Protein Tyrosine Kinase 7 (PTK7) Biomarker Analysis in Patients treated with PF-06647020, a PTK7 Antibody-Drug Conjugate (ADC), in a Phase I Dose Expansion Study

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Amy Jackson-Fisher[1], Navi Mehra[2], Roberto Gianani[2], Pamela Whalen[1], Pamela Vizcarra[1], Shibing Deng[1], Stephen McComish[1], Xiaohua Xin[1], Eric L Powell[1]

[1]Pfizer Early Oncology Development & Clinical Research, La Jolla, CA, USA; [2]Flagship Biosciences Inc, Westminster, CO, USA

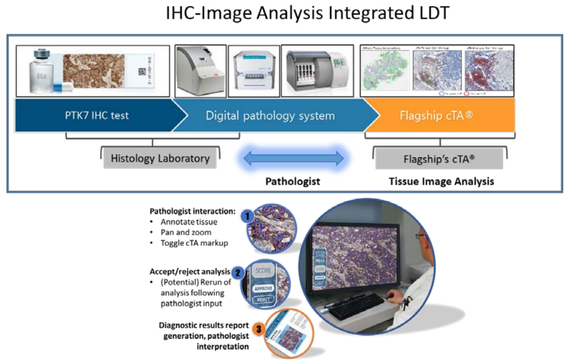
BACKGROUND

- PF-06647020, an ADC comprising a humanized monoclonal antibody against PTK7, a cleavable valine-citrulline linker, and an auristatin payload, is being investigated in an ongoing Phase I clinical trial in patients with advanced solid tumors.
- We hypothesized that response to a PTK7-directed ADC would correlate with PTK7 expression in the patients' tumor.

Approach:

- We developed and validated a novel LDT comprising an anti-PTK7 immunohistochemistry assay with digital tissue analysis using Flagship Biosciences, Inc.'s cTA® platform to detect membrane-associated PTK7 in formalin-fixed paraffin embedded (FFPE) epithelial malignancies of ovary, breast and lung.

Figure 1: PTK7 cTA-based LDT



System design

- The system consists of an analytically validated PTK7 IHC assay, digital pathology system (whole slide scanner and database), and a custom created cTA algorithm by Flagship.
- The entire system was CLIA validated in Flagship's laboratory to create the LDT for patient enrollment.
- The pathologist is central to the workflow, providing key inputs and checks during the tissue image analysis process.

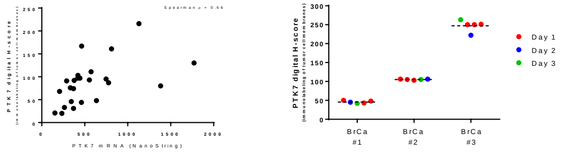
System workflow

- The H-score was determined from the image analysis markup and quantified based on percent positive cells and intensity of staining.
- A board-certified MD pathologist provided a final review and approval of region of analysis (ROA) annotations and confirmed image analysis algorithm accuracy prior to approving export of the tIA endpoint for enrollment decision.
- In order to receive MD pathologist approval, it was required that 90% or more of the cells quantified by the algorithm were tumor cells.

CLIA Validation for cTA-based LDT

- PTK7 IHC Assay was developed at Pfizer, Inc (AACR poster #4925) and transferred to Flagship Biosciences' CAP and CLIA-certified laboratory.
- Validations were performed on Intended Use tumor sets comprising routinely-collected FFPE epithelial malignancies of ovary, breast or lung.
- The LDTs met all of the pre-established performance parameters including accuracy, precision, reportable range as well as positive and negative agreement (analytical sensitivity/specificity).

Figure 2: Accuracy and Precision of LDT in BrCa



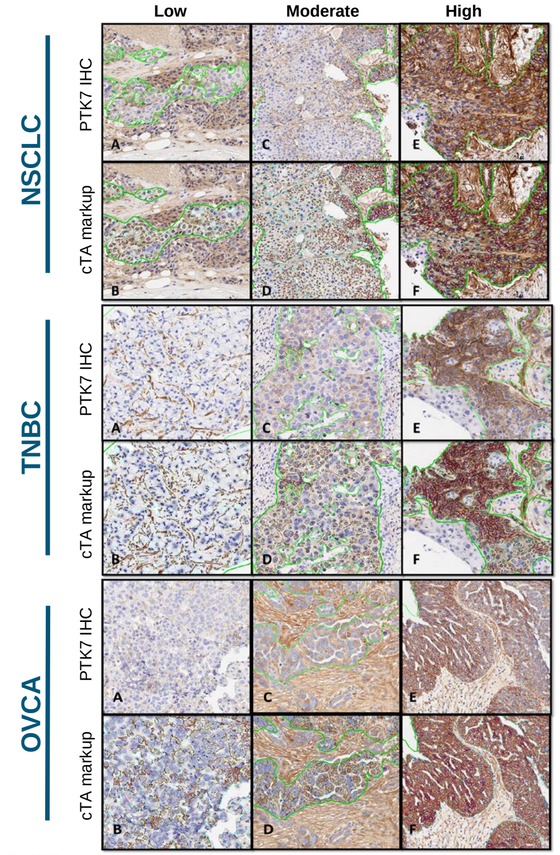
The graph to the left demonstrates the correlation between the PTK7 digital H-scores and PTK7 mRNA (NanoString values) from the same breast cancer samples. This was used to assess accuracy and as shown the assay had a positive Spearman correlation ($\rho = 0.66$). The graph to the right demonstrates the precision of the assay in three BrCa (breast cancer) samples (intra-class correlation value = 0.986).

Accuracy and precision was also assessed in 3 unique NSCLC and OVCA samples. There was positive correlation between digital H-score and PTK7 mRNA and statistically significant inter-run and intra-run precision with both indications (data not shown).

PTK7 Requirement in Phase I Dose Expansion Study Cohorts

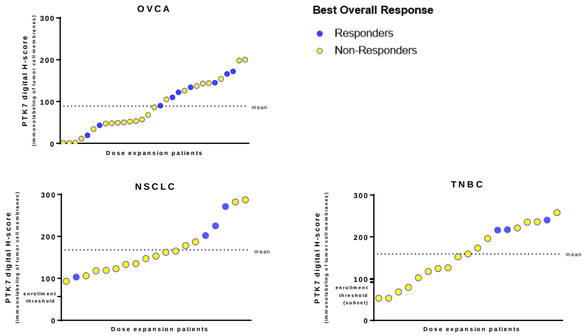
- Non-small cell lung cancer (NSCLC) patients with digital H-scores ≥ 56.8 in archival tumors were eligible for enrollment
- Triple negative breast cancer (TNBC) patients were initially enrolled unselected, but after review a requirement for digital H-scores ≥ 92.8 in archival tumors was implemented for enrollment.
- Ovarian cancer (OVCA) patients were enrolled unselected; however, the archival tumor samples were tested with the PTK7 LDT and digital H-scores were generated.

Figure 3: Representative Low, Moderate and High PTK7 Stained Phase I Tumor Samples



The PTK7 digital H-score was used to separate patients into three groups (low, moderate and high). Representative examples of biopsies classified by digital H-score as low (A & B), moderate (C & D) and high (E & F) are shown for each tumor type. All biopsies are annotated (green line) to include tumor in the analysis and to exclude non-neoplastic or necrotic tissues from the analysis. In the cTA markups (B, D & F), the tumor membranes are labeled (Blue: negative, Yellow: +1, Orange: +2, and Red: +3) according to the intensity of the PTK7 labeling. The classification of cells is then used to calculate the digital H-score and to stratify the patients.

Figure 4: Baseline PTK7 Expression in Phase I Patients' Tumor Samples



OVCA=ovarian cancer; NSCLC=non-small cell lung cancer; TNBC=triple-negative breast cancer
Data cut-off Oct 24, 2017

Table 1: Summary of PTK7 Digital H-scores in Phase I dose expansion cohorts

	Number of Samples	Minimum H-score	Maximum H-score	Mean H-score	Mean H-score of Non-responders	Mean H-score of Responders
OVCA	31	1	200	89.2	80.2	111.2
NSCLC	19	93	287	167.8	159.2	200.3
TNBC	19	53	258	159.2	147.0	224.3

CONCLUSIONS

- A novel CLIA validated LDT was developed and implemented to assess PTK7 baseline levels in FFPE tumors from patients treated with PF-06647020.
- Clinical responses tended to correlate with H-scores that were higher than the mean for each tumor type.

ACKNOWLEDGEMENTS

- We would like to acknowledge Stemcentrx Inc for providing the anti-PTK7 antibody used in the LDTs.