

Preliminary Results From an Ongoing Phase 1/2 Study of INCB053914, a Pan-Proviral Integration Sites for Moloney Virus (PIM) Kinase Inhibitor, in Patients With Advanced Hematologic Malignancies

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Introduction

- The PIM serine/threonine kinases (PIM1, PIM2, and PIM3) integrate multiple signaling networks and phosphorylate downstream substrates important for cell survival and proliferation¹
- PIM kinase isozymes are differentially expressed across cancers and are elevated in hematologic malignancies including acute myeloid leukemia (AML) and multiple myeloma²
- PIM kinase overexpression is associated with poor prognosis in various hematologic malignancies³ and resistance to chemotherapy⁴
- In preclinical studies, INCB053914, a small molecule pan-PIM inhibitor, inhibited PIM kinase-mediated signaling, cell proliferation, and tumor growth in multiple hematologic tumor models^{5,6}

Objectives

- This 4-part, phase 1/2 study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of INCB053914 in patients with advanced malignancies (NCT02587598)
 - Preliminary results from Part 1 (monotherapy dose escalation), including safety, PK/PD, and efficacy are reported

Methods

Monotherapy Study Design and Treatment

- This is an ongoing phase 1/2, open-label, dose-escalation study of INCB053914 in patients with advanced malignancies (Figure 1)
- Part 1: Monotherapy dose escalation
 - 3 + 3 design in 2 treatment groups (TGs) to determine the maximum tolerated dose over a 21-day cycle
 - Dose escalation for TGA and TGB proceeded independently
- Part 2: Monotherapy dose expansion
 - INCB053914 recommended phase 2 dose (RP2D) evaluated in specific disease indications in which PIM kinases are particularly relevant (data from Part 2 are not presented in this poster)
- Key eligibility criteria are presented in Table 1

Assessments

- Safety and tolerability of INCB053914 monotherapy
 - Treatment-emergent adverse events were assessed by the investigator using Common Terminology Criteria for Adverse Events v4.03

Figure 1. Monotherapy Study Design

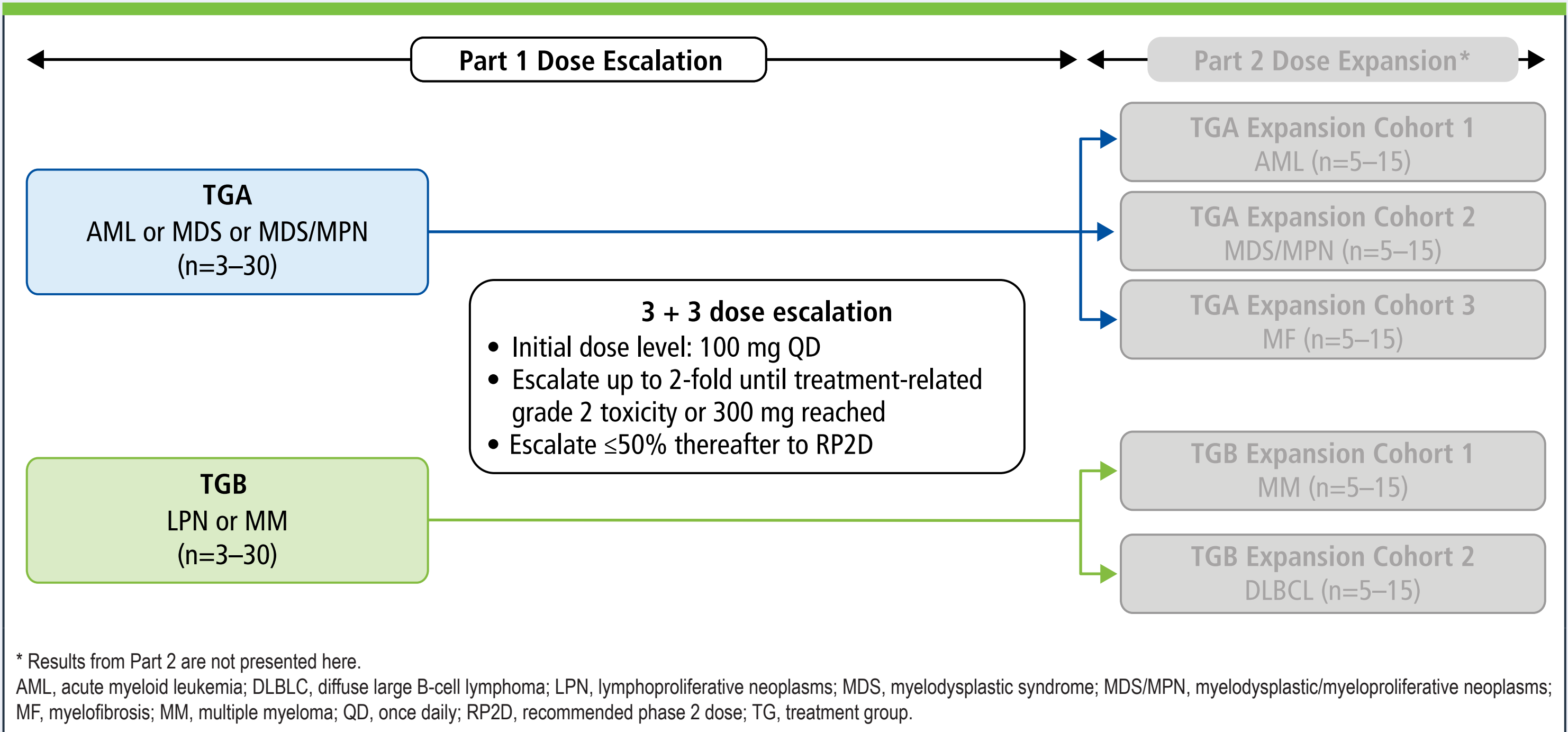


Table 1. Part 1 Key Eligibility Criteria

Key Inclusion Criteria	
<ul style="list-style-type: none">≥18 years of ageTGA, patients with histologically confirmed diagnosis of acute leukemia, high-risk MDS, or MDS/MPN (including aCML, CMML, MDS/MPN-U, and RARS-T); TGB, patients with MM, lymphoma, and other lymphoproliferative neoplasmsMust be unresponsive to currently available therapy with no further standard-of-care therapy available	<ul style="list-style-type: none">Not a candidate for curative treatmentWillingness to undergo a pretreatment bone marrow biopsy and/or aspirate, or archival sample obtained since completion of most recent therapyEastern Cooperative Oncology Group performance status 0 or 1Life expectancy >12 weeks
Key Exclusion Criteria	
<ul style="list-style-type: none">Inadequate hematologic (lymphoma, lymphoproliferative neoplasms, multiple myeloma only), liver, or renal function at screeningInadequate washout of previous anticancer medications or investigational drugs before the first administration of the study drugPrior treatment with autologous hematopoietic stem cell transplant within 3 months, allogeneic stem cell transplant within 6 months before treatment, active GVHD, receipt of immunosuppressive therapy within 2 weeks of cycle 1/day 1 (unless approved by the medical monitor), or radiotherapy within 2 weeks before treatment initiation	<ul style="list-style-type: none">Unresolved toxicity grade ≥2 from previous anticancer therapy except for stable chronic toxicities (grade ≤2) not expected to resolveType 1 diabetes or uncontrolled type 2 diabetes; hemoglobin A1c >8.0%; any history of disease involving the central nervous system; current diagnosis of any chronic or acute respiratory condition or ongoing sequelae; history of clinically significant or uncontrolled cardiac diseaseExcessive alcohol (>2 drinks per day) or chronic acetaminophen use (>2 g per day)Prior treatment with a PIM inhibitor

aCML, atypical chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MDS/MPN-U, myelodysplastic/myeloproliferative neoplasms (unclassifiable); MF, myelofibrosis; MM, multiple myeloma; RARS-T, refractory anemia with ring sideroblasts and thrombocytosis; TG, treatment group.

- PK and PD
 - Blood samples were collected at protocol-specified time points and assessed for PK (maximum observed plasma concentration, time to maximum plasma concentration, minimum observed plasma concentration during the dosing interval, area under the single-dose plasma concentration-time curve, oral dose clearance)
 - Whole blood PD samples were collected in conjunction with PK samples to assess the PD profile of INCB053914 defined by phosphorylation of Bcl-2-associated death promoter (BAD) protein
- Efficacy
 - Objective responses were assessed using disease response criteria applicable for each malignancy under study according to protocol-defined schedule

Results

Patients

- As of data cut-off (July 16, 2017), 42 patients (TGA, n=31; TGB, n=11) have received INCB053914 monotherapy (Figure 2)
- Patient demographics and baseline characteristics are presented in Table 2
- Median (range) duration of treatment was 51 (1–211) days for TGA and 23 (10–63) days for TGB

Figure 2. Patient Disposition

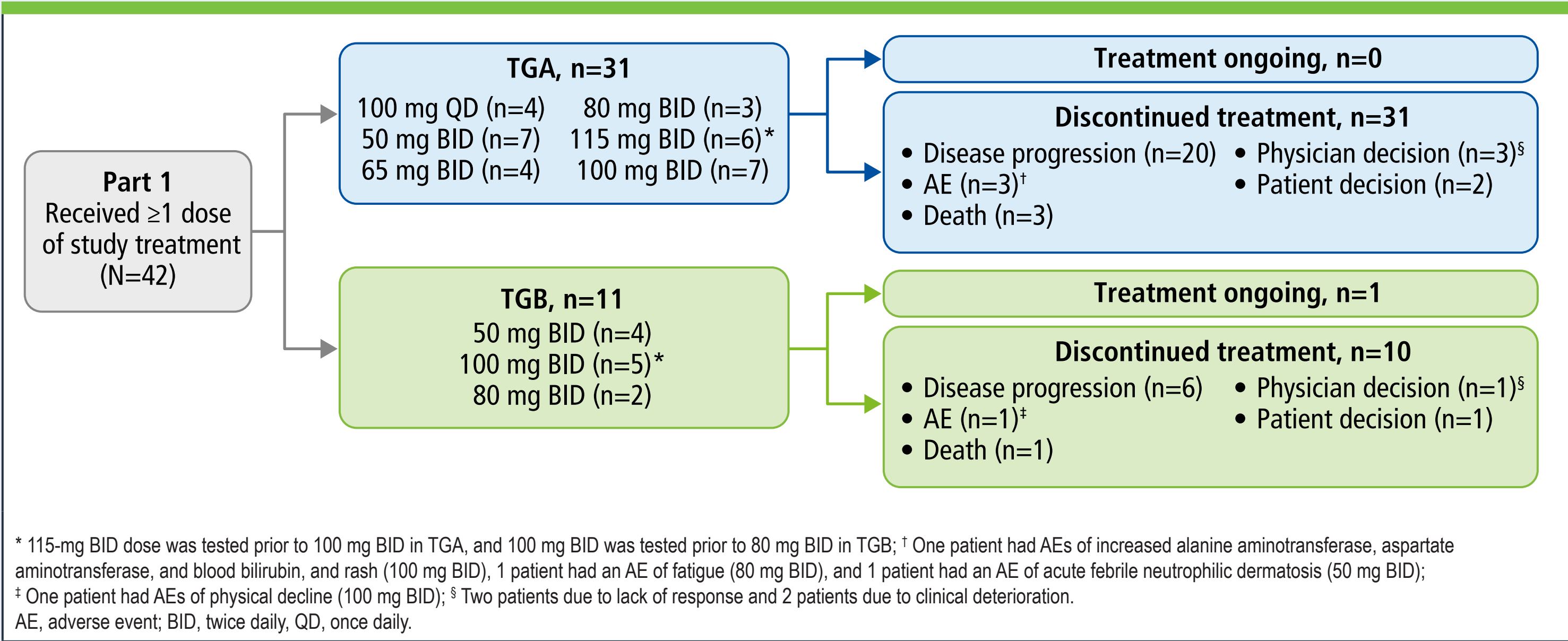


Table 2. Baseline and Demographic Characteristics

Characteristic	Part 1 (N=42)	
	TGA (n=31)	TGB (n=11)
Median (range) age, y	70 (47–89)	72 (28–84)
≥65 y, n (%)	23 (74.2)	8 (72.7)
Women, n (%)	16 (51.6)	3 (27.3)
Race, n (%)		
White/Caucasian	25 (80.6)	10 (90.9)
Black/African American	6 (19.4)	1 (9.1)
Tumor types, n (%)		
AML	22 (71.0)	—
MDS	6 (19.4)	—
Acute leukemia of ambiguous lineage	1 (3.2)	—
MDS/MPN	1 (3.2)	—
MF*	1 (3.2)	—
Lymphoma	—	6 (54.5)
MM	—	5 (45.5)

* Patient with MF was initially enrolled in TGC, which was subsequently absorbed into TGA in accordance with protocol amendment 3.
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; MF, myelofibrosis; MM, multiple myeloma; TG, treatment group.

Safety

- Patients in TGA received INCB053914 monotherapy at a dose of 100 mg once daily (QD) or at doses ranging from 50 to 115 mg twice daily (BID); patients in TGB received INCB053914 monotherapy at 50, 80, or 100 mg BID
 - In TGA, the maximum tolerated dose was 100 mg BID, while 80 mg BID was selected as the RP2D owing to an overall more favorable safety profile compared with 100 mg BID
 - In TGB, 100 mg BID was not tolerated; maximum tolerated dose and RP2D still being evaluated at 80 mg BID
 - Six patients had dose-limiting toxicities (Table 3)

Table 3. Dose-Limiting Toxicities

Patient	Treatment Cohort	Dose-Limiting Toxicity	Grade
1	TGA 115 mg BID	ALT increased AST increased	4 3
2	TGA 115 mg BID	Maculopapular rash	3
3	TGA 100 mg BID	ALT increased AST increased	3 3
4	TGB 100 mg BID	ALT increased AST increased	4 3
5	TGB 100 mg BID	ALT increased AST increased	3 3
6	TGB 100 mg BID	Syncope	3

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; TG, treatment group.

- Thirty-three patients (78.6%) had a treatment-related AEs (TRAEs) (Table 4)
- Twenty-two patients (52.4%) had grade 3 or 4 TRAEs (Table 4)
 - Most common were anemia (new or anemia considered by the investigator to be possibly drug related due to worsening after initiating study treatment when compared with patient's history) (n=6, 14.3%), thrombocytopenia (n=4, 9.5%), elevated alanine aminotransferase (ALT) (n=4, 9.5%), and elevated aspartate aminotransferase (AST) (n=4, 9.5%)
- Seven patients (16.7%) experienced 14 serious TRAEs
 - Elevated AST (n=4, 9.5%), elevated ALT (n=4, 9.5%), and maculopapular rash (n=3, 7.1%) were most common and often reversible with dose interruption or reduction
- Five patients (11.9%) had fatal AEs, none considered to be related to INCB053914

Table 4. Treatment-Related Adverse Events

TRAEs,* n (%)	TGA and TGB (N=42)	
	Any Grade	Grade 3 or 4
Any TRAE	33 (78.6)	22 (52.4)
Elevated ALT	14 (33.3)	4 (9.5)
Elevated AST	14 (33.3)	4 (9.5)
Fatigue	12 (28.6)	3 (7.1)
Decreased appetite	10 (23.8)	0
Nausea	10 (23.8)	0
Diarrhea	8 (19.0)	0
Anemia	7 (16.7)	6 (14.3)
Rash	5 (11.9)	3 (7.1)
Alkaline phosphatase elevated	4 (9.5)	0
Thrombocytopenia	4 (9.5)	4 (9.5)
Dehydration	3 (7.1)	1 (2.4)
Dizziness	3 (7.1)	0
Vomiting	3 (7.1)	0
Weight decreased	3 (7.1)	0
Febrile neutropenia	2 (4.8)	2 (4.8)

* Any grade TRAEs occurring in ≥3 patients and grade 3 or 4 TRAEs occurring in ≥2 patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; TG, treatment group; TRAE, treatment-related adverse event.

PK and PD of INCB053914

- Preliminary PK results demonstrate that exposures appear to increase proportionally with dose
- Geometric mean half-life was ~11 hours (%CV, 53%), and median time to maximal concentrations was 1 hour (range, 0.5–4) across doses and TGs (Figure 3)
- Steady-state trough levels of INCB053914 at RP2D (80 mg BID) inhibited BAD phosphorylation by 76% (range, 63–100%) compared with baseline (Figure 4)
 - Exceeds levels previously shown to be required for maximal efficacy in preclinical studies^{5,6}

Figure 3. INCB053914 Plasma Concentrations at Steady State on Day 8

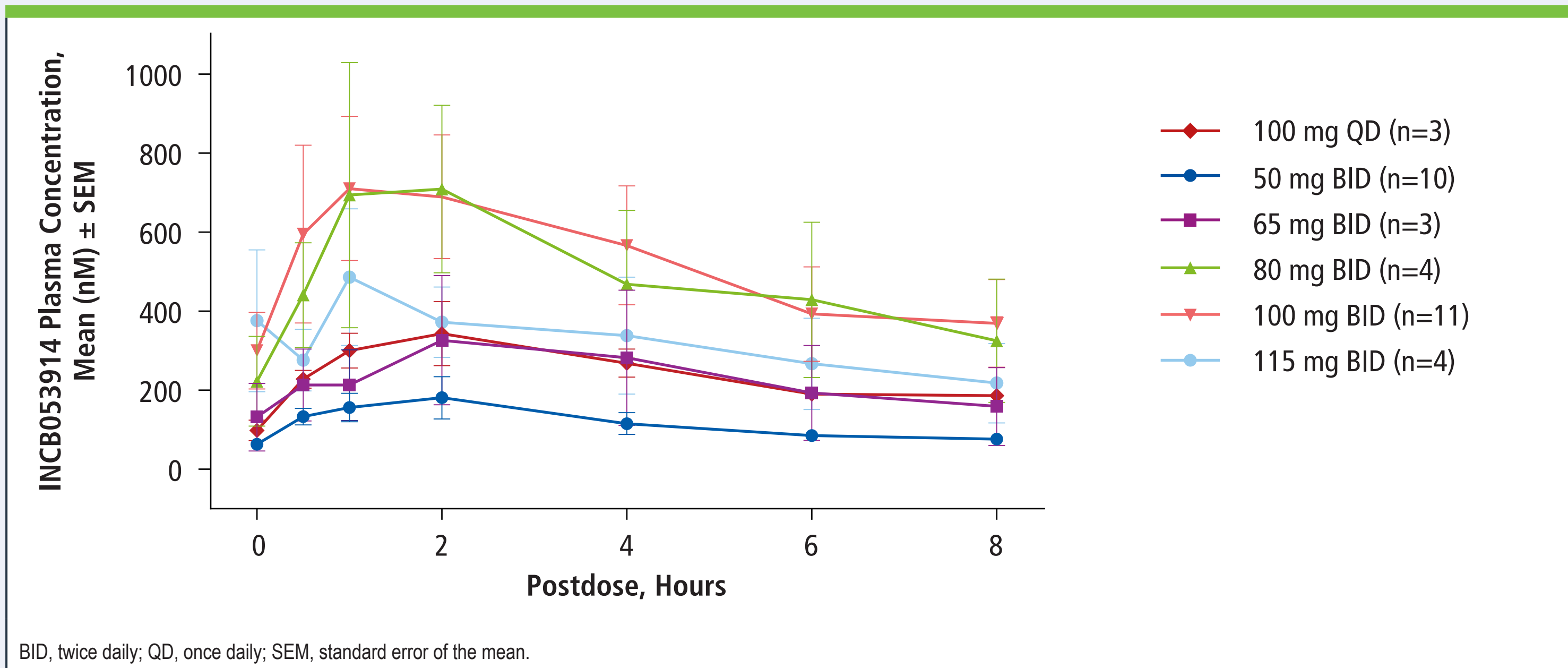
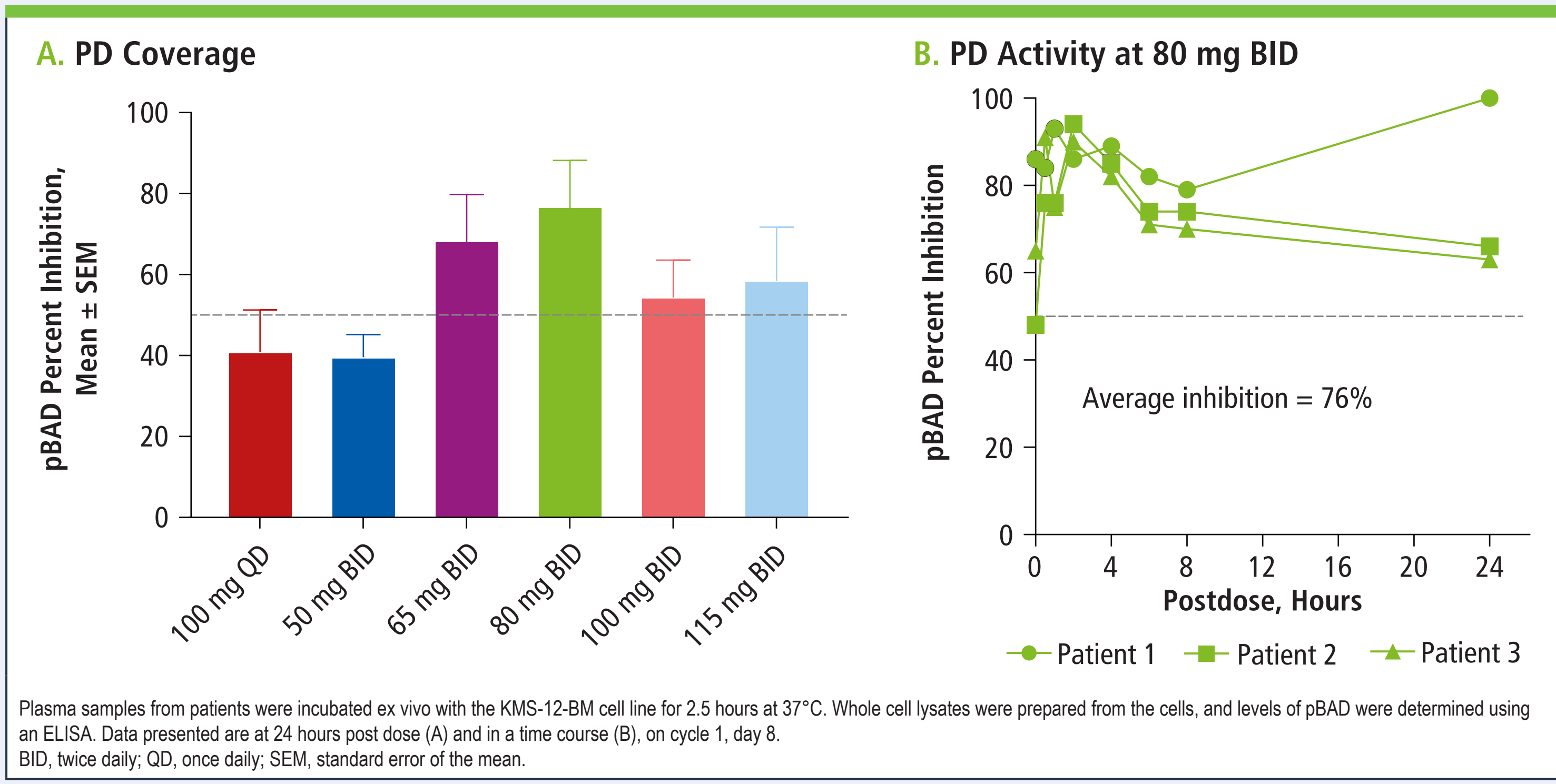


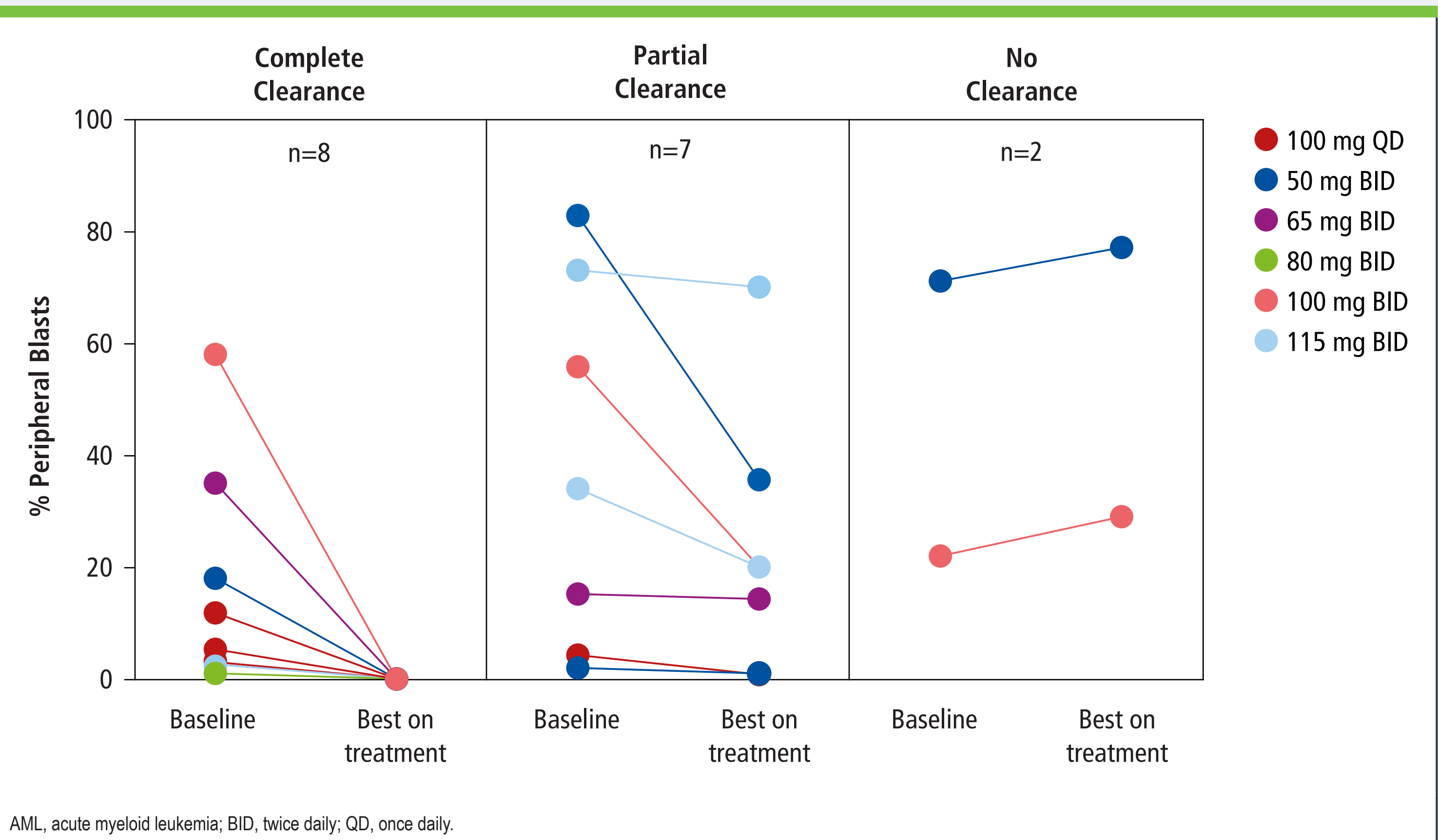
Figure 4. INCB053914 Inhibition of pBAD



Efficacy

- A total of 23 patients with AML (n=22) and acute leukemia with ambiguous lineage (n=1) have been treated with INCB053914 monotherapy in this study
 - Median (range) duration of treatment 41 (1–148) days
- Seventeen patients with AML/leukemia had detectable peripheral blasts at study entry, and their percentages of peripheral blasts at baseline (pre-dose) and NADIR (post-dose) are presented in Figure 5
 - Eight patients cleared their peripheral blasts during treatment with INCB053914 (Figure 5); however, the durations were short, at less than 3 weeks for 6 of the 8 patients (data not shown)
 - Bone marrow blast reductions were seen in several patients (data not shown); however, bone marrow blast data were limited owing to lack of or short duration of peripheral blast response
- No objective responses according to the International Working Group criteria were observed with INCB053914 monotherapy

Figure 5. Best Change in Percent Peripheral Blast From Baseline in Patients With AML/Leukemia



Conclusions

- In Part 1 of this phase 1/2 study, a RP2D of 80 mg BID was identified in patients with acute leukemia and related malignancies (TGA)
- INCB053914 monotherapy demonstrated preliminary safety
 - Elevated ALT/AST were the most common dose-limiting toxicities and TRAEs, but were generally reversible with drug interruption or dose reduction
- PK demonstrated that INCB053914 exposures generally increased with dose
- PD coverage and activity at 65 mg BID and above exceeded levels previously shown to be required for maximal efficacy in preclinical studies
 - The lowest BID dose tested, 50 mg BID, was also close to the IC₅₀ for target inhibition
- Preliminary antitumor activity was demonstrated in some AML patients with complete peripheral blast clearance
- Substantial interconnectivity exists between signaling networks mediated by PIM kinases and those targeted by other anticancer agents
 - Preclinical studies have shown additive or synergistic antitumor effects of INCB053914 combined with other antitumor agents⁸
- Based on preclinical rationale and experimental data, and the Part 1 results presented here, Part 2 of this study is evaluating INCB053914 in combination with other targeted therapies or standard-of-care agents

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Disclosures

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