Pharmacokinetics and Pharmacodynamics effects of Everolimus and Sorafenib combination: Impact of doses and sequence of administration on the combination

Thesis

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List of Abbreviations

Abb.	Full term
([18F] FLT)-PET	[18F]-fluorodeoxy-L-thymine
(AUC_{τ})	Areas under the concentration versus time curves within the dosing interval
4E-BP1	eIF4E-binding proteins
AEs	Adverse event
AGT	Human O^6-alkylguanine-DNA alkyltransferase
AKT Total	Protein kinase B
AKT1	Serine/Threonine Kinase 1
AUC	Area under the curve
CI	Confidence Interval
Cl/F	Apparent oral clearance
Cmax	Peak concentration
CR	Complete response
CRF	Case report form
CTCAE	Common terminology criteria of adverse events
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DCE-MRI	Dynamic contrast enhanced magnetic resonance imaging.
DLT	Dose limiting toxicity
EGFR	Epidermal growth factor receptor
EMA	European medical agency
ERK Total	Total extracellular signal regulated kinase
FOCEI	First order conditional estimation method with an interaction option.
GEMM	Genetically engineered mouse model
HCC	Hepatocellular Carcinoma
HER2	Human epidermal growth factor receptor2
HIF-1α	Hypoxia-inducible factor
IBW	Ideal Body Weight
IC50	Inhibitory concentration 50
IOV	Inter-occasion variability
Ka	Absorption rate constant
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

LC-MS/MS ..... Liquid chromatography MS/MS
M&S ..... Modeling and simulation
MBDD ..... Model based drug design
MEK ..... Mitogen activated protein kinase
MH..... Morris Hepatoma
MP ..... Molecular profiling
MTA ..... Microtubule-targeting agents
MTD ..... Maximum tolerated dose
mTOR..... Mammalian target of rapamycin
NONMEM..... Non-linear mixed effect modeling
NSCLC ..... Non small cell lung cancer
OBD..... Optimal biological dose
p70-S6K..... Phosphorylated p70 ribosomal protein S6 kinase
pAKT..... Phosphorylated protein kinase B
PBMCs ..... Peripheral Blood Mononuclear cells
PD..... Pharmacodynamics
PDXs..... Patient derived xenografts
p-ERK..... Phosphorylated extracellular signal regulated kinase
PFS ..... Progression free survival
PGDE..... Pharmacologically guided dose escalation
PgP..... Glycoprotein P
PI3K..... Phosphatidylinositol 3-kinase
PIK3CA ..... Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PK..... Pharmacokinetics
PK-PD..... Pharmacokinetics-pharmacodynamics
PR ..... Partial response
PtdInsP3..... Phosphatidylinositol 3,4,5-trisphosphate
PTEN ..... Phosphatase and tensin homolog
Q/F..... Intercompartimental clearance.
R&D ..... Research and development
RAF ..... Serine/threonine specific protein kinases
RAS ..... Reticular activating system
RP2D ..... Recommended phase 2 dose
RSE..... Relative standard error
RTK ..... Receptor tyrosine kinase
SAEs..... Serious adverse event
SIGMA ..... Exponential residual error
SOC ..... System Organ Class
SUSARs..... Suspected unexpected serious adverse reactions

TRAIL ..... Tumour Necrosis Factor-Related Apoptosis-Inducing Ligand
UGT1A1 ..... UDP-glucuronosyltransferases 1A1
UGT1A9 ..... UDP-glucuronosyltransferases 1A9
V2/F ..... Peripheral volume of distribution
$Vd_{central}$ ..... Central volume of distribution
VEGF ..... Vascular endothelial growth factor
VEGFR1 ..... Vascular endothelial growth factor receptor 1
VEGFR2 ..... Vascular endothelial growth factor receptor 2
VPC ..... Visual predictive check

Introduction

The translation of cancer research to successful clinical application has been proved to be very challenging over the past decade. The attrition rate of drug development remains high despite the efforts and the financial investments that have been brought by many different parties including scientists, researchers and pharmaceutical companies.

Only 5% of agents that have anticancer activity in preclinical development are licensed after demonstrating sufficient efficacy in phase III testing, which is much lower than, other diseases. This issue involved also many new cancer agents including microtubule-targeting agents (MTA) that were withdrawn or suspended with 40–50% of development programs being discontinued even in clinical Phase III [1,2].

Diverse reasons were reported as factors contributing for the high attrition rate of anticancer agents[3]. The concepts used for development of cytotoxic drugs were not adequate for new targeted agents: toxicity based escalation trials, MTD. Therefore, limitations and major challenges for the research based drug development could be summarized in the following:

- *Poorly predictive preclinical models in cancer research*: the limitations of preclinical tools such as inadequate cancer-cell-line and mouse models might explain the challenging mission of the scientists to make a discovery that will have an impact in the clinic [4]. Despite the progress of genetically engineered mouse model (GEMMs) and patient derived xenografts (PDXs), these models stilll not widely implemented [5]. However, recently, GEMMs have been used to

identify the importance of mTOR and EGFR inhibitors in neuroendocrine cancers, leading to the successful translation of mTOR inhibitors into clinical practice in this tumor type [6,7]. PDXs are also increasingly used to guide personalised therapy [8,9].

- *Lack of reliability of published data*: An analysis by Prinz F et al., 2011 was based on input received from 23 scientists and collected data from 67 projects, revealed that in almost two-thirds of the projects there were inconsistencies between published data and in-house data. This concern has been addressed based on what some scientists have claimed about the presentation of specific experiments that supported their underlying hypothesis which were not reflective of the entire data set. Also, data were not routinely analyzed by investigators blinded to the experimental versus the control group. On the other hand, in studies for which findings could be reproduced, authors had paid close attention to controls, reagents, investigator bias and describing the complete data set [10].

- *Starting dose determination*: endpoints based on optimal biological doses (OBD) were used to determine the recommended phase 2 dose (RP2D) for several FDA approved agents, such as bevacizumab, imatinib and vismodegib, as they didn't reach an established MTD in the phase I trial. Accordingly, a new approach was set using PK or PD as an endpoint to determine biologically active dose in preclinical experiments. This could be applied alongside with preclinical toxicology data to inform starting dose decisions. This binomial approach has the potential to reduce the number of dose escalations while keeping an optimised benefit /risk ratio. A number of

conditional and accelerated approvals have been granted based on phase II data relying on patient benefit [11] [12].

- *Patient selection*: Multiple genomic aberrations that drive oncogenesis may act as treatment targets. Therefore, the identification of a sufficient number of patients with a specific molecular aberration can significantly slow clinical trial accrual as the majority of these abnormalities have been reported with low frequency. In these cases multi-center studies with frequent communications between investigator sites should ameliorate these limitations. Geographic heterogeneity due to spatial variations in molecular aberrations has been demonstrated within a single tumor, or between different lesions. Multiple tumor biopsies, ultra deep sequencing and non-invasive tumor imaging could potentially overcome the limitations of geographic heterogeneity [13-15].

- *The concept of target-based drug discovery with the related complexity of target selection*:.the reliance on standard criteria for evaluating tumour response and the challenges of selecting patients prospectively also play a significant part in the success rate of a new molecule to be translated to clinic [16]. The disappointing results in the clinic produced by some anticancer agents like mitotic kinases could be partially related to the lack of a balanced benefit /risk ratio as their efficacy was at the expense of high toxic effects. This might be explained by a non ‘druggable’ tumor cells which means that the activity of the key target of the anticancer agents was not inhibited in the tumor cells[17].