Tyrosine kinase inhibitors (TKIs) provide effective cancer treatments, but are often associated with cardiotoxicity ranging from heart failure, left ventricular systolic dysfunction and hypertension to arrhythmia. In order to enable the development of a new generation of safer TKIs, it is therefore critical to establish novel strategies that can help rank, early in the discovery process, the cardiotoxicity of molecules in this drug class.

**Methods**

Adult human primary cardiomyocytes isolated from ethically consented donor hearts were used to measure contractility transients using an imaging-based platform. Changes in contractility parameters were used to infer both TKI-induced inotropic (sarcomere shortening) and pro-arrhythmia (after contraction, AC) risk. We addressed the clinical relevance of this approach using a panel of 8 FDA-approved TKIs and one experimental TKI. Each TKI was tested separately at multiple concentrations. Using clinical reference data, we have assessed the ability of non-invasive measurement of cardiomyocyte contractility to predict the cardiac safety risk associated with each one of the TKIs.

**Results**

Cardiotoxic TKIs inhibit human contractility

Cardiomyocytes were loaded with a single excitation / emission fluorescence Ca²⁺ indicator dye, Cal-520. Experiments were performed at physiological temperature and transients were acquired with an imaging station with 20 Hz stream acquisition for 10 s with 50 ms exposure. n=18 and 34 cells for Sorafenib and Afatinib, respectively.

**Summary**

The adult human primary cardiomyocyte-based platform:

1. Can differentiate safe from cardiotoxic TKIs and is predictive of clinical outcomes.
2. Enables mechanistic assessment.
3. Could potentially provide a useful strategy for the early assessment of the ability of new TKIs to cause cardiotoxicity.