Phase I trial of the polo-like kinase (Plk) inhibitor volasertib (BI 6727) combined with cisplatin or carboplatin in patients with advanced solid tumors.

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Background:

Volasertib (V) is a first in class, selective and potent cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Plk. This phase I study evaluates dose-limiting toxicities (DLT), maximum tolerated dose (MTD), safety and pharmacokinetics (PK) of V combined with cisplatin (Cis) or carboplatin (Ca).

Methods:

Sequential cohorts of patients (pts) received a single 2h infusion of V with Cis (arm A) or Ca (arm B) every 3 wks. Cis and Ca were given for up to 6 cycles (Cy); V was continued until progression or intolerance. MTD was the highest dose at which $\leq 1/6$ pts experienced a DLT in Cy 1. MTD cohorts were expanded to 12 DLT-evaluable pts to further characterize safety.

Results:

As of January 11 2012, 61 pts (arm A: 30; arm B: 31) were treated. Pt characteristics were (arm A/B): median age 55/58 yrs, male 16/18 pts, ECOG PS 0: 13/14 pts, PS 1: 17/17 pts. Tumors included (pts): non-small cell lung cancer (15); sarcoma (8); colorectal cancer (6); melanoma (4); urothelial cancer (4); other (24). Pts received V + Cis for a median [range] of 3.5 Cy [1-6], V + Ca for 2 Cy [1-6] and V for 3.5 Cy [1-20] in arm A and 2 Cy [1-14] in B. PK analyses are ongoing. MTD was reached at V 300 mg + Cis 100 mg/m² and V 300 mg + Ca AUC 6. Five partial responses (PR) were seen. 15/30 pts in arm A and

12/31 in B achieved stable disease (SD) or PR. PR or SD for >6 Cy was observed in 6/30 pts and 5/31 pts in arms A and B, respectively.

Conclusions:

In this phase I study, V in combination with Cis or Ca at full single-agent doses was well tolerated. Furthermore, several objective responses and cases of sustained SD were observed in heavily pretreated pts with advanced solid tumors.

Dose levels		N of pts	DLTs in Cy 1 (n of pts)
Arm A: V (mg)/Cis (mg/m ²)	A1: 100/60	3	-
	A2: 100/75	3	-
	A3: 200/75	3	-
	A4: 300/75	3	-
	A5: 300/100*	6+6	Increased serum creatinine (1) + fatigue (1), neutropenia (1)
	A6: 350/75	6	Increased alanine transaminase (1), neutropenia (1)
Arm B: V (mg)/Ca (AUC)	B1: 100/4	3	-
	B2: 100/5	3	-
	B3: 200/5	3	-
	B4: 300/5	6	Thrombocytopenia with neutropenia (1)
	B5: 300/6*	6+7	Thrombocytopenia (1) + (1)
	B6: 350/5	3	Thrombocytopenia (1), neutropenia with thrombocytopenia, febrile neutropenia, fatigue, nausea and anorexia (1)

*** MTD**

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