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# Interim Analysis of a Phase 1b Study Evaluating the Safety of GS-9820, a Second-Generation PI3Kδ-Inhibitor, in Relapsed/Refractory Lymphoid Malignancies

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## Introduction

- In B cells, phosphatidylinositol 3-kinase-δ 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
  - In B-cell malignancies, increased activity of PI3Kδ drives proliferation and survival of malignant B cells, and mediates trafficking to lymphoid tissues

### GS-9820

- GS-9820 is a 2nd-generation, selective, small molecule inhibitor of PI3Kδ under investigation for the treatment of lymphoid malignancies including non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL)

## Objectives

### Primary

- To determine the appropriate GS-9820 dose for future clinical trials in patients with lymphoid malignancies

### Secondary

- To characterize the GS-9820 safety profile
- To explore the onset, magnitude, and duration of tumor control

## Methods

### Study Design

- Phase 1b, open label, 3+3 dose escalation (ClinicalTrials.gov NCT01705847)
- Patients received GS-9820 50, 100, 200, or 400 mg administered orally BID
- Interim analysis based on data cut-off date of 23 July 2014
- Patients could continue receiving GS-9820 indefinitely as needed

### Eligibility

- Age ≥18 years
- Recurrent B-cell indolent NHL (iNHL), diffuse large B-cell lymphoma, mantle cell lymphoma, Hodgkin lymphoma (HL), or CLL, with ≥1 prior therapy
- Presence of radiographically measurable lymphadenopathy

### Endpoints

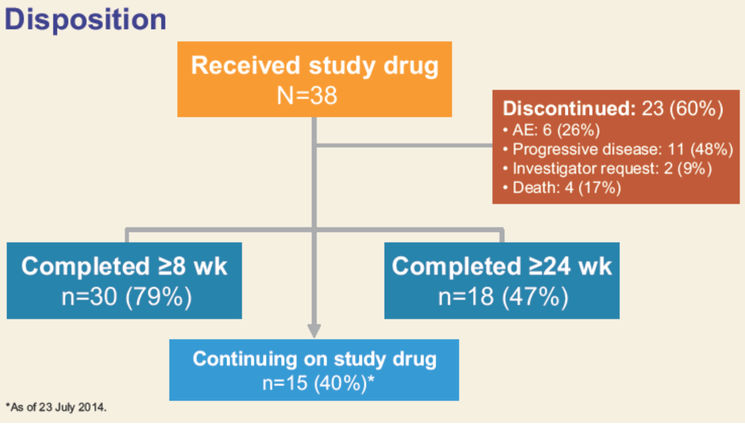
- Primary
  - Maximally tolerated dose (MTD) within tested GS-9820 dose range
- Secondary
  - Overall safety profile of each study treatment regimen characterized by type, frequency, severity, timing of onset, duration, and relation to study therapy of any adverse events (AEs)
  - Antitumor activity—objective response rate (ORR), time to response, duration of response, and progression-free survival—evaluated using standard response criteria for NHL and HL or for CLL, with adjustment of CLL criteria to account for the redistribution lymphocytosis observed with PI3Kδ inhibition

### Disease Assessment

- Computed tomographic or magnetic resonance imaging assessments were used to evaluate tumor response every 2–3 months
- Response per modified International Workshop on Chronic Lymphocytic Leukaemia and International Working Group guidelines[1]
- Safety assessments for MTD occurred after 4 weeks of treatment

## Results

### Disposition




*As of 23 July 2014.

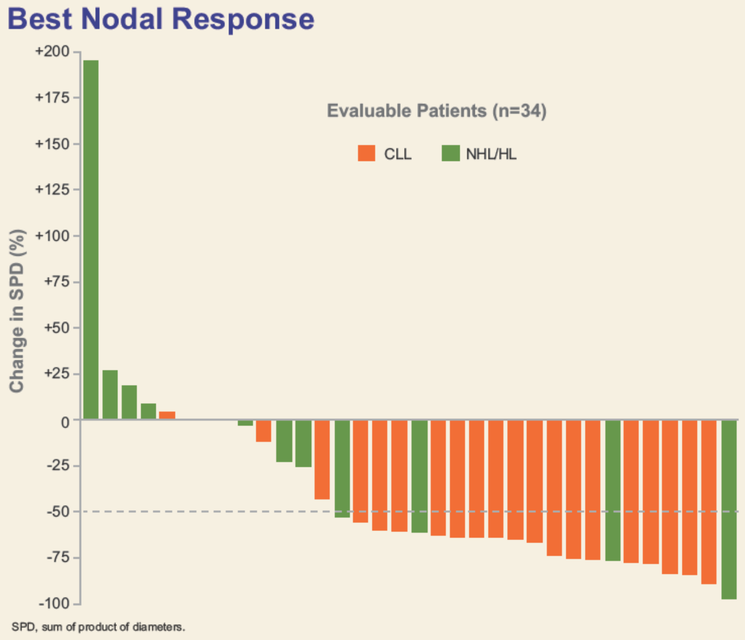
### Baseline Demographics and Disease Characteristics

| | Patients, N=38 |
|---|---|
| Male/female, n (%) | 26/12 (68/32) |
| Median age, y (range) | 69 (48–81) |
| Disease type, n (%) | |
| Follicular lymphoma | 1 (3) |
| Marginal zone lymphoma | 1 (3) |
| Lymphoplasmacytoid lymphoma | 1 (3) |
| Mantle cell lymphoma | 8 (21) |
| Diffuse large B-cell lymphoma | 4 (10) |
| CLL | 22 (58) |
| HL | 1 (3) |
| Median regimens, n (range)* | 3 (1–13) |
| Prior therapy type, n (%) | |
| Rituximab | 34 (90) |
| Alkylating agent | 38 (100) |
| Purine analog | 23 (61) |

| | CLL, n=22 | iNHL, n=15 | HL, n=1 | Total, N=38 |
|---|---|---|---|---|
| Disease status at study entry, n | | | | |
| Refractory disease | 12 | 8 | 1 | 21 (55%) |
| Relapse disease | 7 | 6 | 0 | 13 (34%) |
| Unknown | 3 | 1 | 0 | 4 (11%) |
| Bulky disease, n† | NA | 9 | 0 | 9 (24%) |

*All patients received chemoimmunotherapy or combination chemotherapy; †Presence of ≥1 node >5 cm at baseline. NA, not applicable.

### Best Nodal Response




SPD, sum of product of diameters.

### Overall Response Rate by Dose Cohort

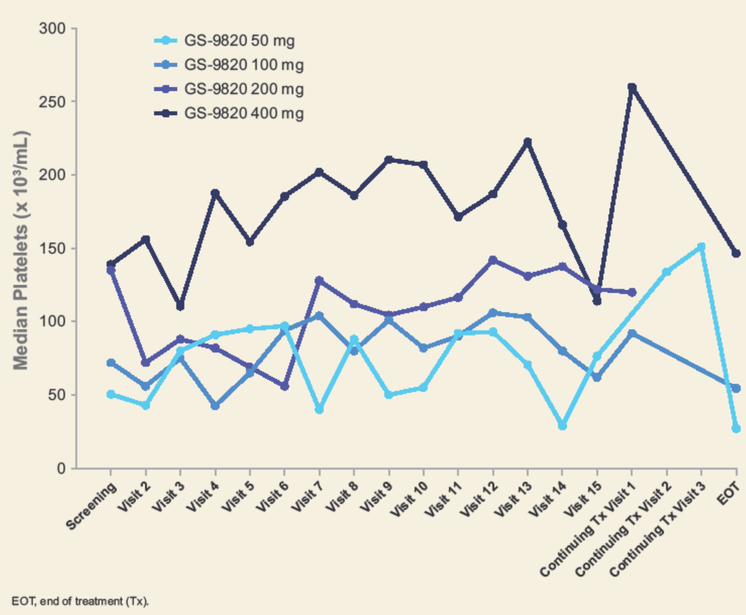
| | GS-9820 | | | | Total |
|---|---|---|---|---|---|
| Patients, n (%) | 50 mg BID n=3 | 100 mg BID n=3 | 200 mg BID n=3 | 400 mg BID n=29 | N=38 |
| Complete response | 0 | 0 | 1 (33) | 1 (3) | 2 (5) |
| Partial response | 1 (33) | 1 (33) | 1 (33) | 8 (28) | 11 (29) |
| Stable disease | 2 (67) | 1 (33) | 0 | 12 (41) | 15 (40) |
| Progressive disease | 0 | 1 (33) | 1 (33) | 4 (14) | 6 (16) |
| Not evaluable | 0 | 0 | 0 | 4 (14) | 4 (11) |

### Overall Response Rate by Disease Type: GS-9820 400 mg BID

| Patients, n (%) | CLL, n=15 | NHL/HL, n=14 | Total, n=29 |
|---|---|---|---|
| Complete response | 0 | 1 (7) | 1 (3) |
| Partial response | 5 (33)* | 3 (21) | 8 (28) |
| Stable disease | 9 (60) | 3 (21) | 12 (41) |
| Progressive disease | 0 | 4 (29) | 4 (14) |
| Not evaluable | 1 (7) | 3 (21) | 4 (14) |
| ORR | 5 (33) | 4 (29) | 9 (31) |

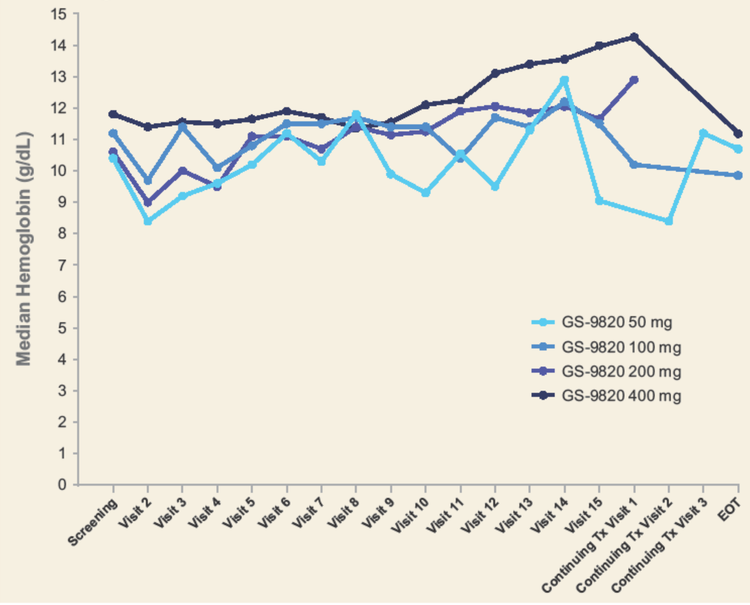
*Including partial response + lymphocytosis (3 of 5).

### Platelet Levels While on GS-9820 Treatment




EOT, end of treatment (Tx).

### Hemoglobin Levels While on GS-9820 Treatment




### Overall Safety Summary

| | GS-9820 | | | | |
|---|---|---|---|---|---|
| Patients, n (%) | 50 mg BID n=3 | 100 mg BID n=3 | 200 mg BID n=3 | 400 mg BID n=29 | Total N=38 |
| Any AE | 3 (100) | 3 (100) | 3 (100) | 28 (97) | 37 (97) |
| Grade ≥3 AE | 3 (100) | 2 (67) | 3 (100) | 19 (66) | 27 (71) |
| Serious AE | 2 (67) | 1 (33) | 2 (67) | 16 (55) | 21 (55) |
| AE leading to drug discontinuation | 0 | 1 (33) | 0 | 13 (45) | 14 (37) |
| AE leading to death | 0 | 0 | 0 | 6 (21) | 6 (16) |

### Treatment-Emergent AEs in ≥15% of Patients

| | | Total, (N=38), n (%) | |
|---|---|---|---|
| | | Any Grade | Grade ≥3 |
| Adverse Events | Fatigue | 17 (45) | 3 (8) |
| | Pyrexia | 11 (29) | 0 |
| | Cough | 10 (26) | 0 |
| | Diarrhoea | 10 (26) | 2 (5) |
| | Oedema peripheral | 10 (26) | 0 |
| | Dyspnoea | 9 (24) | 1 (3) |
| | Rash | 9 (24) | 4 (11) |
| | Weight decrease | 7 (18) | 1 (3) |
| | Anaemia | 6 (16) | 3 (8) |
| | Dysgeusia | 6 (16) | 0 |
| | Pneumonia | 6 (16) | 4 (11) |
| | Vomiting | 6 (16) | 0 |

### Treatment-Emergent Grade ≥3 Laboratory Abnormalities

| | | Total, (N=38), n (%) | |
|---|---|---|---|
| | | Grade ≥3 | Any Grade |
| Laboratory Abnormalities | Anemia | 4 (11) | 10 (26) |
| | Leukocytosis | 9 (24) | 11 (29) |
| | Lymphocytosis | 11 (29) | 13 (34) |
| | Neutropenia | 15 (40) | 23 (61) |
| | Thrombocytopenia | 5 (13) | 12 (32) |
| | Transaminase elevation | 3 (8) | 3 (8) |
| | Leukopenia | 9 (24) | 11 (29) |
| | Lymphocytopenia | 11 (29) | 13 (34) |
| | Hypophosphatemia | 2 (5) | 5 (13) |
| | High triglycerides | 3 (8) | 21 (55) |
| | Hyperuricemia | 1 (3) | 3 (8) |

### Serious Adverse Events in >1 Patient

| | Total, (N=38), n (%) |
|---|---|
| Any serious AE | 21 (55) |
| Pneumonia | 5 (13) |
| Pyrexia | 4 (11) |
| Sepsis | 2 (5) |

## Conclusions

- No MTD was observed in the doses of GS-9820 evaluated
- GS-9820 was tolerable, with no dose-limiting toxicities observed in the doses evaluated
- GS-9820 demonstrated clinical activity in these patients with hard-to-treat disease at the doses tested

### Reference

1. Hallek M, et al. Blood 2008;111:5446-56.

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### Disclosures

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Aggressive B-cell lymphoma

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