, which was collected from multiple global centers and included a variety of imaging protocols and equipment
  - This broad data spectrum enhances the generalizability and clinical applicability of the AI imaging-based biomarker

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Disclosures

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