

Introduction

- Constitutive signaling through the B-cell receptor is critical for the survival and proliferation of human B-cell lymphomas¹ and leads to downstream activation of phosphatidylinositol 3-kinases (PI3Ks), including PI3K δ ²
- Aberrant activation of PI3K δ is associated with proliferation and survival of malignant B cells³
- PI3K δ inhibitors have demonstrated efficacy for the treatment of B-cell malignancies, but off-target toxicity and/or the inability to achieve near-complete inhibition of the PI3K δ pathway may affect the depth and duration of response
- INCB050465 is a novel, potent, and highly specific inhibitor of PI3K δ (Table 1),⁴ with a differentiated profile for potency (whole blood IC₅₀ = 10 nM, IC₉₀ = 77 nM) and dose (<50 mg total daily dose)

Table 1. Comparative Potency, Isoform Selectivity, and Dosing of INCB050465

	INCB050465	Idelalisib ⁵	TGR1202 ⁶
PI3K δ enzyme potency (IC ₅₀ , nM)	1	2.5	22
Fold selectivity			
PI3K α	19,000	>300	>10,000
PI3K β	>20,000	>50	>50
PI3K γ	>20,000	>35	>48
Total daily dose, mg	20–30 ⁴	300	1200

*Expansion doses.

- INCB050465 potently inhibits signaling and proliferation of malignant B cells in vitro⁴
- Preclinical studies indicate a lack of hepatotoxicity at exposures exceeding 10-fold IC₅₀ coverage

Objective

- The objective of this ongoing phase 1/2 study is to assess the safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of INCB050465 in patients with relapsed or refractory B-cell malignancies (NCT02018861)⁵; emerging data from this trial are reported here

Methods

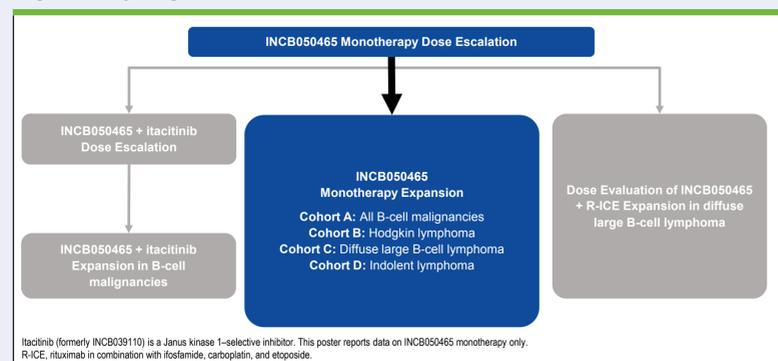
Patients

- ≥18 years of age, with lymphoid malignancies of B-cell origin or with classic Hodgkin lymphoma (HL) who had relapsed or were refractory to prior standard therapy
- Burkitt lymphoma and precursor B-lymphoblastic leukemia/lymphoma were excluded
- Received ≥1 prior treatment regimen
- Had not responded or were not a candidate for stem cell transplant or other potentially curative therapy
- Eastern Cooperative Oncology Group performance status ≤1 (dose escalation) or ≤2 (monotherapy expansion)

Study Design

- This is an ongoing, phase 1/2, open-label, dose-escalation and expansion study (NCT02018861) of INCB050465 given orally once daily (QD; Figure 1)
- Following an initial single-patient cohort treated with 5 mg, subsequent cohorts used a 3 + 3 design and evaluated doses of 10 to 45 mg; based on PK/PD analysis, the 20-mg and 30-mg cohorts were expanded
- A dosing schedule of 20 mg QD for 9 weeks followed by 20 mg once weekly (QW) was also evaluated

Figure 1. Study Design



Itacitinib (formerly INCB039110) is a Janus kinase 1-selective inhibitor. This poster reports data on INCB050465 monotherapy only. R-JCE, rituximab in combination with ifosfamide, carboplatin, and etoposide.

Assessments

- Safety and tolerability of INCB050465 monotherapy
 - Treatment-emergent adverse events (TEAEs) were assessed by the investigator using Common Terminology Criteria for Adverse Events v4.03
- Efficacy was evaluated every 9 weeks by best overall response, defined as the sum of patients achieving a complete response or a partial response based on:
 - The Lugano classification of lymphoma response criteria for HL and non-Hodgkin lymphoma (NHL),⁶ with spleen size used as the primary parameter for response in splenic marginal zone lymphoma
 - The International Working Group on Chronic Lymphocytic Leukemia (IWGCLL) criteria for chronic lymphocytic leukemia^{7,8}
- This analysis includes data from patients enrolled into INCB050465 monotherapy dose-escalation cohorts (5–45 mg) and expansion cohorts (20 mg and 30 mg)

An Ongoing Phase 1/2 Study of INCB050465 for Relapsed/Refractory B-Cell Malignancies (CITADEL-101)

Rod Ramchandren,¹ Tycel J. Phillips,² Michael Wertheim,³ Martin Gutierrez,⁴ William J. Edenfield,⁵ Luke P. Akard,⁶ Paolo F. Caimi,⁷ Justin Call,⁸ Daniel O. Persky,⁹ Douglas J. DeMarini,¹⁰ Li Zhou,¹⁰ Swamy Yeleswaram,¹⁰ Andres Forero-Torres¹¹

Results

Patients

- As of the data cutoff (March 1, 2017), 63 patients were enrolled and treated with INCB050465 at doses ranging from 5 to 45 mg QD; 19 (30%) patients were still on treatment
- Median (range) duration of therapy was 3.7 (0.2–17.1) months; reasons for discontinuation were disease progression (n = 21), adverse events (AEs; n = 13), patient/physician decision (n = 8), loss to follow-up (n = 1), and noncompliance (n = 1)
- Patient demographics and disease characteristics are presented in Table 2

Table 2. Patient Demographics and Disease Characteristics at Baseline

Characteristics	INCB050465 Monotherapy (N = 63)
Age, median (range), years	66.0 (30–89)
>65 years, n (%)	32 (51)
Men, n (%)	36 (57)
Disease type, n (%)	
NHL	47 (75)
DLBCL	17 (27)
FL	13 (21)
MZL ¹	9 (14)
MCL	8 (13)
CLL	6 (10)
HL ²	10 (16)
Number of prior systemic therapy regimens, median (range)	3 (1–6)
Prior HSCT, n (%)	18 (29)

*Includes extranodal MZL of MALT type (n = 2), nodal MZL (n = 5), and splenic MZL (n = 2).

¹Includes classic HL (n = 9) and nodular lymphocytic-predominant HL (n = 1). CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplant; MALT, mucosa-associated lymphatic tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

Pharmacokinetics

- INCB050465 demonstrated approximately linear PK between doses of 5 and 45 mg QD at steady state
- Based on a PK simulation, serum INCB050465 levels resulting from 20 mg QW dosing is predicted to exceed the IC₉₀ for target inhibition for ~36 hours

Exposure and Safety

- No patients experienced dose-limiting toxicities
- As of September 2, 2016, 9 (29%) of 31 patients with NHL discontinued treatment because of TEAEs⁹
- INCB050465 dose modifications due to TEAEs are listed in Table 3
- To improve long-term tolerability, starting in November 2016, new patients were administered INCB050465 20 mg QD for 9 weeks followed by 20 mg QW; existing patients were switched to QW dosing if they had been on study treatment >9 weeks
- Of 12 patients with NHL receiving QW dosing, 2 reported grade 3/4 events (grade 3 neutropenia; grade 3 thrombocytopenia); none discontinued treatment because of a TEAE
- Across all dose levels, 56 (89%) patients reported all-grade TEAEs and 32 (51%) patients reported grade ≥3 TEAEs
 - Nonhematologic TEAEs occurring in ≥20% of patients: nausea (38%), diarrhea/colitis (35%), fatigue (29%), vomiting (27%), cough (24%), rash (22%), and dizziness (21%)
 - New or worsening grade ≥3 neutropenia, thrombocytopenia, or anemia occurred in 22%, 10%, and 5% of patients, respectively
- Among TEAEs of special interest (Table 4)
 - Fifteen (24%) patients experienced grade ≥2 diarrhea/colitis, with a median time to onset of 4.6 (range, 0.4–14.8) months
 - Six patients (10%) experienced grade ≥2 rash, with a median time to onset of 2.8 (range, 2.5–9.3) months
 - No instances of *Pneumocystis jirovecii* pneumonia were reported
 - All events of elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were grade 1, except 1 event each of grade 3 AST and grade 2 ALT elevation, both occurring after the last dose of INCB050465
- Across all dose levels, serious TEAEs (SAEs) were experienced by 23 (37%) patients (Table 4)
 - One death occurred due to an SAE (respiratory failure in a 68-year-old female), which was deemed not related to therapy

Table 3. Dose Modifications Due to TEAEs*

	Any Grade, n (%)
Dose interruption (>2 patients)	26 (41)
Diarrhea/Colitis [†]	10 (16)
Neutropenia	5 (8)
Rash [‡]	1 (2)
Dose reduction	2 (3)
Diarrhea/Colitis [†]	1 (2)
Rash [‡]	1 (2)
Discontinuation (>1 patient) [§]	12 (19)
Diarrhea/Colitis [†]	3 (5)
Rash [‡]	3 (5)

*N = 63 for all doses combined.

[†]Included preferred terms of diarrhea, colitis, enterocolitis, gastrointestinal inflammation.[‡]Included preferred terms of dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, exfoliative rash, rash generalized.[§]Other TEAEs leading to discontinuation in 1 patient: colitis, cytomegalovirus colitis, pneumonitis, neutropenia, hypertriglyceridemia, and pneumonia. One patient discontinued treatment due to a TEAE, but the corresponding TEAE data were not in the database at time of data extraction.

EO3, electrocardiogram; SOC, system organ class; TEAE, treatment-emergent adverse event.

Table 4. TEAEs of Special Interest and Serious TEAEs*

	Any Grade, n (%)	Grade ≥3, n (%)
TEAEs of special interest		
Neutropenia [†]	28 (44)	14 (22)
Diarrhea/Colitis [‡]	22 (35)	6 (10)
AST increased [§]	15 (24)	1 (2)
ALT increased [¶]	15 (24)	0
Rash [‡]	14 (22)	2 (3)
Hypotension	9 (14)	2 (3)
Pneumonitis	6 (10)	3 (5)
Pneumonitis	1 (2)	1 (2)
Serious TEAEs in >2 patients		
Diarrhea/Colitis [‡]	6 (10)	5 (8)
Hypotension	3 (5)	2 (3)

*N = 63 for all doses combined.

[†]Included reported laboratory values.[‡]Included preferred terms of diarrhea, colitis, enterocolitis, gastrointestinal inflammation.[§]Included preferred terms of dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, exfoliative rash, rash generalized.[¶]ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Efficacy

- Responses occurred at all doses (Table 5), except 5 mg QD
- >90% of responses among patients with NHL were observed at first assessment (Figure 2)
- Representative positron emission tomography (PET) images of a patient with mantle cell lymphoma (MCL) achieving a complete response (CR) at week 9 are shown in Figure 3
- Of 35 patients with NHL that had valid baseline and post-baseline target lesion measurements, 20 achieved ≥50% decrease from baseline in target lesion size (Figure 4)
- Sixteen patients with NHL were ongoing (Figure 5); the longest duration of response was >60 weeks in 2 patients with DLBCL (CR) and FL (partial response [PR]), both ongoing as of the cutoff date

Table 5. Best Overall Response Among Evaluable Patients*

Patients	N	ORR, n (%)	CR/CMR, n	PR/PMR, n	SD, n	PD/PMD, n
NHL	42	25 (60)	12	13	7	8
DLBCL	16	5 (31)	3	2	4	6
FL	11	8 (73)	2	6	1	1
MZL ¹	9	7 (78)	3	4	1	1
MCL ²	6	5 (83)	4	1	1	0
CLL ¹	6	2 (33)	0	2	2	1
HL ³	9	1 (11)	0	1	3	4

*Assessed by Lugano Classification or CLL IWGCLL Criteria by Disease Subtype by CT or PET. Evaluable patients include all enrolled patients who have had ≥1 follow-up disease assessment or have discontinued treatment.

¹Includes extranodal MZL of MALT type (n = 2), nodal MZL (n = 5), and splenic MZL (n = 2).²3 patients with MCL and 3 patients with CLL had received ibrutinib; of whom a best overall response of CR was achieved by 1 patient with MCL and a best response of PR was achieved by 1 MCL and 1 CLL patient in this study.³Includes classic HL (n = 8) and nodular lymphocytic-predominant HL (n = 1).

CLL, chronic lymphocytic leukemia; CMR, complete metabolic response; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; CLL IWGCLL, International Working Group for CLL; MALT, mucosa-associated lymphatic tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; SD, stable disease.

Figure 2. Time to Response in Patients With NHL

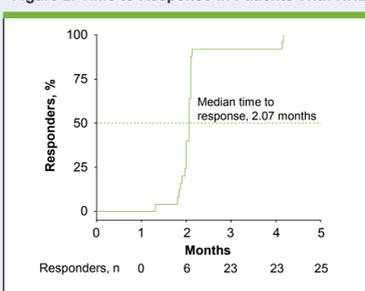
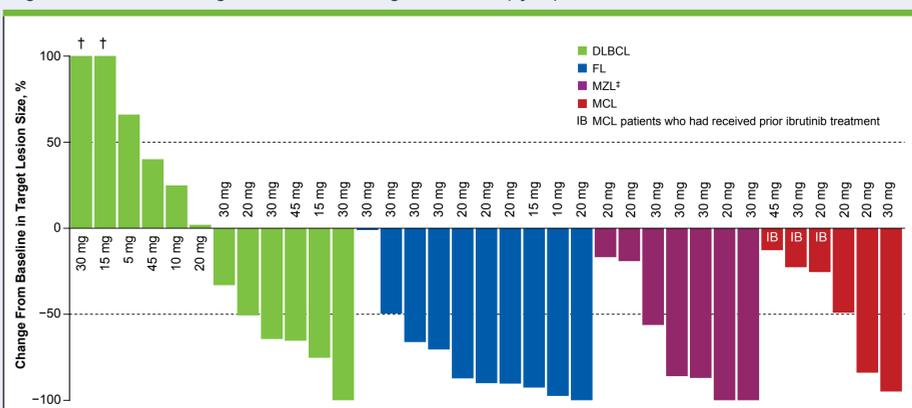


Figure 3. PET Images of a Patient* Who Achieved a Complete Response



*Patient was <65 years of age, with mantle cell lymphoma with no bone marrow involvement (target lesion, 98 mm × 58 mm) and had received 1 prior treatment (R-HyperCVAD). Treated with INCB050465 30 mg once daily; achieved complete response at week 9.

Figure 4. Best Percent Change From Baseline in Target Lesion Size (by CT) in Individual Evaluable* Patients With NHL

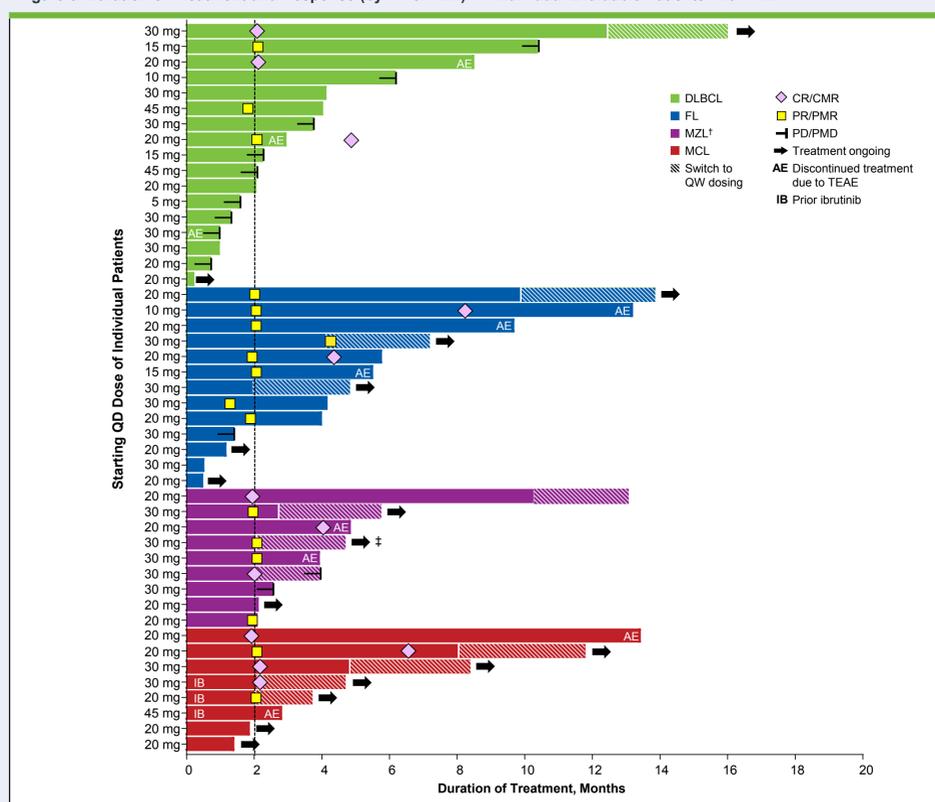


*Data for 4 patients with DLBCL, 1 with FL, and 2 with MZL are not shown due to non-measurable disease at baseline or no valid post-baseline target lesion measurements.

¹Best percentage change from baseline in target lesion size >100%.²Includes extranodal MZL of MALT type (n = 1), nodal MZL (n = 4), and splenic MZL (n = 2); spleen size was used as the primary parameter to assess response in splenic MZL.³Included preferred terms of dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, exfoliative rash, rash generalized.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Figure 5. Duration of Treatment and Response (by CT or PET)* in Individual Evaluable Patients With NHL



*Response assessments occurred every 9 weeks.

¹Includes extranodal MZL of MALT type (n = 2), nodal MZL (n = 5), and splenic MZL (n = 2).²This patient had an assessment of PD by PET but not by overall assessment and continued on treatment.

AE, adverse event; CMR, complete metabolic response; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MALT, mucosa-associated lymphatic tissue; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PD, progressive disease; PET, positron emission tomography; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; QD, once daily, QW, once weekly.

Conclusions

- INCB050465 is a potent, selective next-generation PI3K δ inhibitor that has demonstrated dose-proportional PK and effects a high rate of rapid and deep objective responses in patients with NHL, with notable responses in patients with FL, MCL, and MZL
- INCB050465 monotherapy demonstrated manageable toxicities with no clinically meaningful transaminase elevations, and no reported cases of *Pneumocystis jirovecii* pneumonia. Other adverse events, including diarrhea/colitis, were consistent with PI3K δ inhibition in B-cell malignancies
- Novel dosing regimens, long-term safety, and disease-specific cohorts are being evaluated

Disclosures

Ramchandren: None. Phillips: Pharmacia—Consultancy. Wertheim: None. Gutierrez: Bayer Health Care Pharmaceuticals, Inc.—Other (Traveling and Lodging—Food and Beverage); E.R. Squibb & Sons, LLC (Bristol Myers Squibb)—Consultancy, Other (Travel and Lodging); Inocyte Corporation—Consultancy, Merck Sharp & Dohme Corporation—Consultancy, Other (Travel and Lodging); Pfizer Inc.—Consultancy, Pharmacia—Other (Food and Beverage). Edenfield: Edenvest. Greenville Health System Cancer Institute—Employment; Novartis—Speakers Bureau; Bristol Myers Squibb—Speakers Bureau; Celgene—Speakers Bureau; Gilead Sciences—Speakers Bureau; Millenium—Speakers Bureau; Teva—Speakers Bureau; Astellas—Research Funding; Medivation—Research Funding; Celastor—Research Funding; Inocyte—Research Funding; Pfizer—Research Funding; Teva—Research Funding; Unum Therapeutics—Research Funding; Caimi: Abbvie—Stock; Inocyte—Stock; Seattle Genetics—Stock; Call: None. Persky: Cardinal Health—Consultancy; Genentech—Consultancy; MorphoSys—Consultancy; Spectrum Pharmaceuticals—Consultancy; Verastem—Consultancy; Gilead Sciences—Speakers Bureau; Merck (Inst)—Research Funding; DeMarini: Inocyte—Employee/stock; Zhou: Inocyte—Employee/stock; Yeleswaram: Inocyte—Employee/stock; Forero-Torres: Genentech—Research Funding; Seattle Genetics—Research Funding.

Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study. This study was sponsored by Inocyte Corporation (Wilmington, DE). Medical writing assistance was provided by Simon J. Slater, PhD, of Evidence Scientific Solutions (Philadelphia, PA), and funded by Inocyte Corporation.

References

- Gururajan M, et al. *J Immunol*. 2006;176:5715–5719.
- Benschop RJ, Cambler JC. *Curr Opin Immunol*. 1999;11:143–151.
- Kang S, et al. *Proc Natl Acad Sci USA*. 2005;102:802–807.
- Shin N, et al. American Association for Cancer Research Annual Meeting, April 18–22, 2015; Philadelphia, PA, USA. Abstract 2671.
- Phillips T, et al. 58th American Society of Hematology Annual Meeting, December 3–6, 2016; San Diego, CA, USA. Abstract 4195.
- Cheson BD, et al. *J Clin Oncol*. 2014;32:3059–3068.
- Hallek M, et al. *Blood*. 2008;111:5446–5456.
- Cheson BD, et al. *J Clin Oncol*. 2012;30:2820–2822.

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