Phase 1a Study of the Safety, Pharmacokinetics, and Pharmacodynamics of GDC-0919 in Patients with Recurrent/Advanced Solid Tumors

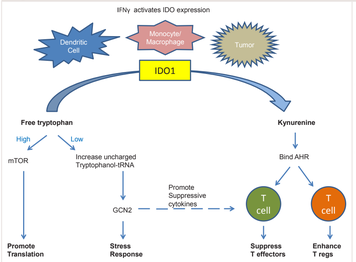
A. Nayak[1], Z. Hao[1], R. Sadek[1], R. Dobbins[1], L. Marshall[1], N.N. Vahanian[2], W.J. Ramsey[2], E. Kennedy[2], M. Mautino[2], C. Link[2], R. Lin[3], S. Royer-Joo[3], K. Morrissey[3], S. Mahrus[3], B. McCall[3], A. Pirzkall[3], D.H. Munn[1], J.E. Janik[1], S.N. Khleif[1]

[1]GRU cancer Center, Georgia Regents University, Augusta, GA; [2]NewLink Genetics, Ames, IA; [3]Genentech, Inc., South San Francisco, CA, USA

BACKGROUND

- Indoleamine 2,3 dioxygenase 1 (IDO1) is a cytosolic enzyme that catalyzes the oxidation of L-tryptophan (Trp) into kynurenine (Kyn)

Fig 1. IDO1 Pathway



- IDO1-expressing cells regulate inflammation and immune response to foreign as well as non pathological antigens
- Several cancers induce the IDO1 pathway in tumor and host immune cells, permitting immune escape and the attainment of immunologic tolerance
- GDC-0919 (RO 7077339; previously NLG919) is a small molecule investigational immunotherapy designed to inhibit IDO1 for the treatment of immune tolerance associated with cancer (Mautino et al.; 2013), intended as combination therapy

IDO1 = Indoleamine 2,3 dioxygenase 1; IFN γ = Interferon γ; mTOR = mammalian Target of Rapamycin; tRNA = transfer ribonucleic acid; GCN2 = general control nonderepressible 2; AHR = aryl hydrocarbon receptor; T effectors = effector T cells; T reg = regulator T cells

Preclinical Efficacy of GDC-0919

- Combined treatment with GDC-0919 and chemo-radiation therapy enhanced survival in mice and compared to without GDC-0919 was associated with enhanced complement deposition (Li et al; 2014)
- Treatment with GDC-0919, upon vaccination of B16F10 tumor-bearing mice, resulted in an increase in the T effector cell response, leading to improved anti-tumor efficacy (Mautino et. al; 2014)
- Dual inhibition of IDO1 and PD-L1 showed greater effect in activating the immune system and inhibiting tumor growth than either treatment alone (Holmgaard et al. 2013; Spranger et al. 2014). Responses showed more pronounced activation (proliferation + cytokine production) of intratumoral CD8+ T cells

OBJECTIVES

Primary Objectives

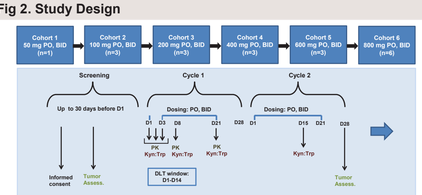
- Evaluate the safety and tolerability of GDC-0919 in patients with advanced solid tumors
- Define maximum tolerated dose (MTD) or maximum biologically effective dose (MBED), and recommended phase 2 dose (RP2D) of GDC-0919 in patients with advanced solid tumors

Secondary Objectives

- Characterize the plasma pharmacokinetics (PK) of GDC-0919
- Evaluate pharmacodynamic (PD) modulation of plasma Kyn and Trp by GDC-0919
- Evaluate response rate and duration of response in patients with advanced solid tumors

METHODS

Fig 2. Study Design



- Patients received escalating doses of GDC-0919 BID for 21 days followed by a 7 day break (21/28 day schedule)
- Modified 3+3 design to evaluate safety and tolerability within a 14-day DLT window

Study Design

- Open label, first in human, dose escalation, single center, phase 1a study to evaluate GDC-0919 in patients with advanced solid tumors
- PK and PD blood draws occurred at different times of day and patients had not been fasting
- Key inclusion/exclusion criteria: Histologically or cytologically confirmed solid tumor that is relapsed/ refractory to standard therapies, or for which no approved or curative therapy exists; Age ≥18 years; Life expectancy ≥4 months; ECOG performance status of 0 or 1; Adequate bone marrow, hepatic, and renal function; QTcF interval <470 msec at baseline ECG; ≥28 days from the administration of any investigational agent or prior cytotoxic therapy; No previous therapy with ipilimumab or tremelimumab; No active or history of autoimmune disease

RESULTS

Disposition

- Enrolled and treated on study: 19 patients (Data cutoff date: 18 Jun 2015)
- Discontinued from study treatment (18): disease progression (17), and patient withdrawal (1)

Baseline characteristics

- Median age 59 years; 14 males (74%); ECOG 0: 7 patients (37%), ECOG 1: 12 patients (63%)
- All patients received ≥ 1 prior systemic therapy; 17 patients received at least 1 prior radiation therapy

Treatment exposure

Table 1. GDC-0919 Treatment Exposure

	Cohort 1 (50 mg) n=1	Cohort 2 (100 mg) n=3	Cohort 3 (200 mg) n=3	Cohort 4 (400 mg) n=3	Cohort 5 (600 mg) n=3	Cohort 6 (800 mg) n=6	TOTAL (N=19)
Number of cycles	3	8	3	3	3	2	3
median, range	(3-3)	(4-14)	(1-6)	(2-6)	(1-4)	(1-7)	(1-14)
Treatment duration days	72	225	77	62	78	56	77
median, range	(72-72)	(105-373)	(29-155)	(43-161)	(21-128)	(13-186)	(13-373)

Safety

Table 2. Adverse Events Regardless of Attribution and Related to Study Drug Occurring in ≥ 10% of Patients Overall, and Corresponding Grade ≥ 3 Adverse Events

	All Grades				Grades ≥ 3	
	Cohort 6 (800 mg) (n=6)		All Cohorts (N=19)		Total (N=19)	
	All	Related	All	Related	All	Related
Any AE	6	5	19 (100%)	16 (84%)	11 (58%)	1 (5%)
Fatigue	3	1	11 (58%)	5 (26%)	-	-
Cough	4	2	9 (47%)	3 (16%)	-	-
Decreased appetite	3	1	9 (47%)	4 (21%)	-	-
Nausea	2	1	8 (42%)	3 (16%)	-	-
Pruritus	1	1	8 (42%)	7 (37%)	-	-
Vomiting	1	-	6 (32%)	2 (10.5%)	-	-
AST increase	2	2	4 (21%)	2 (10.5%)	2 (10.5%)	-
Constipation	1	-	4 (21%)	-	-	-
Dyspepsia	-	-	4 (21%)	1 (5%)	-	-
Dyspnea	2	-	4 (21%)	1 (5%)	-	-
Hypokalemia	1	-	4 (21%)	1 (5%)	1 (5%)	
Wheezing	1	-	4 (21%)	-	-	-
Abdominal pain	1	1	3 (16%)	1 (5%)	-	-
Anxiety	1	-	3 (16%)	-	-	-
Ascites	1	1	3 (16%)	1 (5%)	1 (5%)	-
Neoplasm progression	-	-	3 (16%)	-	3 (16%)	-
Resp. tract infection	1	-	3 (16%)	-	1 (5%)	-
ALT increase	1	1	2 (10.5%)	1 (5%)	-	-
Arthralgia	-	-	2 (10.5%)	-	-	-
Dehydration	-	-	2 (10.5%)	-	-	-
Dry mouth	-	-	2 (10.5%)	1 (5%)	-	-
Flank pain	-	-	2 (10.5%)	-	-	-
Hemoptysis	-	-	2 (10.5%)	-	-	-
Headache	1	-	2 (10.5%)	-	-	-
Muscular weakness	-	-	2 (10.5%)	1 (5%)	1 (5%)	-
Pain	1	-	2 (10.5%)	-	-	-
Pyrexia	1	-	2 (10.5%)	-	-	-
Rash	-	-	2 (10.5%)	2 (10.5%)	-	-
Rash maculopapular	1	1	2 (10.5%)	2 (10.5%)	-	-
Weight decreased	-	-	2 (10.5%)	-	-	-

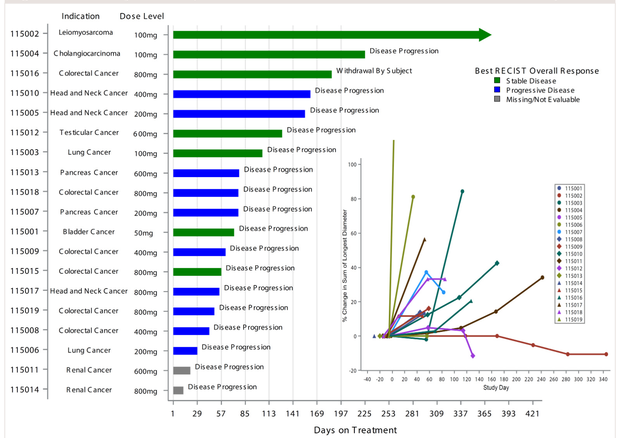
Safety

- All 19 pts experienced at least one AE during the study regardless of attribution to GDC-0919
- MTD not reached; DLT reported in 1 patient (70 yo male) in Cohort 6 (800 mg) with metastatic renal cell carcinoma. Grade 4 lower gastrointestinal hemorrhage on Study Day 14 assessed as possibly related to GDC-0919. The patient exhibited peritoneal and GI serosal metastasis on baseline CT scan
- Grade ≥3 AEs regardless of attribution were reported in 11 (58%) of patients
- Grade ≥3 AE related to GDC-0919 in 1 patient with Grade 4 lower gastrointestinal hemorrhage
- Serious AE reported in 8 (42%) patients included:
  - Grade 5 progression of neoplasm (3, 16%) (within 30 days of last GDC-0919 dose); and 1 patient each with Grade 4 lower gastrointestinal hemorrhage, Grade 4 hypotension, Grade 3 pneumonia, Grade 3 mental status change and Grade 3 small intestinal obstruction, and Grade 2 hypoxia
  - Grade 4 lower GI hemorrhage was the only SAE assessed as possibly related to study drug
- No AEs requiring withdrawal of study drug were reported
- Preliminary review of electrocardiograph (ECG) data collected at baseline, cycle 1 day 1, and cycle 1 day 8 did not suggest a risk of QT prolongation with GDC-0919; further characterization is ongoing
- Liver function: 4 patients (21%) with elevated liver enzymes. AST increased in 4 patients (related in 2 patients), ALT increased in 2 patients (related in 1 patient)
- Two patients required dose modifications: 1 patient, dose interuption in 100 mg cohort (Grade 1 tachycardia, dyspnea, and nausea); 1 patient, dose interruption/reduction 800→600 mg (Grade 2 AST/ALT and maculopapular rash) (Table 1)

Clinical Activity/Efficacy

- No objective responses; Best response limited to stable disease (SD) in 7/17 (37%) patients (no on-study tumor assessments were available for 2 patients who discontinued with clinical progression)

Fig 3. Time on Study Treatment, Reason for Treatment Discontinuation and Best RECIST Response



Patient 115002 (active on study treatment with diagnosis of leiomyosarcoma of the colon) was enrolled on study with presumed tumor progression after prior chemotherapy, though tumor progression was not confirmed upon re-examination of radiographic assessments
Patient 115019 has over 100% change in % change in sum of longest diameter

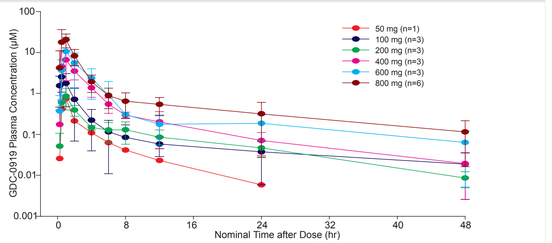
Pharmacokinetics

- Preliminary PK results up to 800 mg BID suggest that GDC-0919 is rapidly absorbed and demonstrates linear and dose proportional increases in exposure, with a half-life supportive of BID dosing ($t_{1/2}$ ~12 hour) (Fig 4)

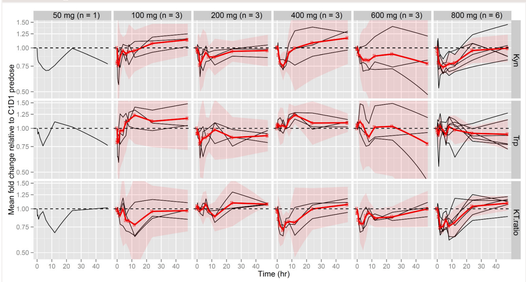
Pharmacodynamics

- GDC-0919 at doses up to 800 mg transiently decreases plasma Kyn at higher doses by ~30%, 4 hrs after dosing, i.e. in a manner that is consistent with the half-life of the drug
- No significant modulation of plasma Trp levels was observed (Fig 5)

Pharmacokinetics: Fig 4. Plasma Concentrations of GDC-0919 Following a Single Oral Dose



Pharmacodynamics: Fig 5. Changes in Plasma Kyn and Trp Relative to C1D1 Pre-Dose Levels After Single Dose GDC-0919



Mean fold changes in plasma Kyn, Trp, and Kyn/ Trp ratio relative to C1D1 predose levels following a single oral dose of GDC-0919. Black lines represent individual patients, red lines represent means, red ribbons represent 95% confidence intervals, and dashed horizontal lines represent no change from baseline

CONCLUSIONS

- Overall, GDC-0919 was well tolerated up to 800 mg BID on a 21/28 day cycle
- Best response was limited to stable disease (SD) in 7 out of 17 patients
- Higher doses of GDC-0919 modulate plasma Kyn in a manner consistent with the half-life of the drug
- Single and multiple dose exposures from 50 to 800 mg GDC-0919 increased in approximately dose-proportional manner
- Evaluation of the PK/PD relationship is ongoing to identify the dose of GDC-0919 that will achieve maximal inhibition of IDO
- No immune-related AEs evident, although a possible relationship between study treatment and elevation of liver enzymes cannot be ruled out at this time
- This study continues to evaluate safety, PK, activity, and pharmacodynamics of GDC-0919 at a continuous dosing schedule (BID 28/28 days) to enable greater flexibility in future dosing regimens
- GDC-0919 is being evaluated in phase 1b in combination with atezolizumab (PD-L1 inhibitor) (NCT02471846)

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