

Conclusions: BIBF 1120 in combination with mFOLFOX6, for first-line mCRC has a similar magnitude of efficacy and safety/tolerability profile but lower incidence of SAE in comparison to BEV. Detailed analysis of SAEs is ongoing.

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	BIBF 1120 arm (n = 85)	BEV arm (n = 41)
Pts with AE Grade ≥ 3 by MedDRA preferred terms $\geq 5\%$, %	88	95
Neutropenia	32	24
Diarrhoea	15	12
Neurotoxicity	14	10
Paraesthesia	13	12
Asthenia	11	10
Decreased appetite	8	2
Thrombocytopenia	6	2
Peripheral neuropathy	5	7
Abdominal pain	4	5
Polyneuropathy	2	5
Serious AEs (SAE), %	34	54
AEs leading to discontinuation of, BIBF 1120 or BEV	25	32
FOLFOX	34	29
Pts receiving all planned mFOLFOX6 cycles in first 6 months, %		
5-FU	66	63
Oxaliplatin	32	17
Total mFOLFOX6 cycles, median		
5-FU	14	13
Oxaliplatin	10	9
Median treatment exposure, days		
5-FU	212	219
Oxaliplatin	158	160

Proffered Papers Sessions

Basic Science/Translational Research

Monday 26 September 2011, 14:45–17:10

15LBA

LATE BREAKING ABSTRACT

Drugging the Undruggable: Small-molecule Inhibition of Ras Oncoprotein

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Background: Ras is a nucleotide-dependent switch that converts from an inactive GDP-bound state to an active GTP-bound state when activated by guanine nucleotide exchange factors, such as SOS. Active Ras^{GTP} then binds to and activates downstream signaling effectors. Ras is the most frequently mutated oncogene and hyperactive mutant Ras constitutively signals to effectors to promote cell survival, proliferation and metastasis. Thus, Ras oncoprotein has been considered by the cancer community to be one of the most important oncology drug targets. Despite the enormous interest and extensive exploratory efforts in industry and academia, small molecules that bind to Ras in a well-defined manner and exert inhibitory effects have not been uncovered to date. We describe in this abstract the identification and characterization of small-molecule inhibitors of the Ras oncoprotein.

Materials and Methods: To explore a new means of directly targeting Ras, we used a fragment-based lead discovery approach via an NMR-based screen. Hits from the fragment screen were characterized for their interactions with Ras by NMR and X-ray crystallography and for their effects on Ras activation and signaling in reconstituted biochemical assays *in vitro* and in cellular assays *in vivo*.

Results: From the fragment-based screen, we identified a group of small molecules that each bind to a common site adjacent to the switch I/II regions in the Ras protein. X-ray crystallography studies of three compound-Ras complexes indicate that the binding site can be expanded upon ligand binding. Nucleotide exchange factors, notably SOS, are required to convert inactive Ras^{GDP} to active Ras^{GTP}. We determined that the compound-binding site is located at the interface of Ras and SOS. A subset of our Ras-binding molecules indeed inhibited SOS-mediated

nucleotide exchange. Further mechanistic studies revealed that through steric hindrance the compounds block the formation of the Ras-SOS complex, a key intermediate of the exchange reaction. At the cellular level, our compounds inhibit the formation of active Ras^{GTP} and prevent Ras signaling to downstream effectors. To define the potential clinic utility of these compounds, we performed biological characterization of Ras-driven tumors and identified a subset of Ras mutant tumors that depend on nucleotide exchange factors for the activation of Ras, suggesting a specific profile for the use of exchange inhibitors.

Conclusions: We conclude that the compounds act as competitive inhibitors of nucleotide exchange to prevent the activation of Ras. The discovery of a binding pocket on Ras with functional significance represents a breakthrough finding that will offer a new direction for therapeutic intervention of the Ras oncoprotein. Our findings provide new opportunities to target the “undruggable” Ras oncoprotein.

Breast Cancer – Advanced Disease

Sunday 25 September 2011, 09:00–11:35

16LBA

LATE BREAKING ABSTRACT

Reversal of Tamoxifen Resistance (Hormone Resistance) by Addition of Sirolimus (mTOR Inhibitor) in Metastatic Breast Cancer

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Introduction: The estrogen receptor was first proven therapeutic target identified in breast cancer cells.

Because it is present in 50–75% of breast cancer and has direct correlation with cancer phenotype ER modulation has been in main stay of treating this disease in this phenotype in last 40 years. A key protein in the pathway tumorigenesis is AKT kinase which antagonises the hormone therapy like Tamoxifen because of cross-tak. In fact Tamoxifen resistance are associated with high levels of activity of AKT.

mTOR (mammalian Target Of Rapamycin) inhibitors block the downstream pathway of AKT and addition of this to Tamoxifen may overcome resistance to Tamoxifen.

Materials and methods: The study was done in two phases

- In metastatic breast cancer patients who were ER/PgR positive and HER-2 negative and could not afford AI inhibitors were randomised to Tamoxifen (20 mg once a day) or Tamoxifen with Sirolimus (2 mg per day).
- In patients who had failed AI and/or Tamoxifen were randomised to the above combination also.

Each phase had 200 patients that is total 400 patients.

All patients had ER/PgR, HER-2/neu, KI-67 done.

The primary end point was Response Rate and Time to Progression. Secondary end points were Safety, Toxicity and Preliminary Pharmacoeconomic Analysis.

Results: The results of the phase I study showed response rate of 36% vs 68% (average ER status 4 to 8, median = 6) and time to progression – 9 months vs 16 months.

The phase II study showed response rates of 4% vs 40% and time to progression – 3 months vs 11 months.

The study was done for the period 2004–2010, single center with 3 referral centers. The combination was effective and safe.

The Sirolimus used was of certified and generic version. Tamoxifen was of certified and generic version.

Conclusion: Pharmacoeconomic analysis shows it to be cost effective combination with a good toxicity profile.