Phase Ib Dose Escalation Study of the Akt Inhibitor GDC-0068 with Docetaxel or mFOLFOX6 in Patients with Advanced Solid Tumors

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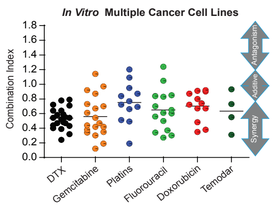
BACKGROUND

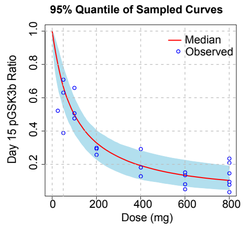
- Aberrant activation of the PI3K/Akt pathway, via loss of PTEN tumor suppressor and/or mutations of the *PIK3CA* gene, is frequent in cancers and may lead to enhanced survival and chemoresistance
- GDC-0068 is a potent ATP-competitive small molecule inhibitor of all Akt isoforms1
- In preclinical models, GDC-0068 synergistically combined with taxanes and 5-FU/platinum (Figure 1a)
- In an ongoing Phase Ia study, GDC-0068 has been well tolerated with maximum tolerated dose (MTD) of 600 mg daily (21 days on/7 days off); pharmacodynamic (PD) down-regulation of Akt signaling in tumors has been observed at doses ≥ 100 mg (Figure 1b)

Figure 1a. Enhanced Activity when GDC-0068 is Combined with Chemotherapeutic Agents.



GDC-0068 combines well with several classes of chemotherapy agents *in vitro*.

Figure 1b. Substantial PD Effects Achieved at Clinical GDC-0068 Doses ≥ 100 mg QD.



Phase Ia study: Percent inhibition of pGSK3β at Day 15 as a function of GDC-0068 daily dose. Blue area represents 95% CI.

OBJECTIVES

Primary Objectives

- Evaluate the safety and tolerability and estimate the MTD of increasing oral doses of GDC-0068 in combination with docetaxel or mFOLFOX6

Additional Objectives

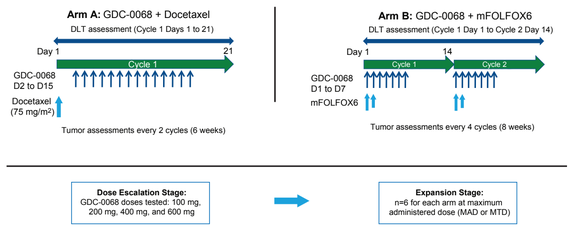
- Evaluate the anti-tumor activity (overall response and duration of treatment) of GDC-0068 in combination with chemotherapy
- Evaluate the PK of GDC-0068 given in combination with chemotherapy
- Evaluate the relationship between preliminary clinical activity and PI3K/Akt pathway alterations (PTEN loss, *PIK3CA* and *AKT1* mutations)

METHODS

Study Design

- Open-label, multi-center, two-stage, Phase Ib dose-escalation combination study using a standard 3+3 design

Figure 2. Dosing Schedule.



RESULTS

Patient Characteristics

Table 1. Baseline Characteristics, Data Cutoff 27 Aug 2012.

Number (%) of Patients	Arm A (n=27)	Arm B (n=34)
Age (year), median (range)	62 (28–75)	59 (33–77)
Sex, male	74	56
ECOG Score 0	44	38
Prior systemic therapies, median (range)	4 (0–12)	5 (0–11)
Prior taxane	17 (63)	9 (27)
Prior platinum agents	20 (74)	26 (77)
Prior 5-FU	12 (44)	21 (62)

Safety

- All Grade ≥ 2 GDC-0068-related AEs are shown in Tables 2a and 2b

Table 2a. Grade ≥ 2 AEs Related to GDC-0068: Arm A (GDC-0068 + Docetaxel) Safety Population, n (%). GDC-0068 Doses are Shown.

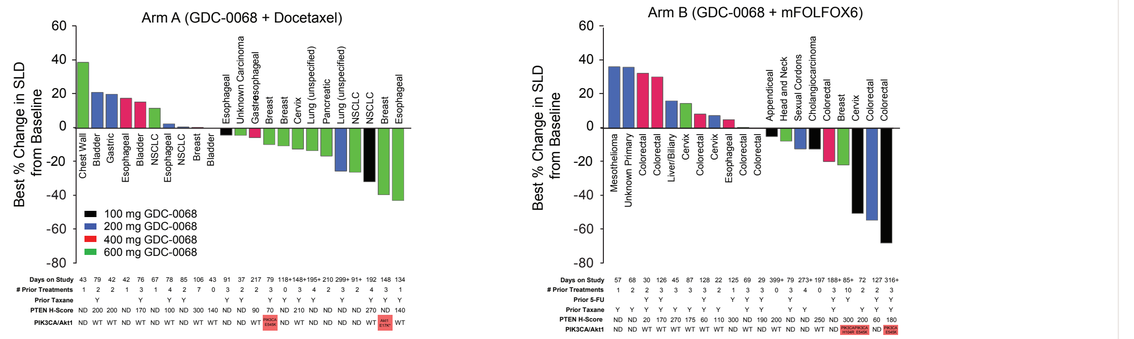
Event Term	100 mg (n=3)	200 mg (n=4)	400 mg (n=7)	600 mg (n=13)	All Subjects (N=27)
Any AE	1 (33)	2 (50)	4 (57)	10 (77)	17 (63)
Diarrhea	0	2 (50)	2 (29)	5 (38)	9 (33)
Nausea	0	0	3 (43)	2 (15)	5 (19)
Asthenia	0	0	0	4 (31)	4 (15)
Fatigue	1 (33)	1 (25)	1 (14)	1 (8)	4 (15)
Vomiting	0	0	2 (29)	1 (8)	3 (11)
Anemia	0	0	1 (14)	1 (8)	2 (7)
Hypophosphatemia	0	1 (25)	1 (14)	0	2 (7)
Rash	0	0	0	2 (15)	2 (7)
Decreased appetite	0	0	0	1 (8)	1 (4)
Dyspepsia	0	0	1 (14)	0	1 (4)
Gastroesoph. reflux	1 (33)	0	0	0	1 (4)
Hematemesis	0	0	1 (14)	0	1 (4)
Hyperglycemia	0	0	0	1 (8)	1 (4)
Hypocalcemia	0	0	0	1 (8)	1 (4)
Hypomagnesemia	0	0	0	1 (8)	1 (4)
Leukopenia	0	0	1 (14)	0	1 (4)
Mucosal inflammation	0	0	0	1 (8)	1 (4)
Maculo-papular rash	0	0	0	1 (8)	1 (4)

Table 2b. Grade ≥ 2 AEs Related to GDC-0068: Arm B (GDC-0068 + mFOLFOX6) Safety Population, n (%). GDC-0068 Doses are Shown.

Event Term	100 mg (n=6)	200 mg (n=9)	400 mg (n=6)	600 mg (n=13)	All Subjects (N=34)
Any AE	3 (50)	6 (67)	4 (67)	7 (54)	20 (59)
Nausea	1 (17)	2 (22)	1 (17)	4 (31)	8 (24)
Diarrhea	0	3 (33)	2 (33)	2 (15)	7 (21)
Asthenia	0	2 (22)	0	4 (31)	6 (18)
Fatigue	0	2 (22)	0	2 (15)	4 (12)
Neutropenia	0	0	2 (33)	1 (8)	3 (9)
Thrombocytopenia	1 (17)	0	1 (17)	1 (8)	3 (9)
Vomiting	1 (17)	0	0	2 (15)	3 (9)
Decreased appetite	0	0	0	1 (8)	1 (3)
Defecation urgency	0	0	0	1 (8)	1 (3)
Hyperbilirubinemia	0	0	0	1 (8)	1 (3)
Hyperglycemia	0	0	0	1 (8)	1 (3)
Hyperlipasemia	0	0	1 (17)	0	1 (3)
Hypokalemia	0	0	0	1 (8)	1 (3)
Mucosal inflammation	0	0	0	1 (8)	1 (3)
Neurotoxicity	1 (17)	0	0	0	1 (3)

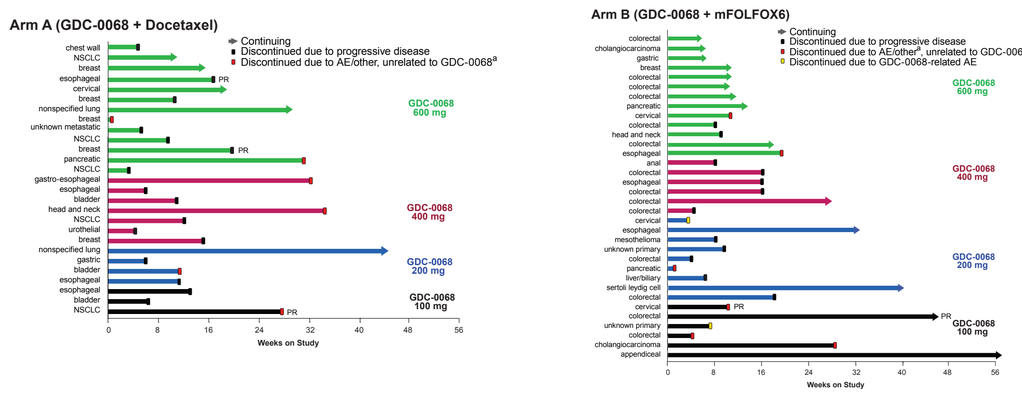
- No DLTs, or GDC-0068-related Grade 4 or 5 events were observed in either arm
- Grade 3 GDC-0068-related AEs:
  - Arm A: Diarrhea (n=2), hypophosphatemia (n=2), rash, leukopenia, hypocalcemia, and hypomagnesemia (each n=1)
  - Arm B: Nausea (n=2), neutropenia, thrombocytopenia, fatigue, hyperglycemia, hyperlipasemia, and hypokalemia (each n=1)

Figure 4. Anti-Tumor Activity: Best Change in Target Lesions.



PTEN H-Score scoring system based on IHC (CST clone 138G6) and % of tumor cells at each intensity level. *AKT1* and *PIK3CA* mutations determined using TaqMan genotyping.[2] Four patients in Arm A and 14 patients in Arm B did not have a post-baseline scan at the time of analysis. SLD = Sum of Target Lesion Diameters; ND = Not Determined. *Per investigator.

Figure 5. Time on Study.



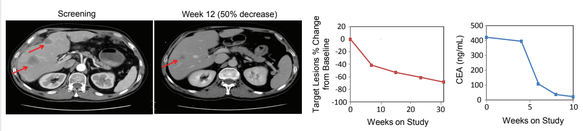
[a]Includes clinical deterioration, withdrawal of consent, and loss to follow-up.

Pharmacokinetics and Pharmacodynamics

- Dose-proportional increases in exposure were observed in both cohorts
- PK parameters for GDC-0068 were consistent with what was observed in single agent Phase I studies
- Docetaxel, platinum, and 5-FU exposures were comparable to historic data
- As a PD marker, glucose increased within 6 h after GDC-0068 dosing, but hyperglycemia was transient, typically occurred post-meals, and usually resolved within 24 h. Predose glucose levels were generally stable over treatment.

Clinical Activity

Figure 6. Partial Response in a Patient with *PIK3CA* E545K Mutant CRC.



Patient previously progressed on mFOLFOX4, cetuximab and irinotecan, and panitumumab before treatment with GDC-0068 (100 mg starting dose) + mFOLFOX6. CT scans showed a confirmed RECIST response, with maximum decrease in liver and lymph node target lesions of 69%, with corresponding decline in the CEA. Patient continues on study at Cycle 24.

CONCLUSIONS

- GDC-0068, when combined with docetaxel or mFOLFOX-6, was safe and well-tolerated up to the single agent MTD dose (600 mg)
- No DLTs were observed up to the maximum administrated dose; 2/61 patients discontinued due to GDC-0068-related AEs
- There were no PK interactions between GDC-0068 and docetaxel or mFOLFOX6
- Both combinations showed evidence of anti-tumor activity, including in patients with PI3K/Akt pathway alterations and prior treatment with taxanes (Arm A) and platinum and/or 5-FU agents (Arm B)
- A Phase II trial in first line metastatic gastric/GEJ cancer testing FOLFOX ± GDC-0068 will soon commence

REFERENCES

1. Lin K, Lin J, Wu WI, et al. Sci Signal 2012; 5:ra37.
2. Punnoose EA, et al. Clin Can Res 2012; 18:2391-2401.

ACKNOWLEDGMENTS

- We thank the patients who participated in the study, and their families
- We thank the Genentech/Array GDC-0068 Akt team
- Genentech provided support for this poster

European Society for Medical Oncology (ESMO), Vienna, Austria, 2012