Phase I Study of Safety and Pharmacokinetics of GDC-0917, an Antagonist of Inhibitor of Apoptosis Proteins in Patients with Refractory Solid Tumors or Lymphoma

A Tolcher,[1] K Papadopoulos,[1] A Patnaik,[1] WJ Fairbrother,[2] H Wong,[2] N Budha,[2] WC Darbonne,[2] F Peale,[2] M Mamounas,[2] S Royer-Joo,[2] R Yu,[2] CC Portera,[2] JC Bendell,[3] HA Burris,[3] JR Infante[3]

[1]South Texas Accelerated Research Therapeutics, LLC., San Antonio, TX
[2]Genentech, Inc., South San Francisco, CA
[3]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

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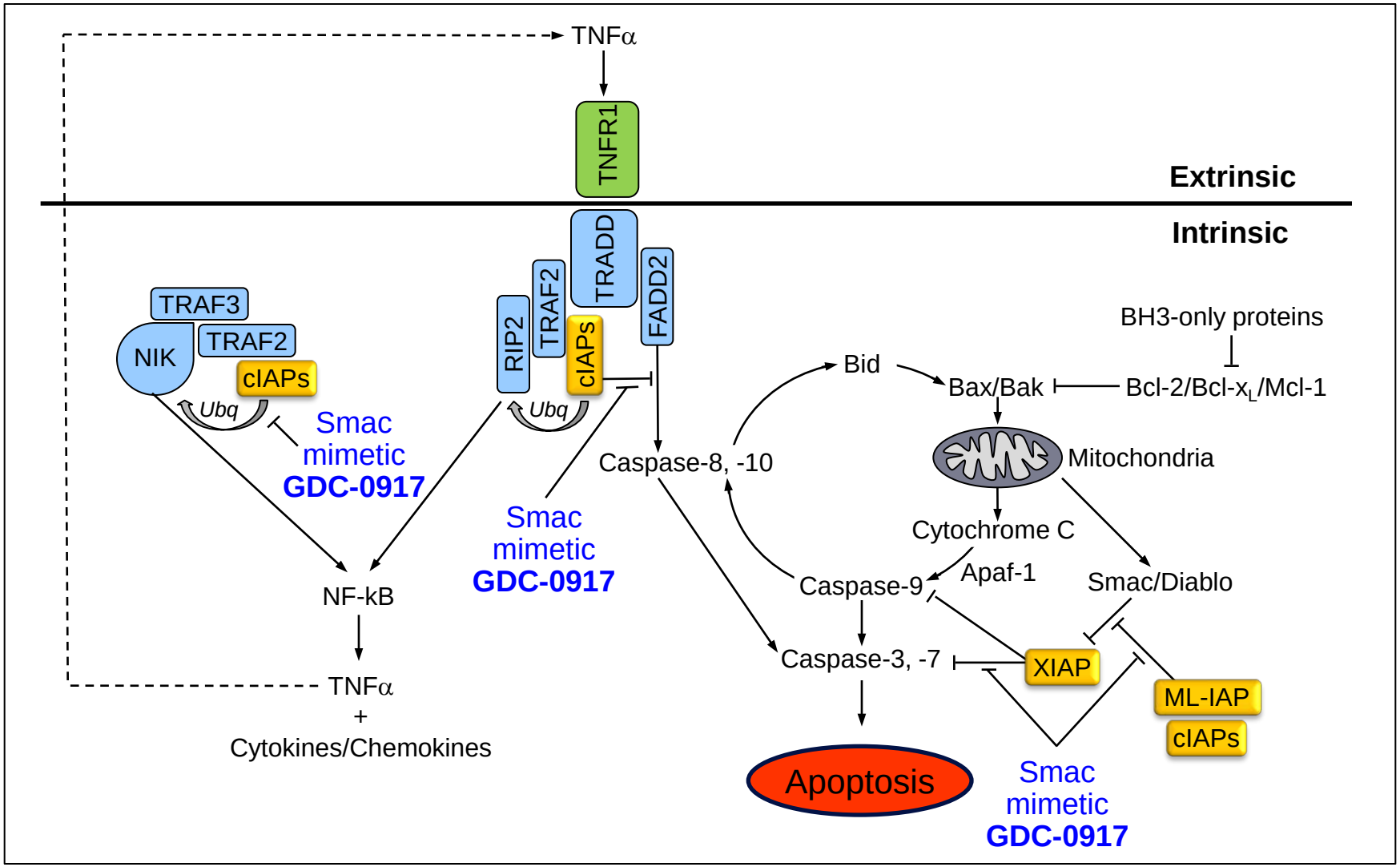
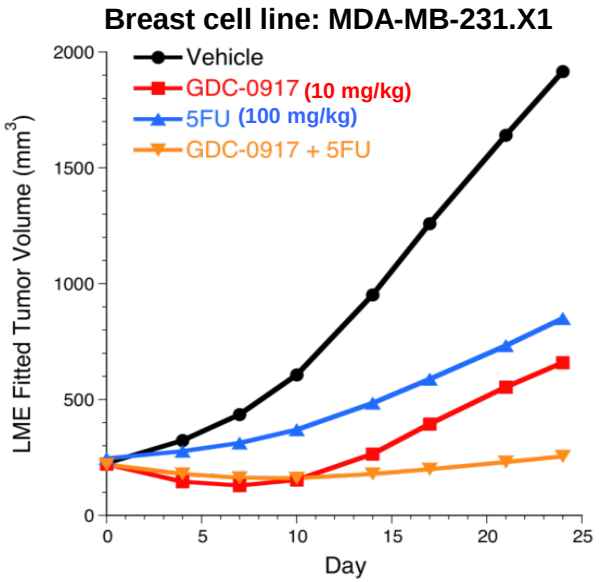
IAP antagonists promote cell death through both intrinsic and extrinsic pathways

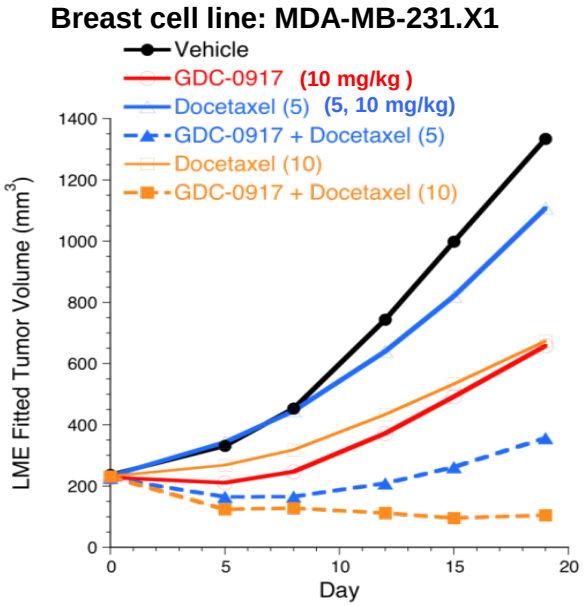


Varfolomeev et al. Cell 2007; Vince et al. Cell 2007; Petersen et al. Cancer Cell 2007; Gaither et al. Cancer Res. 2007.

IAP selective antagonist: GDC-0917

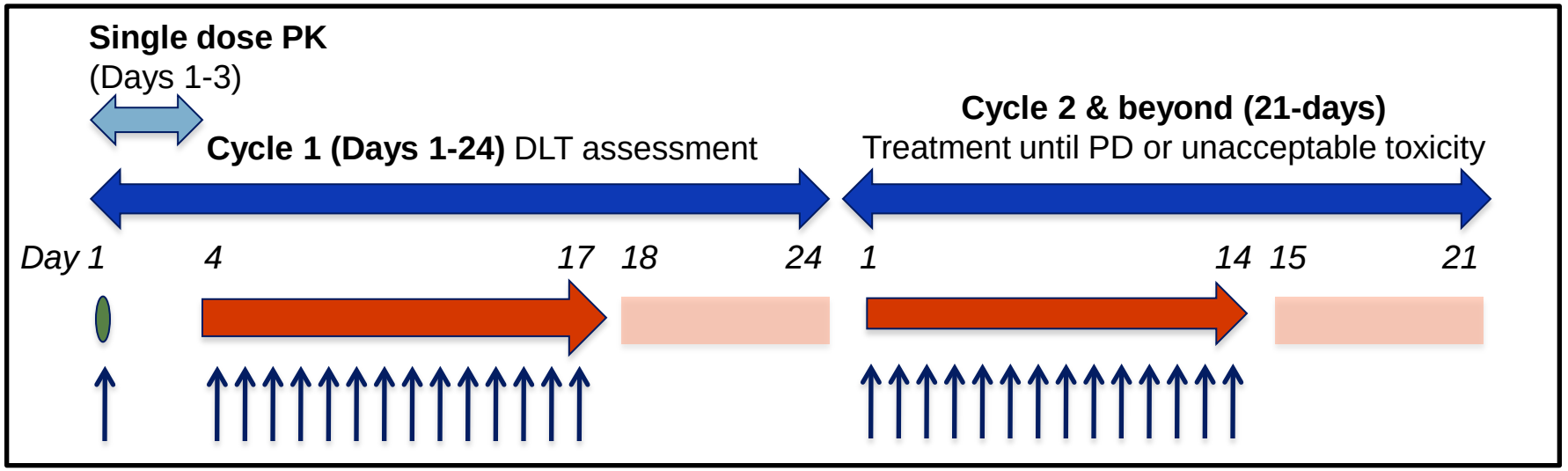
- GDC-0917, a Smac mimetic, binds to the same sites on the IAP proteins as the IAP protein-interaction motifs of Smac and caspase-9
- GDC-0917 binding *in vitro* induces apoptosis via caspase-3 and -7 activation in several types of cancer cell lines
- Up-regulates the expression of several cytokines and chemokines, including TNFα *in vitro* and *in vivo*
- Induces auto-ubiquitination and rapid proteasomal degradation of cIAP1





GDC-0917 Phase I study design

- Phase I, dose-escalation study using a modified continual reassessment method (mCRM) design in patients with refractory solid tumors or lymphoma
- Endpoints:
  - Primary: Dose-limiting toxicities (DLT, assessed D1-24), adverse events (AEs), and pharmacokinetics (PK)
  - Secondary/exploratory: clinical activity (RECIST v.1.1); pharmacodynamics (PD; cIAP1 and MCP1 to assess pathway modulation in surrogate and tumor tissues)
- Study dosing: GDC-0917 oral, daily dosing 14 days on and 7 days off, 21-day cycle. Treatment until disease progression or unacceptable toxicity.



Patient demographics and baseline characteristics

(N=42 patients)	All patients, N (%)
Age in years , median (range)	61 (36−86)
Sex	
Female	20 (48)
Male	22 (52)
ECOG status	
0	21 (50)
1	21 (50)
Primary tumor type	
Breast	10 (24)
Colorectal	10 (24)
Prostate	6 (14)
Small cell lung	4 (10)
Ovarian	2 (5)
Other	10 (24)
Metastatic sites, median (range)	2 (0−4)
Prior treatments, median (range)	
Surgery	3 (1−7)
Chemotherapy	3 (1−9)
Hormonal	3 (1−5)
Radiotherapy	2 (1−5)
Biologic	2 (1−5)

Treatment exposure and disposition

(N=42 patients)	All patients, N (%)
Total treated	42 (100)
Extent of exposure to GDC-0917, median cycles (range)	2 (1−15)
Reason for study discontinuation Disease progression Adverse event Physician decision Death* Patient decision	 28 (67) 7 (17) 3 (7) 2 (5) 2 (5)

Dose Level	5 mg	10 mg	20 mg	40 mg	60 mg	90 mg	135 mg	200 mg	300 mg	450 mg	600 mg
No. PTs	3	3	3	2	5	3	4	3	6	7	3

*Two patients with breast cancer (5 and 135 mg dose levels, respectively) died of Disease Progression during the 30-day safety follow-up; 1 patient with SCLC (90 mg dose level) died while on study treatment due to Grade 5 pneumonia (reported as discontinued from study due to AE).

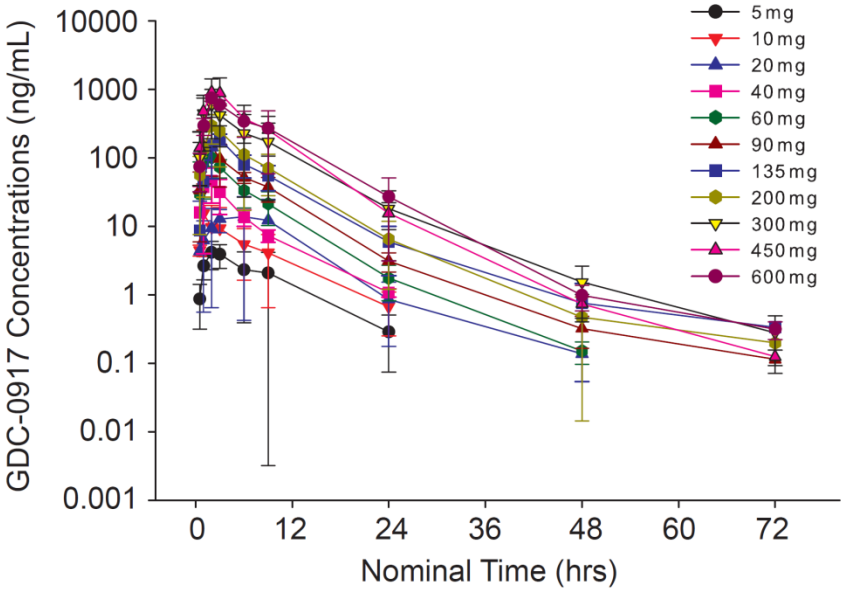
Safety summary

Safety Events	Description
DLTs	Grade 3 fatigue (1 pt, 450 mg dose level)
Most frequent GDC-0917-related AEs (in > 10% of pts)	• Fatigue: n=9 (1 Grade 3 [DLT], 4 Grade 2, 4 Grade 1) • Nausea: n=9 (2 Grade 2, 7 Grade 1) • Rash: n=6 (1 Grade 3, 1 Grade 2, 4 Grade 1) • Vomiting: n=6 (6 Grade 1)
Grade ≥ 3 GDC-0917-related AEs	ALT increase and AST increase (2 pts each), and anemia, fatigue, neutropenia, pruritus, pyrexia, and rash (1 pt each)
GDC-0917-related AEs leading to discontinuation	N=6 AEs in 5 pts (12%) Grade 2 ECG QT prolongation (1 pt) • Grade 2 drug hypersensitivity (1 pt) • Grade 2 pneumonitis (1 pt) • Grade 3 fatigue (1 pt) • Grade 3 pruritus and Grade 2 rash (same pt)
SAEs	N=14 SAEs in10 pts (24%) None reported as related to GDC-0917
Deaths	n=3: 2 patient due to breast cancer progression; 1 pt due to pneumonia

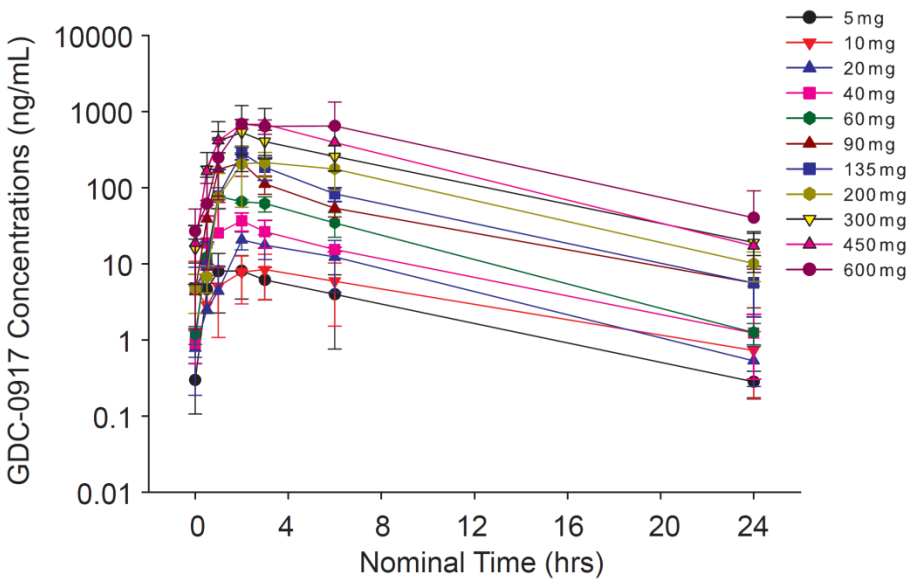
Note: No Bell's palsy was reported

GDC-0917 pharmacokinetics

- GDC-0917 peak concentrations T_{max}: 2−3h post dosing
- Mean plasma elimination $t_{1/2}$: 4−8h
- Dose-proportional exposure with no apparent accumulation at steady state



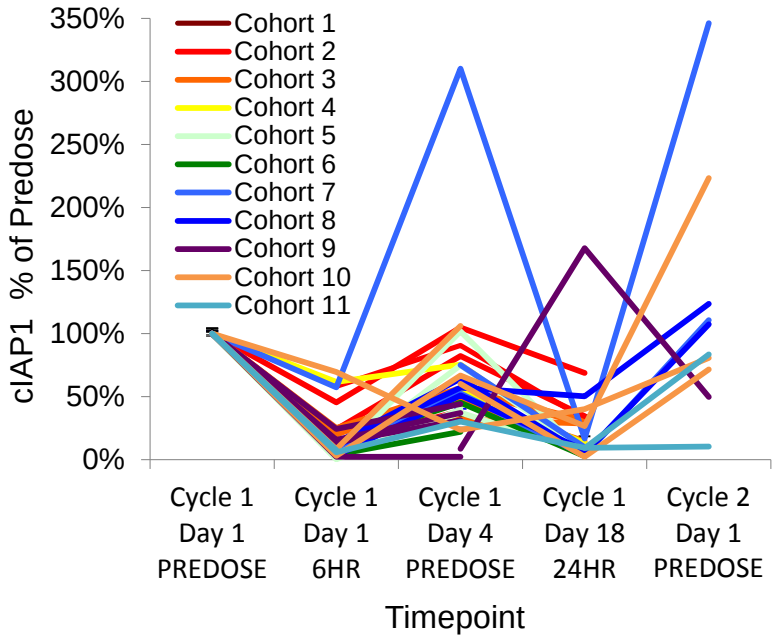
Cycle 1 mean plasma concentration-time profiles of GDC-0917 after single dose (Day 1)

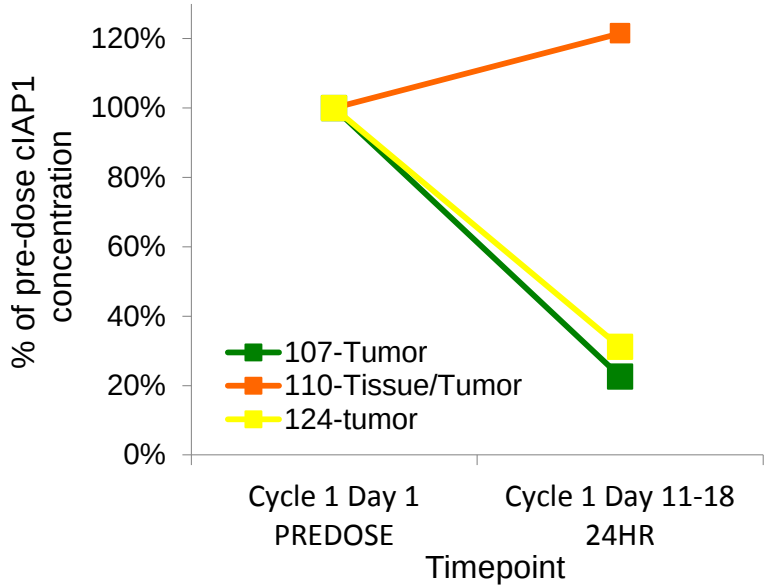


Cycle 1 mean plasma concentration-time profiles of GDC-0917 at steady-state (Day 17)

GDC-0917 pharmacodynamics

- Rapid down modulation of cIAP1 in PMBCs at all dose levels
- Decreased cIAP1 (2 pts, at 40 and 200 mg) and increased activated caspase-3 and cPARP (1 pt at 200 mg) in tumor biopsies*
- GDC-0917 dosed at 60 mg or higher resulted in a 40-70% increase in plasma MCP1 nine hours after a single dose*
- No changes were observed in other cytokines evaluated*



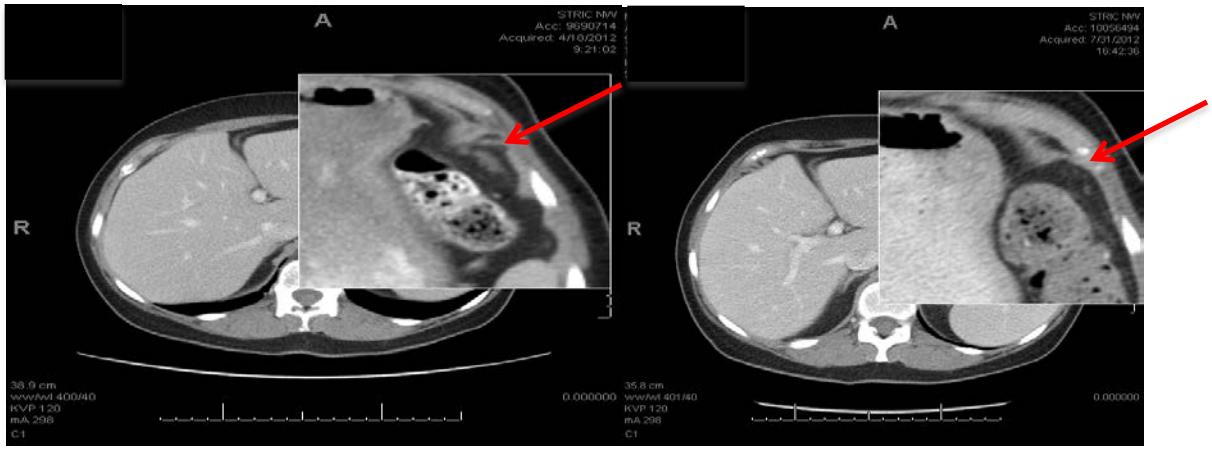


Tumor sample 110 contained very low amount of tumor tissue and a high degree of necrotic tissue

**Genentech data on file*

Preliminary signs of efficacy

- Two patients (4.8%) had unconfirmed complete response (uCR)
  1. MALT lymphoma (300 mg): PET CR end of Cycle 5 (off study after 5 Cycles per patient's choice)
  2. Ovarian cancer (450 mg): CR end of Cycle 2 (off study after 2 Cycles due to AE), continued follow-up showed sustained CR with most recent scan in Feb 2013



April 18, 2012 July 31, 2012

- One patient (carcinoma of unknown primary, 40 mg) had a mixed response after 2 cycles (reduction in extra-hepatic lesions; increased and new hepatic lesions, off study after 2 Cycles due to PD)
- Four patients (9.5%) had stable disease for ≥ 3 months; including 1 patient on study for > 10 months

Responses were based on investigators assessment

Summary and overall conclusions

- GDC-0917 had a favorable safety and PK profile in patients with advanced malignancies
- MTD was not determined, although ED90 based on preclinical xenograft studies was reached
- Pharmacodynamic modulation was observed
- Antitumor activity was observed in some patients
- These encouraging results support further clinical evaluation of GDC-0917

Acknowledgements

Thank you to the many patients for their participation in this trial

Genentech exclusively licensed GDC-0917 to Curis, Inc. Curis designated the molecule CUDC-427 and has the sole right and responsibility for all research, development, manufacturing and commercialization activities related to CUDC-427.