

# Novel potent and selective mTOR/PI3K inhibitors that inhibit tumor growth in animal models through efficient and sustained shut down of the PI3K/Akt signaling pathway



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## Introduction:

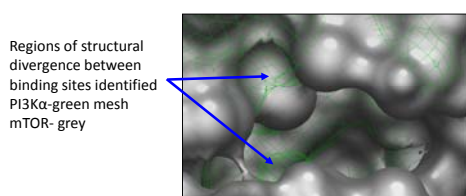
The PI3K signaling pathway is crucial to many aspects of cell growth and survival via its regulation of widely divergent physiological processes that include cell cycle progression, differentiation, transcription, translation and apoptosis. Dysregulation, either through amplification of PI3K, deletion of PTEN or activating mutations, has been closely linked to the development and progression of a wide range of hyperproliferative diseases and cancers. This has prompted intense interest in the development of small molecule modulators of key proteins in this signaling cascade. mTOR and PI3K have received particular attention as cancer targets. These kinases belong to the PIKK family and therefore have considerable homology in their active sites enabling the discovery of small molecule inhibitors with varying degrees of activity against mTOR and the isoforms of PI3K.

The SAR understanding we have developed in our mTOR/PI3K program has led to the generation a full spectrum of compounds from the most mTOR-selective to the most PI3K-selective. These compounds provide valuable tools to determine the relative roles of these kinases in cancer biology and facilitate the development of compounds that will have the best therapeutic potential for the treatment of cancer and other proliferative diseases.

## Lead Identification/Optimization:

- Initial leads were derived from published structures and virtual screening/docking experiments used in the evolution of these lead series
- Inhibitor design was guided by PI3K X-ray structures and mTOR homology model
- A unique combination of side chains and core scaffolds gives low nanomolar mTOR and PI3K activity
- Selectivity in favor of each target achievable

## Overlay of PI3K $\alpha$ and mTOR:



Regions of structural divergence between binding sites identified PI3K $\alpha$ -green mesh mTOR- grey

Fig.1

## In vitro Profile:

**Kinase activity:** Potent inhibition of mTOR and or PI3K $\alpha$ , no significant activity against kinases outside PIKK family

**Cellular activity:**

- Inhibition of biomarker phosphorylation levels and inhibition of cell proliferation in PC3 and other cancer cells
- Activity against both mTOR complexes demonstrated through inhibition of both pS6 and pAkt (S473) using Alphascreen Surefire platform and Western blot analysis
- Advanced leads have shown activity in a range of cancer cell lines

(IC <sub>50</sub> ) nM	SB2090	SB2015	SB2343	SB2342
mTOR kinase	1400	122	36	40
PI3K $\alpha$ kinase	20	18	11	15
p70 S6K (PC3)	253	110	24	13
pAkt S473 (PC3)	125	42	9	14
Proliferation (PC3)	210	139	nt	73

\*nt: not tested

Table 1

## SB2015 Biomarker Modulation in vitro:

- MDA-MB-468 cells, 4 h treatment
- SB2015 inhibits mTORC2 activity not affected by rapamycin analogues such as RAD001 (Everolimus)

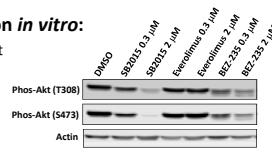


Fig.2

## SB2015 Modulation of cell proliferation:

SB2015		
Cell Line	Origin	IC <sub>50</sub> (nM)
PC3	Prostate	139
A2780 <sup>a</sup>	Ovarian	130
MDA-MB-231 <sup>a</sup>	Breast	225
T47D	Breast	180
U87MG	Glioma	161
RPMI-8226	Multiple myeloma	120

<sup>a</sup>Rapamycin-resistant cell line

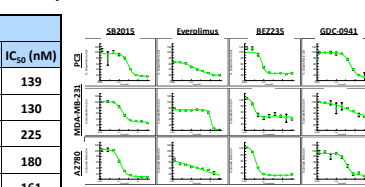


Fig.3

- SB2015 shows efficacy in a broad spectrum of rapamycin-sensitive as well as -resistant cancer cell lines

## Biomarker Modulation in vivo:

**In vivo evaluation:** Single dose PK/PD experiment in PC3 tumor bearing mice (n=3/time point) at 150 mg/kg

- Inhibition of both mTOR complexes in tumor tissue achieved
- Superior PK/PD compared to Genentech clinical compound, GDC-0941

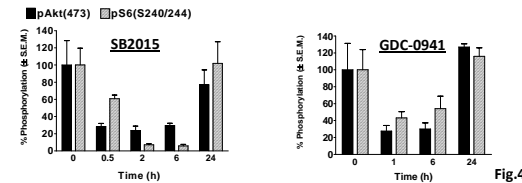


Fig.4

## Pharmacokinetics:

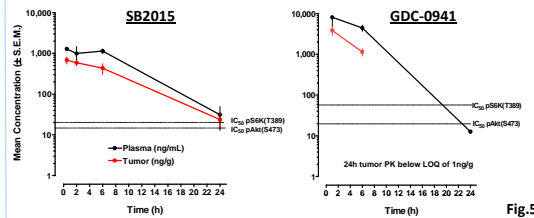


Fig.5

- SB2015: 21% bioavailability in non-tumor bearing BALB/c nude mice
- PK/PD analysis carried out in PC3 tumor bearing mice
- Excellent PK/PD correlation
- Sustained drug levels achieved in tumor tissue

## SB2015 Safety and ADME:

- Remarkable specificity for the PIKK family (shown in Ambit profiling)
- IC<sub>50</sub> > 25  $\mu$ M for 3A4, 2D6, 1A2, 2C19, 2C9
- t<sub>1/2</sub> > 60 min for HLM, MLM, RML, DLM
- hERG IC<sub>50</sub> > 10  $\mu$ M
- MDS Receptors (30 Receptors): Clean @10  $\mu$ M
- AMES: non-mutagenic

## SB2015 Efficacy Study:

- Comparison of SB2015 with BEZ-235, once oral daily dosing in PC3 prostate carcinoma model (n=7/group)

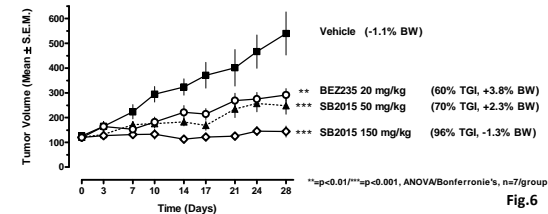


Fig.6

- SB2015 shows dose-dependent tumor growth inhibition
- Minimal body weight loss and excellent tolerability (MTD > 200 mg/kg) compared to BEZ-235 (published MTD 50 mg/kg)

## PK/PD Analysis of SB2015 on Day 28:

- Dose-dependent drug concentrations in plasma, no accumulation
- Inhibition of both mTOR complexes after chronic dosing

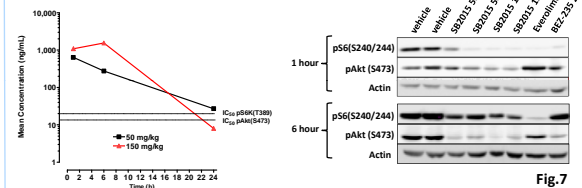


Fig.7

## Conclusions:

- SB2015 a potent mTOR/PI3K inhibitor, demonstrates high selectivity towards mTOR and PI3K compared to other kinases.
- SB2015 shows excellent drug-like properties, tolerability and *in vivo* anti-tumor efficacy.
- Access to a full spectrum of proprietary compounds (ranging from the most mTOR-selective through potent dual inhibitors to the most PI3K-selective) enables us to further explore the biological effects, disease modifying benefits and tolerability of the various inhibitory profiles and to select compounds with the best therapeutic profile for evaluation in patients.