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Interim Analysis of the Dose-escalation Stage of a Phase 1b Study Evaluating Safety and Pharmacology of GS-9820, a Second-Generation, Selective, PI3Kδ-Inhibitor in Recurrent Lymphoid Malignancies

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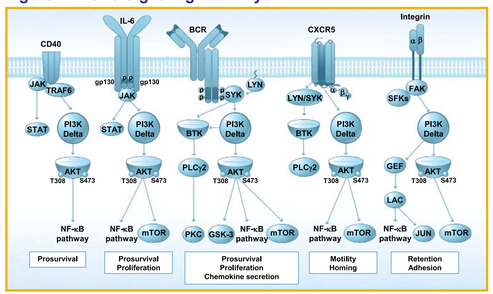
Introduction

- In B-cells, phosphatidylinositol 3-kinase delta (PI3Kδ) mediates a positive effect on cell survival, proliferation, growth, and metabolism
- PI3Kδ activity is critical for homing and retaining B cells in lymphoid tissues, and in B-cell malignancies, increased activity of PI3Kδ drives proliferation and survival of malignant B-cells and mediates trafficking to lymphoid tissues

Figure 1. PI3Kδ Signaling Pathways



Background

- GS-9820 is a second-generation, selective, small molecule inhibitor of PI3Kδ under investigation for the treatment of lymphoid malignancies including non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL)

Objectives

- The primary endpoint for the dose-escalation stage of the phase 1b study is to determine the maximally tolerated dose (MTD) and to assess safety including the incidence and severity of elevation in transaminase levels, which has been observed to varying degrees with other PI3K inhibitors
- In this interim analysis, we report safety, efficacy and pharmacokinetics (PK) for the first four dose cohorts

Methods

- Stage 1 is a dose escalation stage with a 3+3 design to evaluate the safety, efficacy and pharmacology of GS-9820
- Subjects with recurrent lymphoid malignancies with measurable lymphadenopathy who had > 1 prior therapy were enrolled and received GS-9820 at doses of 50, 100, 200, or 400 mg, administered orally twice daily (BID)
- Antitumor activity was evaluated every 2 months and was adjusted for redistribution lymphocytosis
- Nodal PR (nPR) is defined as a ≥50% reduction in lymphadenopathy.
- Safety assessments for maximally tolerated dose occurred after four weeks of treatment

Methods (cont'd)

- Subjects could continue receiving GS-9820 indefinitely as needed
- All subjects are monitored for elevations in transaminase levels
- Updated analysis based on data cut-off date – September 23, 2013
  - 18 subjects enrolled; 14 evaluable subjects had at least one post-dose CT scan
  - Pharmacokinetics data on first 12 subjects were enrolled in dose-escalation cohorts 50, 100, 200 and 400 mg

Pharmacokinetics

- Plasma PK samples were collected at the following time points at GS-9820 initial dosing (Day 1) and at steady state (Day 29): pre-dose, 0.5, 1, 1.5, 2, 3, 4, and 6 hours post dose
- Plasma PK samples were analyzed to quantify GS-9820 and its inactive metabolite GS-563600 concentrations using a validated LC/MS method with a lower limit of quantitation (LLOQ) of 1 ng/mL for both GS-9820 and GS-563600
- PK parameters were generated using non-compartmental analysis in WinNonLin (version 6.3, Pharsight, Cary, North Carolina)

Table 1. Baseline Disease Characteristics

Characteristics, n (%)	N=18
Gender, male/female	13/5 (72/28)
Age, median [range], years	69 [48-81]
Disease type	
Follicular lymphoma	1 (6)
Marginal zone lymphoma	1 (6)
Lymphoplasmacytoid lymphoma	1 (6)
Mantle cell lymphoma	2 (12)
CLL (Chronic lymphocytic leukemia)	13 (72)
Cytopenias, Any Grade(%)/≥G3(%)*	
Neutropenia	(59/12)
Anemia	(94/0)
Thrombocytopenia	(65/24)

*data for subject 1003 is missing

Table 2. Disease Characteristics for Evaluable Subjects N=14

Characteristics	Number of Subjects
Response to last therapy	
Refractory Disease	12
Relapsed Disease	2
Bulky Disease (presence of at least 1 node >5cm at baseline)	12

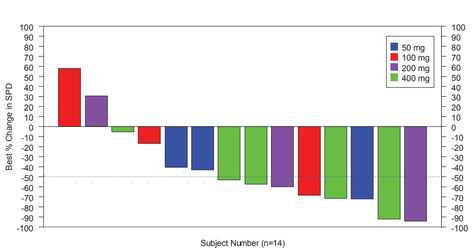
Table 3. Prior Therapies, N=18

# of Regimens, median [range]	3 [1-7]
Prior therapy type	**(%)**
Rituximab	92
Alkylating agent	100
Purine analog	83

Note: Subjects received combination therapy that included rituximab, alkylating agents and/or purine analogs

Results

Figure 2. Best Nodal Response for Evaluable Subjects (n=14)



Note: 13/14 evaluable subjects had lymphocytosis post treatment

Figure 3. Platelet Levels While on Treatment

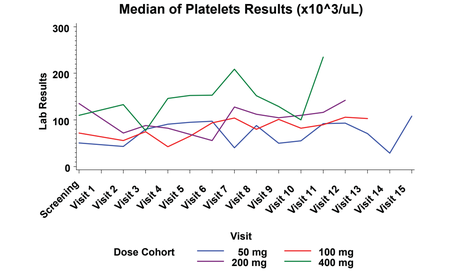


Figure 4. Hemoglobin Levels While on Treatment

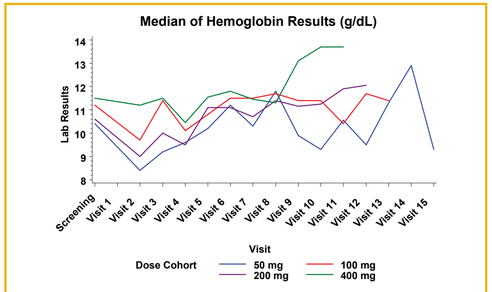
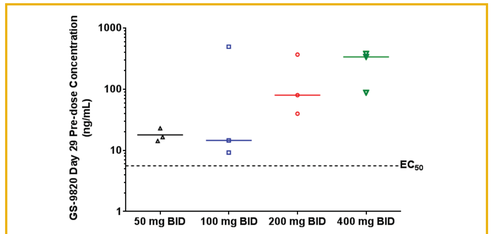


Figure 5. GS-9820 Day 29 Pre-Dose Concentration vs. Dose (N=12)



Note: bars represent medians

- GS-9820 pre-dose concentrations remain above the human whole-blood assay EC_{50} (14 nM or 5.6 ng/mL) at all doses tested

Table 4. Summary of PK Parameters (Day 29)

Analyte	PK Parameters	50 mg BID (n=3)	100 mg BID (n=3)	200 mg BID (n=3)	400 mg BID (n=3)
GS-9820	C_{max} (ng/mL)[a]	1150 (28)	1480 (26)	1330 (81)	2760 (32)
	T_{max} (h)[b]	0.53 (0.50, 2.00)	0.50 (0.50, 0.50)	1.00 (0.50, 1.00)	1.00 (1.00, 2.00)
	$AUC_{0\text{-}6h}$ (ng•h/mL)[a]	2020 (30)	2600 (35)	3420 (35)	8440 (42)
GS-563600	C_{max} (ng/mL)[a]	5510 (48)	11400 (62)	8840 (52)	7210 (32)
	T_{max} (h)[b]	2.00 (1.03, 4.00)	1.50 (0, 2.00)	2.00 (0, 4.00)	4.00 (1.00, 4.00)
	$AUC_{0\text{-}6h}$ (ng•h/mL)[a]	25700 (56)	57400 (73)	46300 (48)	37800 (38)

[a]mean (%CV); [b]median (Q1, Q3); $AUC_{0\text{-}6h}$=area under the concentration-time curve from 0 to 6 h post dose; C_{max}=maximum observed concentration; T_{max}=time to reach maximum plasma concentration

Table 5. Adverse Events

Event >10% or ≥ Grade 3	All (%) N=18	Grade ≥ 3
Pain	9 (50)	0
Fatigue	7 (39)	1
Cough	5 (28)	0
Rash	4 (22)	2
Edema	4 (22)	0
Anemia	3 (17)	0
Anorexia	3 (17)	0
Bloating	3 (17)	0
Dyspnea	3 (17)	0
Diarrhea	3 (17)	1
Fever	3 (17)	0
Constipation	2 (11)	0
Headaches	2 (11)	0
Neutropenia	2 (11)	1
Pneumonia	2 (11)	2
Vomiting	2 (11)	0

Table 6. Serious Adverse Events

Event	Outcome
Pneumonia	Resolved
Progressive Herpes Infection	Ongoing
Basal Carcinoma	Resolved
Fever	Resolved

Table 7. Treatment-related AEs

Event	Grade (s)
Neuropathy Footpads	1
Diarrhea (3 subjects)	1,2,3
Neutropenia	4
Edema	1
Elevated Creatinine	2
Hyperkalemia	2
Bloating (2 subjects)	1,2
Varicella Zoster	2
Dermatitis Medicamentosa	2
Flatulence	1

Conclusions

- **Interim analysis of the first 4 cohorts of a dose-escalation phase 1b study of GS-9820 in patients with recurrent lymphoid malignancies demonstrates clinical activity and reduction in lymphadenopathy. Nodal PRs were seen in 8 (57%) of subjects and at 400 mg BID, the highest dose tested, nodal PRs were seen in 4/5 subjects**
- **Doses ranging from 50 mg to 400 mg BID are not associated with disease limiting toxicity. No subjects had elevations of transaminase levels ≥ grade 3**
- **Based on analysis of PK parameters measured, enrollment was expanded at 400 mg BID to include up to 30 subjects**

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Disclosures

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- Jun: Gilead Sciences: Employment