

## Introduction

- Constitutive signaling through the B-cell receptor is critical for the survival and proliferation of human B-cell lymphomas<sup>1</sup> and leads to downstream activation of phosphatidylinositol 3-kinases (PI3Ks), including PI3K $\delta$ <sup>2</sup>
  - Aberrant activation of PI3K $\delta$  is associated with proliferation and survival of malignant B cells<sup>3</sup>
- PI3K $\delta$  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 $\delta$  pathway may affect the depth and duration of response
- INCB050465 is a novel, potent, and highly specific inhibitor of PI3K $\delta$  (**Table 1**),<sup>4</sup> with a differentiated profile for potency (whole blood IC<sub>50</sub> = 10 nM, IC<sub>90</sub> = 77 nM) and dose (<50 mg total daily dose)

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

	INCB050465	Idelalisib <sup>5</sup>	TGR1202 <sup>6</sup>
PI3K $\delta$ enzyme potency (IC <sub>50</sub> , nM)	1	2.5	22
Fold selectivity			
PI3K $\alpha$	19,000	>300	>10,000
PI3K $\beta$	>20,000	>50	>50
PI3K $\gamma$	>20,000	>35	>48
Total daily dose, mg	20–30 <sup>4</sup>	300	1200

\*Expansion doses.

- INCB050465 potently inhibits signaling and proliferation of malignant B cells in vitro<sup>4</sup>
- Preclinical studies indicate a lack of hepatotoxicity at exposures exceeding 10-fold IC<sub>90</sub> 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)<sup>5</sup>; emerging data from this trial are reported here

## Methods

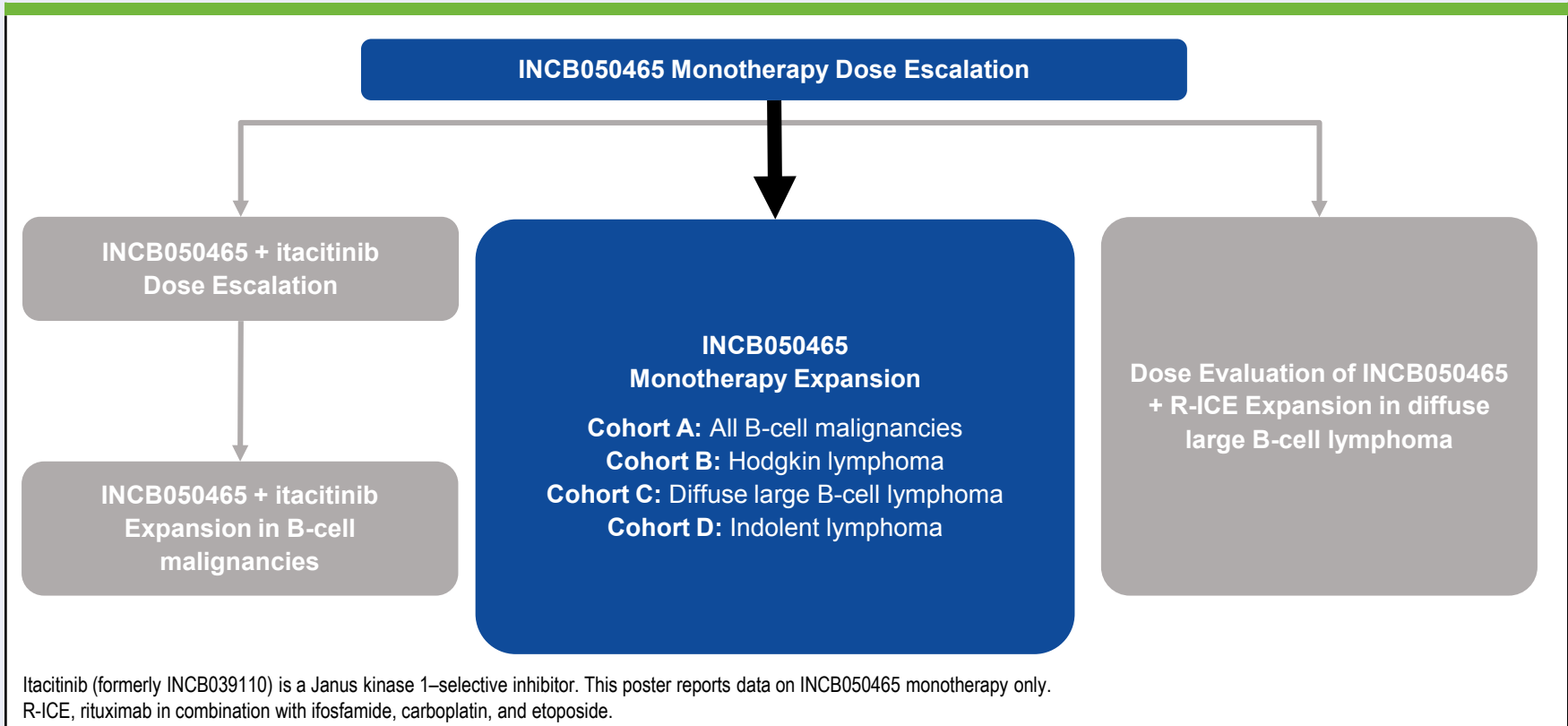
### Patients

- ≥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



### 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),<sup>6</sup> 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<sup>7,8</sup>
- 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)

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## 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 <sup>†</sup>	9 (14)
MCL	8 (13)
CLL	6 (10)
HL <sup>‡</sup>	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).

<sup>†</sup> Includes classic HL (n = 8) 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 IC<sub>90</sub> 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 TEAEs<sup>9</sup>
- 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 <sup>†</sup>	10 (16)
Neutropenia	5 (8)
Rash <sup>‡</sup>	1 (2)
Dose reduction	2 (3)
Diarrhea/Colitis <sup>†</sup>	1 (2)
Rash <sup>‡</sup>	1 (2)
Discontinuation (>1 patient) <sup>§</sup>	12 (19)
Diarrhea/Colitis <sup>†</sup>	3 (5)
Rash <sup>‡</sup>	3 (5)

\* N = 63 for all doses combined.

<sup>†</sup> Included preferred terms of diarrhea, colitis, enterocolitis, gastrointestinal inflammation.

<sup>‡</sup> Included preferred terms of dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, exfoliative rash, rash generalized.

<sup>§</sup> Other TEAEs leading to discontinuation in 1 patient: colitis, cytomegalovirus colitis, pneumonitis, neutropenia, hypercalcemia, 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.

ECG, 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 <sup>†</sup>	28 (44)	14 (22)
Diarrhea/Colitis <sup>‡</sup>	22 (35)	6 (10)
AST increased <sup>§</sup>	15 (24)	1 (2)
ALT increased <sup>¶</sup>	15 (24)	0
Rash <sup>‡</sup>	14 (22)	2 (3)
Hypotension	9 (14)	2 (3)
Pneumonia	6 (10)	3 (5)
Pneumonitis	1 (2)	1 (2)
Serious TEAEs in >2 patients		
Diarrhea/Colitis <sup>†</sup>	6 (10)	5 (8)
Hypotension	3 (5)	2 (3)

\* N = 63 for all doses combined.

<sup>†</sup> Based on reported laboratory values.

<sup>‡</sup> Included preferred terms of diarrhea, colitis, enterocolitis, gastrointestinal inflammation.

<sup>§</sup> Included preferred terms of dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculopapular, rash pruritic, exfoliative rash, rash generalized.

<sup>¶</sup> 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 <sup>†</sup>	9	7 (78)	3	4	1	1
MCL <sup>‡</sup>	6	5 (83)	4	1	1	0
CLL <sup>‡</sup>	6	2 (33)	0	2	2	1
HL <sup>§</sup>	9	1 (11)	0	1	3	4

\* Assessed by Lugano Classification or CLL IWG 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.

<sup>†</sup> Includes extranodal MZL of MALT type (n = 2), nodal MZL (n = 5), and splenic MZL (n = 2).

<sup>‡</sup> 3 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.

<sup>§</sup> Includes 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 IWG, 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

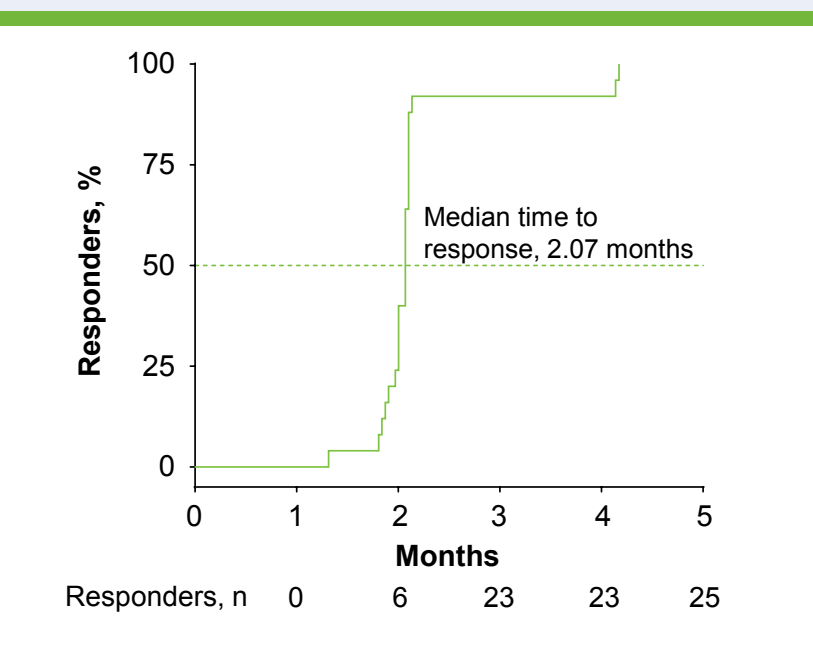
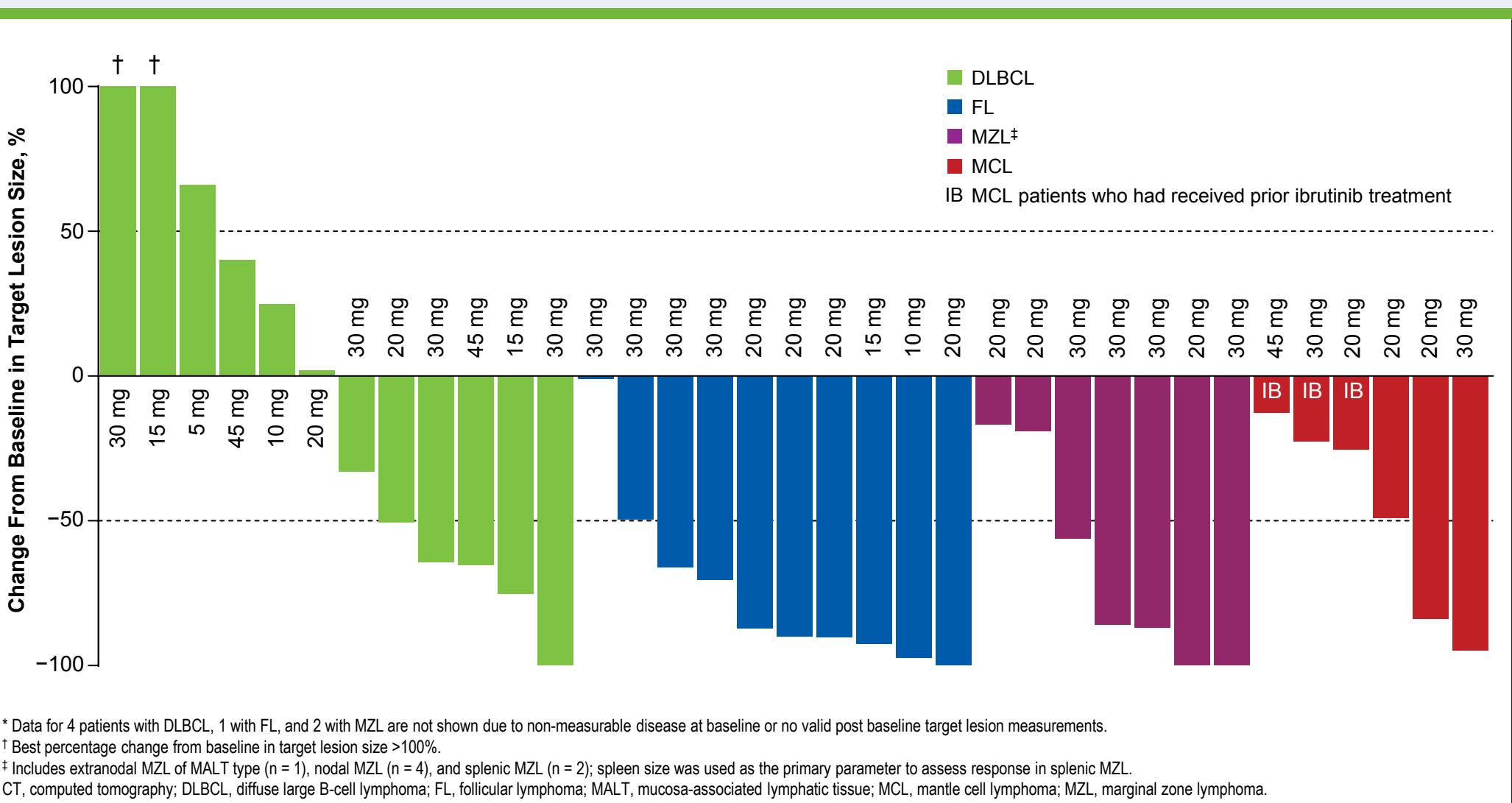


Figure 3. PET Images of a Patient\* Who Achieved a Complete Response



\* 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



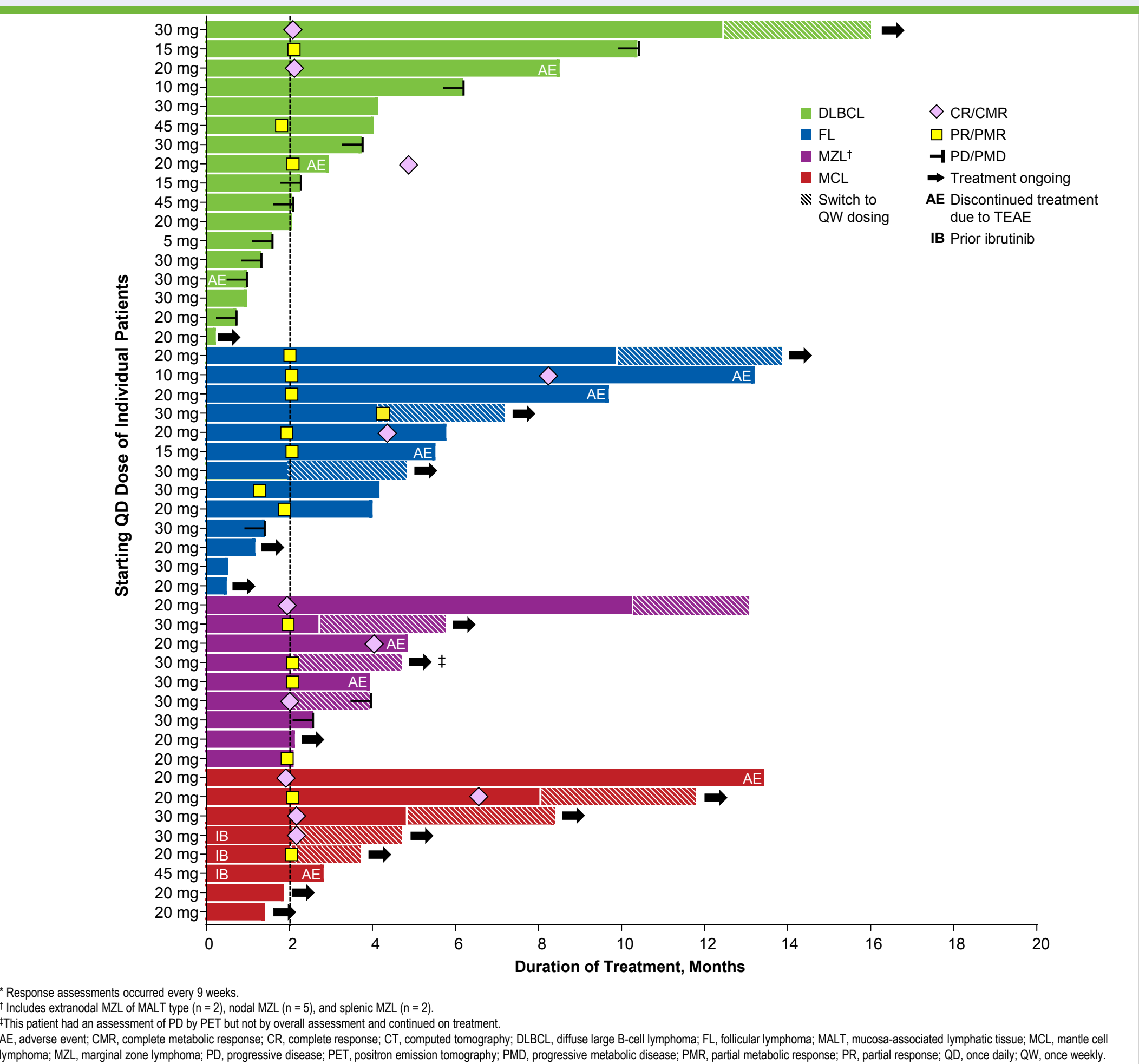
\* Data for 4 patients with DLBCL, 1 with FL, and 2 with MZL are not shown due to non-measurable disease at baseline or no valid post baseline target lesion measurements.

<sup>†</sup> Best percentage change from baseline in target lesion size >100%.

<sup>‡</sup> Includes 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.

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.

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



\* Response assessments occurred every 9 weeks.

<sup>†</sup> Includes extranodal MZL of MALT type (n = 2), nodal MZL (n = 5), and splenic MZL (n = 2).

<sup>‡</sup> This 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 $\delta$  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 $\delta$  inhibition in B-cell malignancies
- Novel dosing regimens, long-term safety, and disease-specific cohorts are being evaluated

### Disclosures

**Ramchandren:** None. **Phillips:** Pharmaceuticals – 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); Incyte Corporation – Consultancy; Merck Sharp & Dohme Corporation – Consultancy; Other (Travel and Lodging); Pfizer Inc. – Consultancy; Pharmaceuticals LLC, An AbbVie Company – Other (Food and Beverage). **Edenfield:** Greenville Health System Cancer Institute – Employment; Novartis – Speakers Bureau; Akard: Novartis – Consultancy; Speakers Bureau; Bristol Myers Squibb – Speakers Bureau; Celgene – Speakers Bureau; Gilead Sciences – Speakers Bureau; Millennium – Speakers Bureau; Teva – Speakers Bureau; Astellas – Research Funding; Medivation – Research Funding; Cellcrux – Research Funding; Incyte – Research Funding; Pfizer – Research Funding; Teva – Research Funding; Unum Therapeutics – Research Funding; Caimi: Abbvie – Stock; Incyte – 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: Incyte – Employment/Stocks. **Zhou:** Incyte – Employment/Stocks. **Yeleswaram:** Incyte – Employment/Stocks. **Forero-Torres:** Genentech – Research Funding; Seattle Genetics – Research Funding.

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