Fatty Acid Synthase (FASN)  
- Mediates neoplastic lipogenesis  
- Generates palmitate  
  o Acylation of signaling proteins such as KRAS  
  o Building block for long chain fatty acids, membranes and lipid rafts  
  o 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)  

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

3-V Biosciences, Menlo Park, USA.

FASN expression in human NSCLC  

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 IC50 < 0.05 μM  
- Multicenter, open label, phase 1 FIH study  
- Oral, once daily with 21 day continuous cycles (monotherapy)  
- TVB-2640 has half-life of approx. 16 hours  
- Ongoing expansion phase dose of 100 mg/m2  
- 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

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

Serum Metabolomics

TVB-2640 inhibits de novo lipogenesis

N=4:2 KRAS-MUT
N=5:3 KRAS-WT

Novel Non-Invasive Sebum Lipidomics

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

Tumor RNA expression showed high MUC5AC in PI 042 (KRAS-MUT, prolonged stable disease) versus other patients  
- Serum ELISA showed higher baseline MUC5AC in PI 042 and other NSCLC KRAS-MUT patients, decreased with TVB-2640 treatment  
- MUC5AC has a patolysin 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 show  
- Additional biomarker analyses are ongoing  
- Additional opportunities in other RAS mutant populations

Acknowledgements

Thanks to the clinical site teams, the patients and their families. Also to Metabolon, Mosaic, Paracelis, Triagene and BioAnalytx for sample analysis. Poster available at www.3-vbio.com

Phase 1 Investigators: 3V2640-CLIN-002

Y. Yoon, M. Xiao, W. Tang, X. Li, C. Lin, H., Y. Zhang, W. Tang, J. Zhang, W. Li, J. Zhang, S. Wang, H. Wang, L. Kuang, M. Ma, Z. Xie, L. Wu, Cancer Metabolism and lipidomics of human NSCLC cell lines and tumor xenografts. Cancer Metabolism and lipidomics of human NSCLC cell lines and tumor xenografts. Tumor RNA expression showed high MUC5AC in PI 042 (KRAS-MUT, prolonged stable disease) versus other patients  
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