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Clinical development of a predictive biomarker with 58 tumor genes for dovitinib treatment of solid tumors

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Introduction

Dovitinib is a tyrosine kinase inhibitor that inhibits VEGFR1-3, PDGFR, FGFR1-3, c-KIT, FLT3 and topoisomerase 1 and 2. Dovitinib is in development with a tumor agnostic biomarker based on 58 genes associated with sensitivity and resistance to dovitinib. The most advanced development is in renal cell carcinoma (RCC).

Methods

A multinational phase 3 study enrolled 570 patients treated with either dovitinib or sorafenib in a third line setting. Archival tumor samples were obtained from consenting patients to determine the predictive score in a prospective/retrospective design. The DRP-Dovitinib was applied in a blinded manner following a pre-specified statistical analysis plan. The biomarker algorithm combines the expression of 58 mRNAs relevant to the in vitro sensitivity or resistance of dovitinib (Figure 1) that include genes associated with FGFR, PDGF, VEGF, PI3K/Akt/mTOR and topoisomerase pathways as well as ABC drug transport (Table 1) and provides a likelihood score between 0-100%. A cut-point of the median of an RCC reference population was applied to make all statistical analysis categorical. A DRP Dovitinib score of > 67% was also applied to demonstrate that higher scores mean better efficacy.

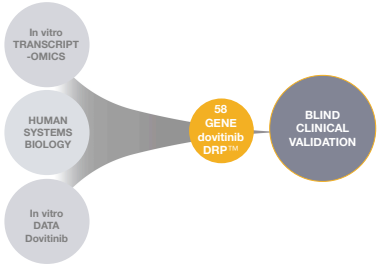

Fig 1. DRP Methodology of combining in vitro growth inhibition and mRNA expression data

Results

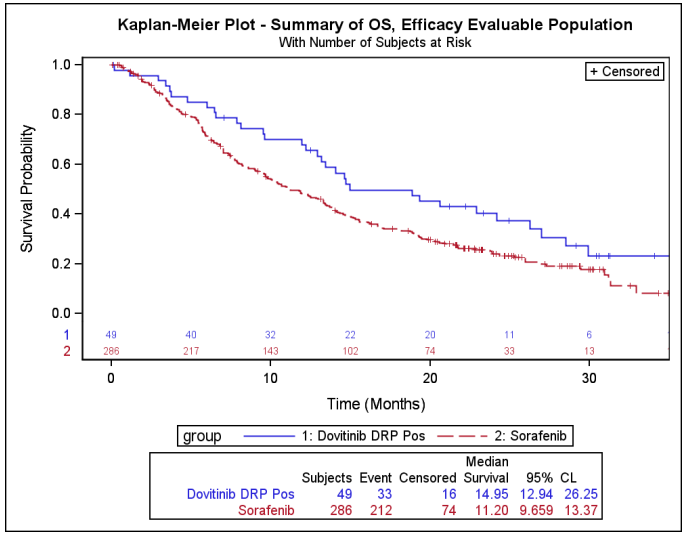

Fig 2. 188 patients consented in the dovitinib group, of these 135 passed established biomarker quality criteria. The DRP-dovitinib divided the patients into two groups, sensitive (n=49, DRP score >50%) or resistant (n=86, DRP score < 50%) to dovitinib. The overall survival in the DRP sensitive population (blue) was compared to the unselected sorafenib group (red, N=286). HR=0.69 (95% CI 0.48-0.99).

With a score of 67% the survival in the DRP selected group increases to a median 20.6 months (95% CI 9.53-35.6, N=15)

Table 1 58 DRP genes are associated with relevant 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*

Conclusion

The DRP-Dovitinib is a predictive biomarker and a tool for the physician in identifying advanced RCC patients most likely to experiencing clinical benefit from dovitinib treatment. The clinical benefit in terms of overall survival is significant at a score of 50% and even greater at a score of 67%

Conflict of Interest for presenting author

Roberto Pili MD is a paid consultant for Allarity