Establishment of Patient-derived Succinate Dehydrogenase-deficient Gastrointestinal Stromal Tumor (GIST) Models for Predicting Therapeutic Response

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Genomic Alterations in GISTs

- KIT 63%
- PDGFRA 11%
- NF1 9%
- SDH 7%
- BRAF 3%
- Unknown 3.50%
- RAS 2%
- TACC1 1%
- FGFR1-HOOK3/FGFR1-TACC1 1%
- ETV6-NTKR3 0.50%
Succinate Dehydrogenase (SDH)-Deficient GIST Only Occur in the Distal Stomach

Sharma, de la Torre et al, *Clinical Cancer Research*, July 2021
Succinate Dehydrogenase (SDH)-Deficient GIST

**Carney-Stratakis Syndrome**
- Germline mutations
- Hereditary
- Often in late teens to 30s
- Paraganglioma (PGL)

**Carney’s Triad**
- Promoter hypermethylation
- Sporadic
- Teenage females
- PGL + Pulmonary Chondroma

Modest response rates to tyrosine kinase inhibitors (ORR 10-20%)

Major Unmet Needs in Field

- Limited patient-derived tumor models to understand the disease pathobiology and drug screening
- Limited therapeutic options
Workflow

GISTs with mutations in SDHA, SDHB and SDHC → Resected tumor → Dissociation of tumor into single cells → Establishment of patient-derived mSDH GIST models → Test if established models recapitulate parent tumor metabolic and transcriptomics profiles

Parent tumors → mSDH GIST models
Establishment of Mutant SDH Cell Models

*SDH* mutant GIST

- FX-437A
  - *SDHA* splice site
  - 1432_1432+1delGG

- FX-424B
  - *SDHB* R90*

- FX-435C
  - *SDHC* R133*

*SDH* mutant primary cell models

Ex vivo establishment

Mutant SDH Cell Models Express GIST Markers & SDHB Loss

GIST Marker Expression

SDHB Immunoblot

SDHB Immunofluorescence

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
Metabolic Characterization & Complex II Inhibition in Mutant SDH Models

A

B

Succinate
Fumarate
TCA cycle

Modified from Moosavi et. al., Biol Chem., Feb 2020

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
Transcriptome Characterization of Mutant SDH GIST Models

A

Mutant SDH GIST models

SD-437A

SD-424B

SD-435C

r² = 0.944

r² = 0.927

r² = 0.938

FX437A

FX424B

FX435C

Parent tumors

B

SDH-loss related genes

APLP1

CACNB3

COL1A1

EDN1

EMP1

FEZ1

FHL2

FSTL1

IGF1R

IL1B

INHBA

JAM2

JAMC2

LOX2

MFAP4

MYO1F

PCDH9

PCS25

PLXDC2

PRSS23

RAB20

S100A6

SGCB

SLC1A1

SLC25A24

SOCS2

ST7

TNFRSF19

VDR

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
Hypoxia Related HIF Stabilization and Gene Upregulation

Belinsky et al, Frontiers in Oncology, May 2013

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
Hypoxia Related HIF Stabilization and Gene Upregulation

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
SDH-Deficient GIST Cell Models are Imatinib/Sunitinib Insensitive

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
Therapeutic Vulnerability to DNA Alkylating Agent – Temozolomide (TMZ)

Hap1 near-haploid line derived from KBM-7 CML line

Relative Cell viability

SDHA: WT KO KO+WT

TMZ (µM)

50.0 12.5 3.125 0.0

SDHA WT SDHA KO SDHA KO+WT
TMZ Induces DNA Damage & Double Stranded DNA Breaks

Comet Assay

γ-H2AX positive cells

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
Patient Case: Stage IV $SDHB$ R90* GIST

- 22 yo male treatment with TMZ

TMZ Efficacious in SDH-Deficient GIST Patients

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021

Objective Response Rate 40%

SDHA SDHB SDHC SDHD

Patients

Best Tumor Response

SD

PR

Pt 1 (SDHA)
Pt 2 (SDHC)
Pt 3 (SDHD)
Pt 4 (SDHB)
Pt 5 (SDHB)

Months

Partial Response
Stable Disease
Progressive Disease
Summary

Currently Enrolling

Phase II Study of Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient GIST (ClinicalTrials.gov NCT03556384)

open at:

UC San Diego
OREGON HEALTH & SCIENCE UNIVERSITY
FOX CHASE CANCER CENTER
TEMPLE HEALTH
UNIVERSITY OF MIAMI HEALTH SYSTEM

Target Accrual: 23 patients
To Date: 13 patients treated

Yebra, Bhargava, et al, Clinical Cancer Research, July 2021
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