FASN inhibitor TVB-2640 shows pharmacodynamic effect and evidence of clinical activity in KRAS mutant NSCLC patients in a Phase 1 study

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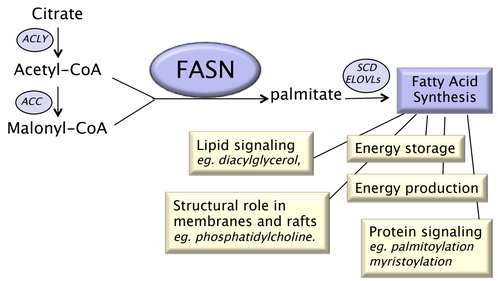
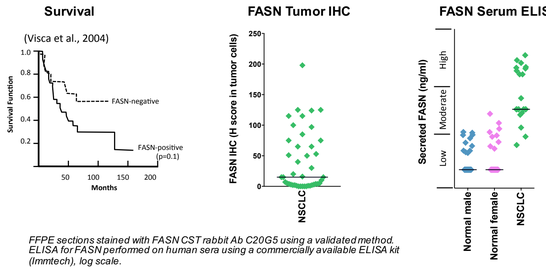
3-V BIOSCIENCES™

Fatty Acid Synthase (FASN)

- Mediates neoplastic lipogenesis
- Generates palmitate
  - Acylation of signaling proteins such as KRAS
  - Building block for long chain fatty acids, membranes and lipid rafts
  - Converts glucose and other carbon sources into lipids to support cancer cell signaling
- Upregulated in tumor vs normal tissue
- Correlates with poor prognosis in certain tumor types including NSCLC (Visca et al., 2004)
- KRAS-mutant cell lines show increased sensitivity to FASN inhibitors than KRAS-WT cell lines (Ventura et al., 2015, Heuer et al., AACR 2016



FASN expression in human NSCLC



FFPE sections stained with FASN CST rabbit Ab C20G5 using a validated method. ELISA for FASN performed on human sera using a commercially available ELISA kit (Immtech), log scale.

Phase 1 Investigators: 3V2640-CLIN-002

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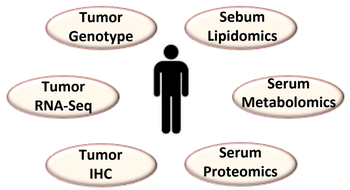
Phase 1 solid tumor study 3V2640-CLIN-002 with TVB-2640, a novel FASN inhibitor

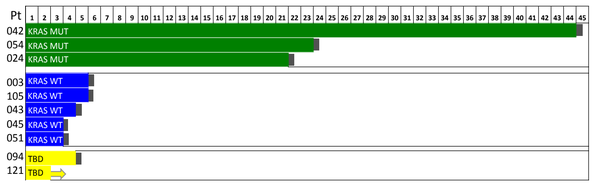
- TVB-2640 is an oral, first-in-class, small-molecule reversible inhibitor of FASN with IC_{50} < 0.05 µM
- Multicenter, open label, phase 1 FIH study
- Oral, once daily with 21 day continuous cycles (monotherapy)
- TVB-2640 has a half-life of approx. 16 hours
- Ongoing expansion phase dose of 100 mg/m^2
- To date, 10 evaluable NSCLC patients enrolled on monotherapy

Comprehensive biomarker sampling for first in class agent



KRAS-MUT NSCLC patients have longer duration on study than KRAS-WT

Weeks on study for monotherapy NSCLC patients



- N=10 NSCLC; 3 KRAS-MUT, 5 KRAS-WT, 2 KRAS-unknown
- Similar plasma TVB-2640 exposure across groups

- **100% (3/3) KRAS-MUT > 12 weeks on study**
- **0% (0/5) KRAS-WT > 12 weeks on study**

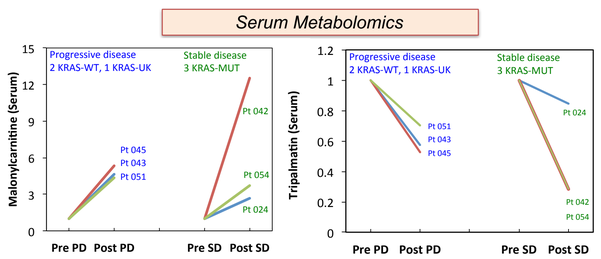
Pt	KRAS	Dose (mg, mg/m^2)	Cmax (ng/ml)	AUC_{0-24} (hr*ng/ml)
003	WT	450, 240	4650	72740
043	WT	250, 130	7410	101200
045	WT	150, 100	2800	43960
051	WT	200, 100	3320	45440
		Average	4545	65835

Pt	KRAS	Dose (mg, mg/m^2)	Cmax (ng/ml)	AUC_{0-24} (hr*ng/ml)
024	MUT Q61H	100, 80	3320	41360
042	MUT G13C	250, 130	3460	40900
054	MUT (nd)	150, 100	3990	42490
		Average	3950	41583

TVB-2640 plasma PK parameters calculated from day 1 of administration. All NSCLC monotherapy patients with PK data available are shown. Pts 094 and 121 pending. Un-monitored clinical data

TVB-2640 inhibits FASN in both KRAS-WT and KRAS-MUT NSCLC patients

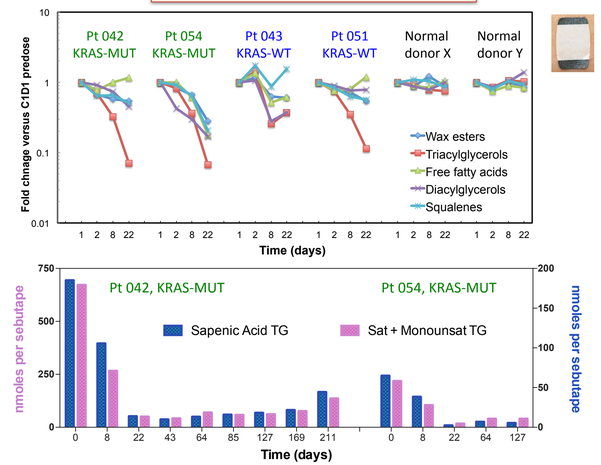
Serum Metabolomics



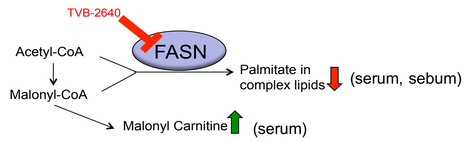
Serum used for global metabolite profiling by UPLC-MS/MS, performed at Metabolon. All NSCLC monotherapy patients with data available are shown. Similar effect observed in other tumor types.

TVB-2640 inhibits de novo lipogenesis

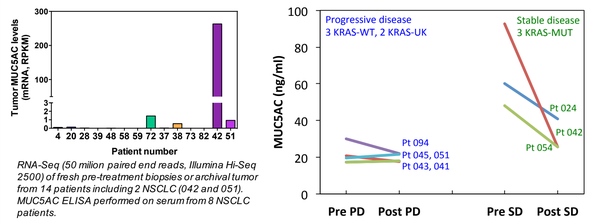
Novel Non-Invasive Sebum Lipidomics



Sebum was collected using Sebutape® patches on the forehead for 30 minutes, and profiled by GC-MS and MS-flame ionization detection for lipid content at Metabolon. Normal donors were not administered TVB-2640. Similar inhibition of DNL observed across all patients tested (approx. 20).



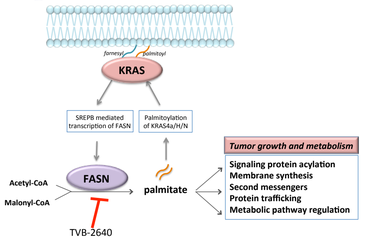
MUC5AC is a potential biomarker of response in KRAS-MUT patients



RNA-Seq (50 milion paired end reads, Illumina Hi-Seq 2500) of fresh pre-treatment biopsies or archival tumor from 14 patients including 2 NSCLC (042 and 051). MUC5AC ELISA performed on serum from 8 NSCLC patients.

- Tumor RNA expression showed high MUC5AC in Pt 042 (KRAS-MUT, prolonged stable disease) versus other patients
- Serum ELISAs showed higher baseline MUC5AC in Pt 042 and other NSCLC KRAS-MUT patients, decreased with TVB-2640 treatment
- MUC5AC has a palmitoylation site conserved with other mucins, which may require FASN-derived palmitate for function

Potential mechanism of action against KRAS-MUT



Summary

- TVB-2640 is a first in class FASN inhibitor
- Inhibition of FASN and inhibition of de novo lipogenesis shown
- KRAS-MUT NSCLC pts show increased clinical activity, and provide a niche population with unmet need for clinical development of TVB-2640
- Potential mechanisms include KRAS4a palmitoylation, KRAS reliance on metabolism, maintenance of membrane architecture, and acylation of other signaling proteins
- Additional biomarker analyses are ongoing
- Additional opportunities in other RAS mutant populations

Acknowledgements

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