A novel drug response predictor (DRP) mRNA biomarker of the tumor response to the multi tyrosine kinase inhibitor dovitinib

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Introduction

Tyrosine kinase inhibitors (TKIs) have been approved by the FDA for numerous indications, but no effective biomarker of response has been identified. Dovitinib is a multikinase inhibitor currently being developed for the treatment of renal cell carcinoma, and other solid tumors where patients are selected by the DRP biomarker specific to dovitinib. Other drug specific DRPs are also in clinical trials selecting patients with high likelihood of responding to the treatment.

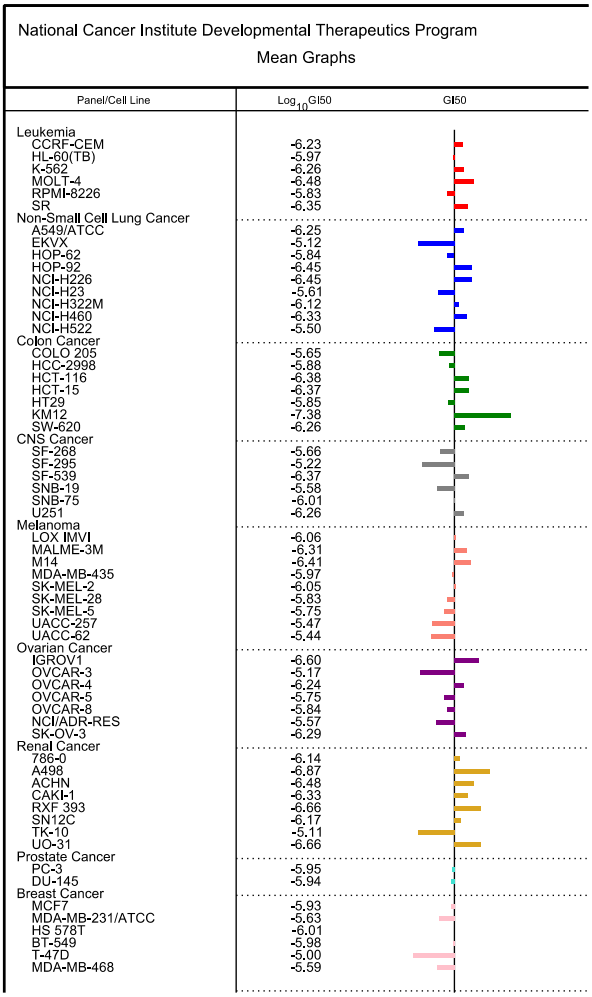

Fig 1. Dovitinib growth inhibition (GI_{50}) ranges from 42nM to 10μM

DRP Development

A biomarker for dovitinib was developed based on in vitro data of growth inhibition of the NCI60 cell line panel in the presence of dovitinib. It was found that 58 out of 25,000 mRNAs were relevant to the in vitro sensitivity or resistance of dovitinib. The biomarker algorithm combines the expression of these 58 genes in a DRP-Dovitinib likelihood score between 0-100%.

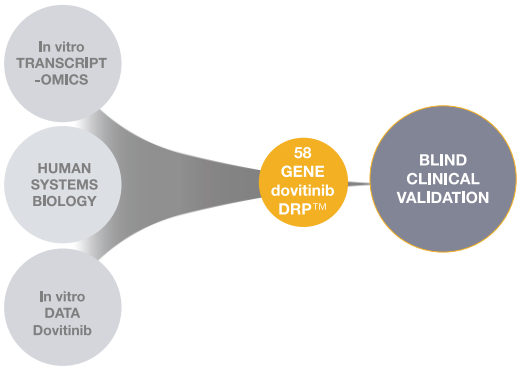

Fig 2. Methodology of combining in vitro growth inhibition and mRNA

Genes associated with pathways

Pathway/process	Genes
FGF	SEL1L3 LSM4 STAT6 - *GATA3*
VEGF	VEGFA FABP5 DPP4 LDLR TMSB10 P4HA1 STAT6 RPL38 - *HRAS UCP2 ATM GATA3 SPDEF CUL3*
PDGF	STAT6 UCP2 - *TUG1 ATM GATA3*
PI3K/Akt/mTOR	REDD1 TRIM22 FABP5 MCT4 INSIG1 - *HRAS SCAMP3 IGFBP5 ATM SRM CUL3*
Drug resistance	ABCF1 IGFBP5
Metastasis and hypoxia	DPP4 REDD1 - *ATM NDUFV1 CERS2 CKB*
Topoisomerase	HRAS APITD1
Other	RPS20 TPK1 MIR196B HSPE1 CAV2 APOL1 PTPRE DPYSL2 ANP32B RPL27A EPB41L2 RPL3 - *BAG5 BAG6 MARCH6 EMC3 CLPTM1 MAGEA1 LDOC1 ZNF331 TOB1 NDUFV1 MCUR1 NBPF10 PPP1R11*

The mRNAs that are identified by the Dovitinib DRP have in the literature been associated with a number of pathways relevant to the action of dovitinib, and some mRNAs have been associated with more than one pathway. Genes in black are those overexpressed in dovitinib sensitive cell lines, genes in red italic are those that are overexpressed in dovitinib resistant cell lines. However, about half of the genes have no published link to the known biology of dovitinib action in tumor cells (grouped as Other)

Conclusion

The DRP-Dovitinib biomarker confirms many of the pathways known to be targeted by dovitinib, but also proposes novel mechanisms of resistance, such as ABC transporter F1. The DRP-Dovitinib is currently being employed in retrospective and prospective clinical trials with dovitinib (manuscript in preparation).