Presidential Session IV
Tuesday 27 September 2011, 09:00−11:00
12LBA LATE BREAKING ABSTRACT

Cognitive and Cardiac Outcome After Prenatal Exposure to Chemotherapy in Children 18 Months or Older

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Background: The effect of prenatal exposure to chemotherapy on cardiac and neurodevelopmental outcomes is still uncertain.
Methods: This is a prospective multicenter study examining children who were prenatally exposed to maternal cancer staging and treatment, including chemotherapy. Children were examined at the age of 18 months, 5−6, 8−9, 11−12, 15−16 and 18 years. The tests comprised a clinical neurologic examination, testing of the general level of cognitive functioning(Bayley/IQ-test), an electro/echocardiography and questionnaire on general health and development. From the age of 5 years, also an audiometry, Auditory Verbal Learning Test and subtasks of the Children's Memory Scale and Test of Everyday Attention for Children were performed and the Child Behavior Checklist was completed.
Results: In total, 236 cycles of chemotherapy were administered in 68 pregnancies. Seventy children, born at a median gestational age of 35.7 weeks (range, 28.3–41.0; 47/70 <37 weeks), were included with a median follow up period of 22.3months (range, 16.8–211.6). Although neurocognitive outcome results were within normal ranges, the high frequency of preterm birth had a negative influence on cognitive development. A severe neurodevelopmental delay was seen in both members of a twin (3%). Child's behavior, general health, hearing and growth was reported as in a general population. Cardiac dimensions and functions were within normal ranges.
Conclusion: Fetal exposure to chemotherapy was not associated with increased morbidity at the level of the central nervous system, cardiac, and auditory functions, as well as general health and growth. However, prematurity was frequently encountered, and associated with impaired cognitive development.

Presidential Session IV
Tuesday 27 September 2011, 09:00−11:00
13LBA LATE BREAKING ABSTRACT

Efficacy of Veliparib (ABT-888) Plus Temozolomide Versus Temozolomide Alone: a Randomized, Double-blind, Placebo-controlled Trial in Patients with Metastatic Melanoma

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Background: Veliparib (ABT-888) is a novel, orally bioavailable, small molecule, potent inhibitor of the enzymes PARP-1 (Ki 5nM) and PARP-2 (Ki 3nM), involved in DNA repair. Veliparib enhances antitumor activities of multiple cytotoxic agents preclinically, including temozolomide (TMZ).
Materials and Methods: This multicenter, double-blind, placebo (pbo)-controlled trial (ABT-888 in combination with TMZ in metastatic melanoma [MM]; trial ID NCT00804908; sponsor Abbott Laboratories) evaluated the efficacy of veliparib+TMZ vs pbo+TMZ in prolonging progression free survival (PFS). Adult patients (pts) with unresectable Stage III or IV MM, $\geqslant$1 measurable lesion on CT scan (RECIST), and ECOG 0−1, were randomized in a 1:1:1 ratio to pbo BID+TMZ, veliparib 20 mg BID+TMZ or veliparib 40 mg BID+TMZ. Toxicity was assessed by NCI-CTCAE v3.0. Efficacy endpoints included PFS, overall survival (OS), and objective response rate (ORR). Tumor response and disease progression were evaluated every 8 weeks (per RECIST), with CT scans reviewed centrally.
Results: Between February 2009 and January 2010, 346 pts were randomized. Although median PFS nearly doubled numerically in the veliparib groups vs pbo (table), these differences were not statistically significant.

Efficacy endpoints	Pbo +TMZ (N = 115)	Veliparib 20 mg +TMZ (N = 116)	Veliparib 40 mg +TMZ (N = 115)	Hazard Ratio (HR); P-value Veliparib 20 mg vs Pbo	Veliparib 40 mg vs Pbo
Median PFS, days [95% CI]	60 [57,111]	113 [92,168]	110 [57,125]	HR = 0.737 p = 0.071[a]	HR = 0.822 p = 0.233[a]
Median OS, days [95% CI]	390 [299,436]	327 [274,399]	412 [346,483]	HR = 1.009 p = 0.955[a]	HR = 0.790 p = 0.162[a]
ORR, n (%)	8 (7.0)	12 (10.3)	10 (8.7)	p = 0.372[b]	p = 0.598[b]

[a]Stratified log-rank test. [b]Stratified CMH test.

Toxicities were as expected for TMZ. The frequency of thrombocytopenia, neutropenia and leukopenia increased significantly in the veliparib groups. Grade 3/4 adverse events (AEs), mainly of hematological toxicities, were seen in 38% (pbo), 54% (veliparib 20 mg), 57% (veliparib 40 mg) of pts. Veliparib-//pbo-related AEs were reported by 79% (pbo), 89% (veliparib 20 mg), 93% (veliparib 40 mg) of pts, and TMZ-related AEs were reported by 89% (pbo), 93% (veliparib 20 mg), 96% (veliparib 40 mg).
Conclusion: Veliparib-treated pts had numerically increased median PFS (20 and 40 mg) and median OS (40 mg), but these trends were not significant. No new toxicity signals were identified.

Presidential Session IV
Tuesday 27 September 2011, 09:00−11:00
14LBA LATE BREAKING ABSTRACT

A Phase I/II, Open-label, Randomised Study of BIBF 1120 Plus mFOLFOX6 Compared to Bevacizumab Plus mFOLFOX6 in Patients with Metastatic Colorectal Cancer

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Background: This Phase I/II study evaluated BIBF 1120, an oral triple angiokinase inhibitor of VEGFR 1−3, PDGFR-α and -β, and FGFR 1−3, plus modified FOLFOX6 (mFOLFOX6) compared to bevacizumab (BEV) plus mFOLFOX6 in chemo-naïve metastatic colorectal cancer (mCRC) patients (pts).
Material and Methods: Eligible pts had unresectable, measurable histologically confirmed mCRC (adenocarcinoma) and ECOG PS $\leqslant$2 with adequate organ function. Pts stratified by ECOG PS, LDH levels, and receipt of adjuvant treatment were randomised 2:1 to receive first-line treatment with continuous BIBF 1120 plus mFOLFOX6 q2w (BIBF 1120 arm) or 5 mg/kg IV BEV plus mFOLFOX6 q2w (BEV arm) until disease progression or non-tolerable toxicity. Primary endpoint was progression-free survival (PFS) rate at 9 months; secondary endpoints included additional efficacy measures (PFS, objective response rate [ORR], resection rate) and adverse event (AE) profile.
Results: 128 pts were randomised (BIBF 1120 arm: 85 pts; BEV arm: 41 pts; not treated: 2 pts), with balanced baseline characteristics (mean age 63 years, 48% women). Three and 11 pts received 150 and 200 mg bid BIBF 1120, respectively, in the Phase I part. Interim database lock was performed 9 months after the last patient was first treated. At database lock, 47 pts (37%) continued on the study (BIBF 1120 arm, 35% vs BEV arm, 41%). The Kaplan–Meier 9-month PFS rate was 63% (95% CI: 50−75%) in the BIBF 1120 arm and 69% (95% CI: 53−86%) in the BEV arm. Median PFS was 10.6 months in both arms; confirmed ORR was 61% vs 54% and resection rate was 14% vs 20%, BIBF 1120 vs BEV arms, respectively. Treatment with BIBF 1120 did not impact exposure and intensity of mFOLFOX6 treatment compared with BEV.

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.
Funded by Boehringer Ingelheim; ClinicalTrials.gov NCT00904839.

	BIBF 1120 arm (n = 85)	BEV arm (n = 41)
Pts with AE Grade ⩾3 by MedDRA preferred terms ⩾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

G. Fang[1], T. Maurer[2], L. Garrenton[1], N. Skelton[3], B. Fauber[3], S. Malek[4], A. Giannetti[4], P. Jackson[1], J. Rudolph[3], W. Wang[2]. *[1]Genentech Inc., Cell Regulation/Oncology, South San Francisco CA, USA; [2]Genentech Inc., Structural Biology, South San Francisco CA, USA; [3]Genentech Inc., Discovery Chemistry, South San Francisco CA, USA; [4]Genentech Inc., Biochemical Pharmacology, South San Francisco CA, USA*

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 tumorogenesis 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
a. 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).
b. 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.