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## Introduction

- The bromodomain and extraterminal (BET) proteins (ie, BRD2, BRD3, BRD4, BRDT) are epigenetic readers of acetylated histones that regulate gene transcription<sup>1</sup>
- BET protein inhibitors attenuate tumor growth by regulating key cell fate, cell cycle, and survival genes such as *c-MYC*<sup>2</sup>
- Studies using genetic knockdown and small-molecule inhibitors demonstrate that targeting BET proteins in models of cancer and acute inflammation has therapeutic potential<sup>3</sup>
- INCB057643, a potent and selective small-molecule inhibitor of BET proteins, inhibited growth of model cell lines derived from solid and hematologic tumors in vitro and in vivo<sup>4,5</sup>
- This ongoing, phase 1/2 study evaluates INCB057643 in patients with advanced malignancies

## Objective

- To evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of INCB057643 in patients with advanced malignancies (NCT02711137)

## Methods

### Study Design and Treatment

- Phase 1/2 study (Figure 1)
- Part 1: Dose escalation (esc)
  - 3 + 3 design in 3 treatment groups (TGs) to determine the maximum tolerated dose or a tolerated pharmacologically active dose (dose at which plasma concentrations of INCB057643 exceed the  $IC_{50}$  for the inhibition of *c-MYC* expression for approximately 6–12 hours or achieve clinical response)
  - Dose escalation began in Cohort 1 of TGA<sub>esc</sub> (starting dose: oral 8 mg once daily [QD] continuously)
  - Enrollment in TGB<sub>esc</sub> began at the pharmacologically active dose identified in TGA<sub>esc</sub>
- Part 2: Dose expansion (exp)
  - The dose selected in Part 1 will be evaluated in Part 2
- Key eligibility criteria are presented in Table 1

Figure 1. Study Design

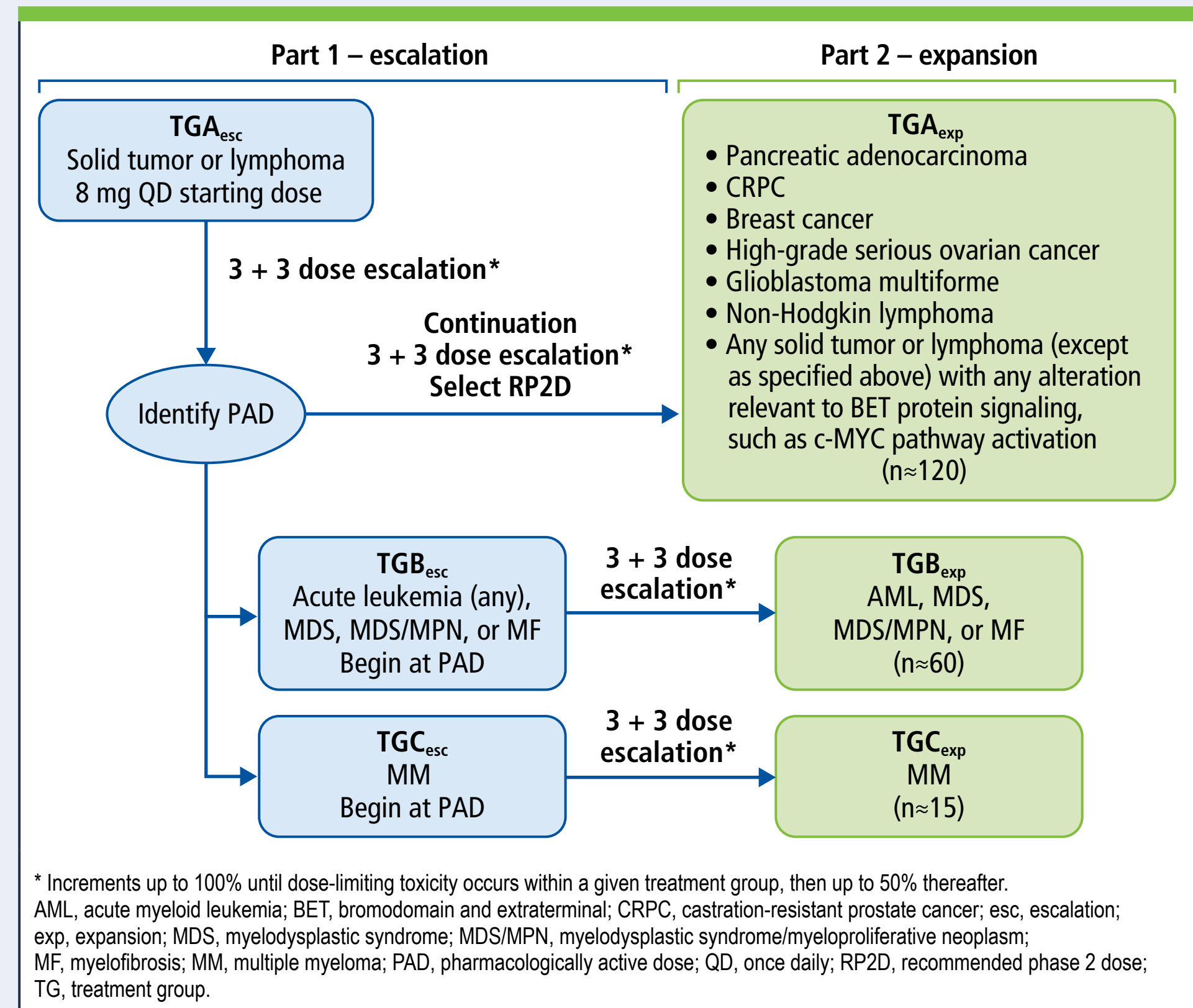


Table 1. Key Eligibility Criteria

<b>Key Inclusion Criteria</b>
• Age ≥18 years
• Progressed following ≥1 line of prior therapy, with no further established therapy that is known to provide clinical benefit (including patients who are intolerant to the established therapy)
– Patients with MM must have relapsed from or have been refractory to ≥2 prior therapies, including a proteasome inhibitor and an immunomodulatory drug, and have no current standard options available
• ECOG PS – Part 1: ≤1; Part 2: ≤2
• Life expectancy >12 weeks
<b>Key Exclusion Criteria</b>
• Inadequate hematologic, liver, or renal function at screening
• Inadequate washout of prior treatment with anticancer medications or investigational drugs before the first administration of the study drug
• Known HIV infection, active hepatitis B, or hepatitis C infection
• Current active and uncontrolled infectious disease requiring systemic treatment
• Diagnosis of type 1 diabetes or uncontrolled type 2 diabetes
– HbA1c ≥8%
• Any sign of clinically significant bleeding
• Use of prohibited concomitant medications including strong modulators of CYP3A4
• Prior treatment with any BET inhibitor

BET, bromodomain and extraterminal; CYP, cytochrome P450; ECOG PS, Eastern Cooperative Oncology Group performance status; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; MM, multiple myeloma.

# Preliminary Results From an Ongoing Phase 1/2 Study of INCB057643, a Bromodomain and Extraterminal Protein Inhibitor, in Patients With Advanced Malignancies

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### Assessments

- Safety/tolerability and efficacy were reported for patients who received ≥1 dose of INCB057643
  - Treatment-related adverse events (TRAEs) were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
  - Objective response was assessed at protocol-specified intervals using disease response criteria applicable to each malignancy under study
    - Efficacy assessments included objective response rate, progression-free survival, duration of response (DOR), and overall survival
- PK and PD were assessed for patients who received ≥1 dose of INCB057643 and had ≥1 PK and PD sample collected and analyzed
  - Blood samples were collected at protocol-specified time points and assessed for PK (maximum concentration, time to maximum concentration, minimum concentration, area under plasma concentration-time curve [AUC] calculated to last measured concentration, AUC over 1 dosing interval, apparent clearance) and PD biomarkers predictive of response
  - An ex vivo assay was developed to measure PD effect of INCB057643 on the inhibition of BET proteins based on the reduction of total *c-MYC* expression (*c-MYC* is a target for BRD4, and protein levels are well correlated with the transcription of *c-MYC*)

## Results

### Patients

- As of the data cutoff (August 18, 2017), 21 and 40 patients were treated in Parts 1 and 2, respectively (Figure 2)
- Patient demographics and baseline characteristics are presented in Table 2
- Median (range) durations of treatment were:
  - Part 1 TGA<sub>esc</sub>: 59.5 (6–379) days; TGB<sub>esc</sub>: 16 (2–43) days
  - Part 2 TGA<sub>exp</sub>: 39 (1–106) days

Figure 2. Patient Disposition

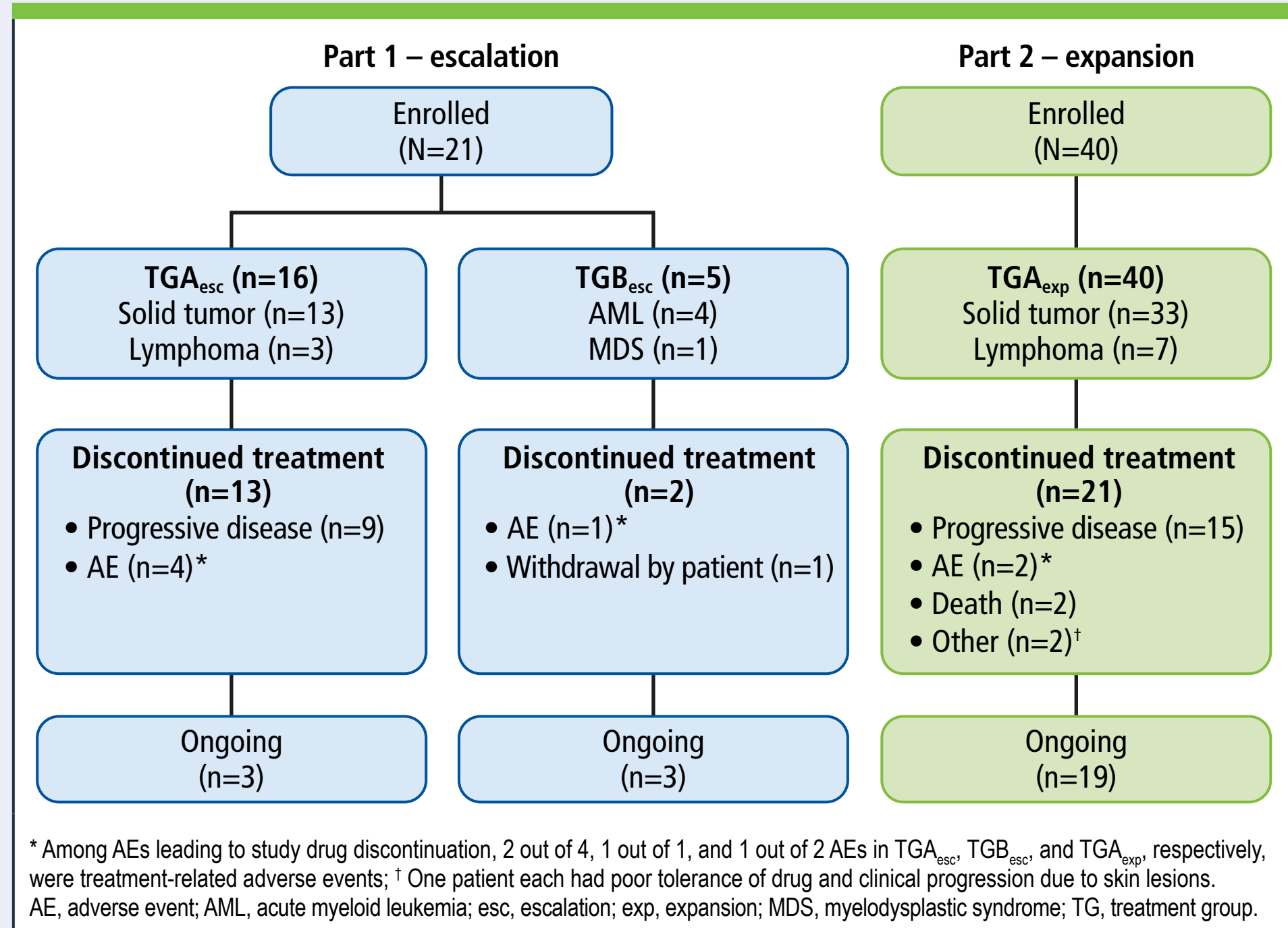


Table 2. Patient Characteristics

Characteristic*	Part 1		Part 2	
	TGA <sub>esc</sub> (n=16)	TGB <sub>esc</sub> (n=5)	TGA <sub>exp</sub> (n=40)	
Median age (range), y	58.5 (44–81)	71.0 (60–73)	65.5 (34–80)	
Women, n (%)	8 (50)	2 (40)	26 (65)	
Race, n (%)				
White/Caucasian	11 (69)	4 (80)	33 (83)	
Black/African American	3 (19)	1 (20)	5 (13)	
Native Hawaiian/Pacific Islander	1 (6)	0	1 (3)	
Other	1 (6)	0	0	
Missing	0	0	1 (3)	
ECOG PS, n (%)				
0	7 (44)	0	10 (25)	
1	9 (56)	5 (100)	27 (68)	
≥2	0	0	3 (8)	
Number of prior systemic therapies, n (%) <sup>†</sup>				
0	0	0	1 (3) <sup>‡</sup>	
1	4 (25)	1 (20)	5 (13)	
2	0	0	2 (5)	
≥3	12 (75)	3 (60)	29 (73)	
Most common tumor types, n (%) <sup>§</sup>				
Lymphoma <sup>¶</sup>	3 (14)	7 (18)		
Colorectal cancer	6 (29)	2 (5)		
Breast cancer	0	7 (18)		
Ovarian cancer	1 (5)	9 (23)		
Glioblastoma	0	6 (15)		
Other	11 (52)	9 (23)		

\*Percentages may not total 100 due to rounding. <sup>†</sup>Preliminary data: include (but not limited to) neoadjuvant, adjuvant, induction/consolidation, local relapse, or in metastatic setting. <sup>‡</sup>Patient had no known standard-of-care therapies available. <sup>§</sup>Occurring in >5 patients in all Parts 1 and 2 (GAs combined). <sup>¶</sup>Lymphoma subtypes according to disease history assessed at screening included follicular lymphoma (n=6), diffuse large B-cell lymphoma (n=3), and splenic marginal zone lymphoma (n=1). ECOG PS, Eastern Cooperative Oncology Group performance status; esc, escalation; exp, expansion; TG, treatment group.

### Safety

- Doses of 8, 12, and 16 mg QD were explored in Part 1 TGA<sub>esc</sub> (Table 3)
  - 16 mg QD was deemed to be not tolerated; 12 mg QD was the maximum tolerated dose and the recommended phase 2 dose for Part 2

### TRAEs leading to dose interruption/dose reduction

- Part 1: TGA<sub>esc</sub>:** data shown in Table 3; TGB<sub>esc</sub>: none
- Part 2: TGA<sub>exp</sub>:** 7 patients (18%) had TRAEs leading to dose interruption, most commonly (≥2 patients) due to thrombocytopenia, fatigue, and decreased appetite (n=2 for each event); 1 (6%) had TRAEs of fatigue and nausea leading to dose reduction

### TRAEs leading to treatment discontinuation

- Part 1: TGA<sub>esc</sub>:** 2 patients (13%) had TRAEs leading to treatment discontinuation: hyperglycemia and increased international normalized ratio (INR; n=1 for each event); TGB<sub>esc</sub>: 1 (20%) had a TRAE of nausea leading to treatment discontinuation
- Part 2: TGA<sub>exp</sub>:** 1 patient (3%) had a TRAE of thrombocytopenia leading to treatment discontinuation

Table 3. Dose Escalation in Part 1 TGA<sub>esc</sub>: Cycle 1

Part 1 TGA <sub>esc</sub> Cohorts	Patients Enrolled, n	Dose	Number of Patients With Dose Interruption/ Dose Reduction Due to TRAEs*	Escalation Decision
1	4	8 mg QD	n=1 Gr 2 decreased appetite	Well tolerated and identified as the PAD; enroll Cohort 2 (16 mg QD)
2	8	16 mg QD	n=3 Gr 3 increased INR (DLT) Gr 3 thrombocytopenia Gr 3 conjugated bilirubin increased; then Gr 2 conjugated bilirubin increased after dose interruption <sup>†</sup>	Not tolerated dose; enroll Cohort 3 (12 mg QD)
3	4	12 mg QD	n=1 Gr 2 dyspnea	Maximum tolerated dose and recommended phase 2 dose for Part 2

\*Gr 2 conjugated bilirubin increased led to dose reduction; all other TRAEs shown led to dose interruption. <sup>†</sup>Patient had Gr 3 conjugated bilirubin increased on day 15 leading to dose interruption, and Gr 2 conjugated bilirubin increased on day 17 leading to dose reduction. DLT, dose-limiting toxicity; esc, escalation; Gr, grade; INR, international normalized ratio; PAD, pharmacologically active dose; QD, once daily; TG, treatment group; TRAE, treatment-related adverse event.

- All-grade TRAEs are shown in Table 4

Table 4. All-Grade TRAEs

TRAEs, n (%) <sup>*</sup>	Part 1		Part 2	
	TGA <sub>esc</sub> (n=16)	TGB <sub>esc</sub> (n=5)	TGA <sub>exp</sub> (n=40)	
Decreased appetite	7 (44)	2 (40)	5 (13)	
Nausea	6 (38)	1 (20)	11 (28)	
Hyperglycemia	5 (31)	0	6 (15)	
Thrombocytopenia	4 (25)	0	9 (23)	
Dysgeusia	3 (19)	0	5 (13)	
Fatigue	3 (19)	0	7 (18)	
Weight decreased	3 (19)	0	1 (3) <sup>†</sup>	
Anemia	2 (13)	0	1 (3) <sup>‡</sup>	
Constipation	2 (13)	0	0 <sup>§</sup>	
Diarrhea	2 (13)	3 (60)	6 (15)	
Dizziness	2 (13)	0	2 (5) <sup>‡</sup>	
Dry mouth	2 (13)	0	2 (5) <sup>‡</sup>	
Vomiting	1 (6) <sup>‡</sup>	2 (40)	4 (10)	

\*TRAEs that occurred in ≥10% of patients in Parts 1 or 2 TGA or in any patients in Part 1 TGB. <sup>†</sup>Although this TRAE occurred in <10% of patients in Part 1 TGA, it is listed because it occurred in Part 1 TGB. <sup>‡</sup>Although these TRAEs occurred in <10% of patients in Part 2 TGA, they are listed because they occurred in ≥10% of patients in Part 1 TGA. <sup>§</sup>Missing response due to treatment discontinuation prior to first tumor response assessment (due to adverse events [n=5], death [n=2], withdrawal of consent [n=1], other reason [poor tolerance of drug, n=1]), or did not reach first tumor response assessment at data cutoff date (n=4), or overall assessment not provided by investigator (n=1). AML, acute myeloid leukemia; asc, escalation; exp, expansion; MDS, myelodysplastic syndrome; TG, treatment group.

### Grade ≥3 TRAEs

- Part 1: TGA<sub>esc</sub>:** 4 patients (25%) had 6 grade ≥3 TRAEs: thrombocytopenia (n=2); anemia, increased conjugated bilirubin, hyperglycemia, and increased INR (n=1 for each event); TGB<sub>esc</sub>: 1 (20%) had 1 grade ≥3 TRAE: nausea
- Part 2: TGA<sub>exp</sub>:** 7 patients (18%) had 8 grade ≥3 TRAEs: thrombocytopenia (n=4), anemia, diarrhea, fall, and hyperglycemia (n=1 for each event)

### Serious TRAEs

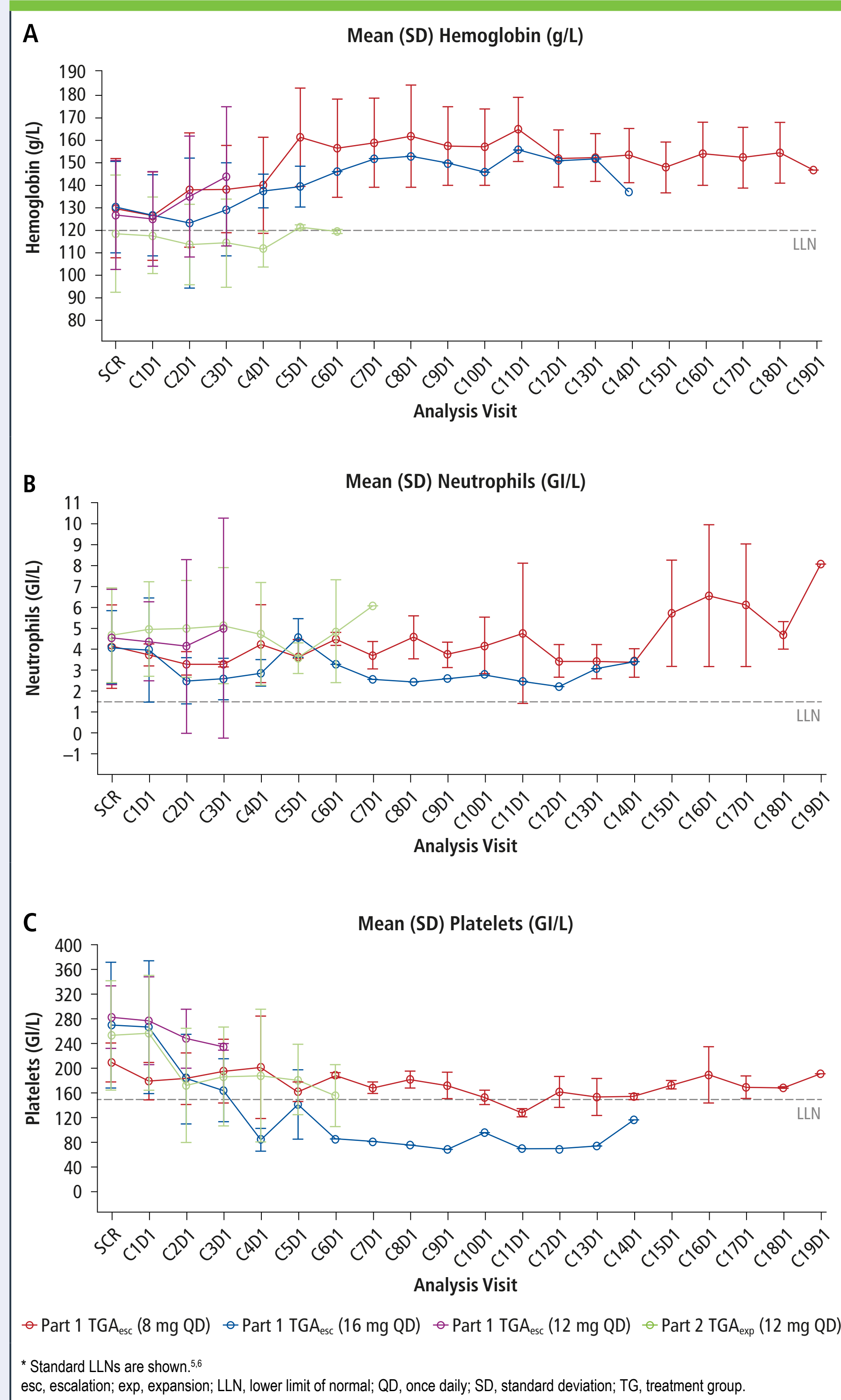
- Part 1: TGA<sub>esc</sub>:** 2 patients (13%) had 2 serious TRAEs: hyperglycemia and increased INR (n=1 for each event); TGB<sub>esc</sub>: none
- Part 2: TGA<sub>exp</sub>:** 4 patients (10%) had 6 serious TRAEs: thrombocytopenia (n=2), and diarrhea, fall, headache, and syncope (n=1 for each event)

### Fatal AEs

- Part 1: TGA<sub>esc</sub>:** 2 patients (13%) had 2 fatal AEs: hepatic failure and pneumonia (n=1 for each event); TGB<sub>esc</sub>: 1 (20%) had 1 fatal AE: sepsis. None of the fatal AEs reported in Part 1 were deemed treatment-related
- Part 2: TGA<sub>exp</sub>:** 3 patients (8%) had 3 fatal AEs: cardiac arrest, disease progression, and respiratory failure (n=1 for each event). None of the fatal AEs reported in Part 2 were deemed treatment-related

### Laboratory AEs

- Mean values for hemoglobin, neutrophils, and platelets were recorded by visit and are shown in Figure 3A–C
  - For each analyte measured, a majority of the patients had values above the lower limit of normal

Figure 3. Laboratory Values, by Visit (Part 1 TGA<sub>esc</sub> and Part 2 TGA<sub>exp</sub>)<sup>\*</sup>

### Efficacy

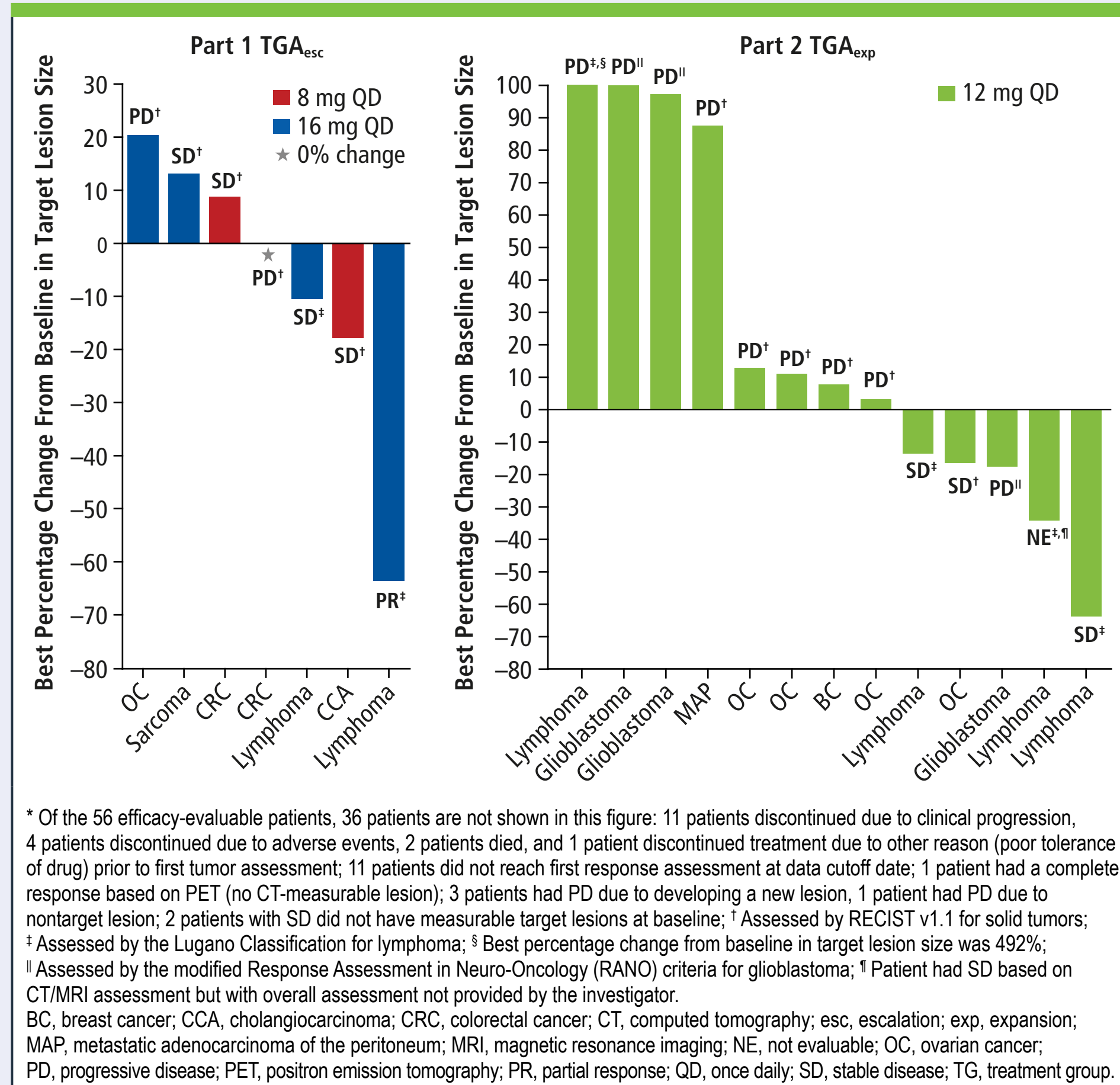
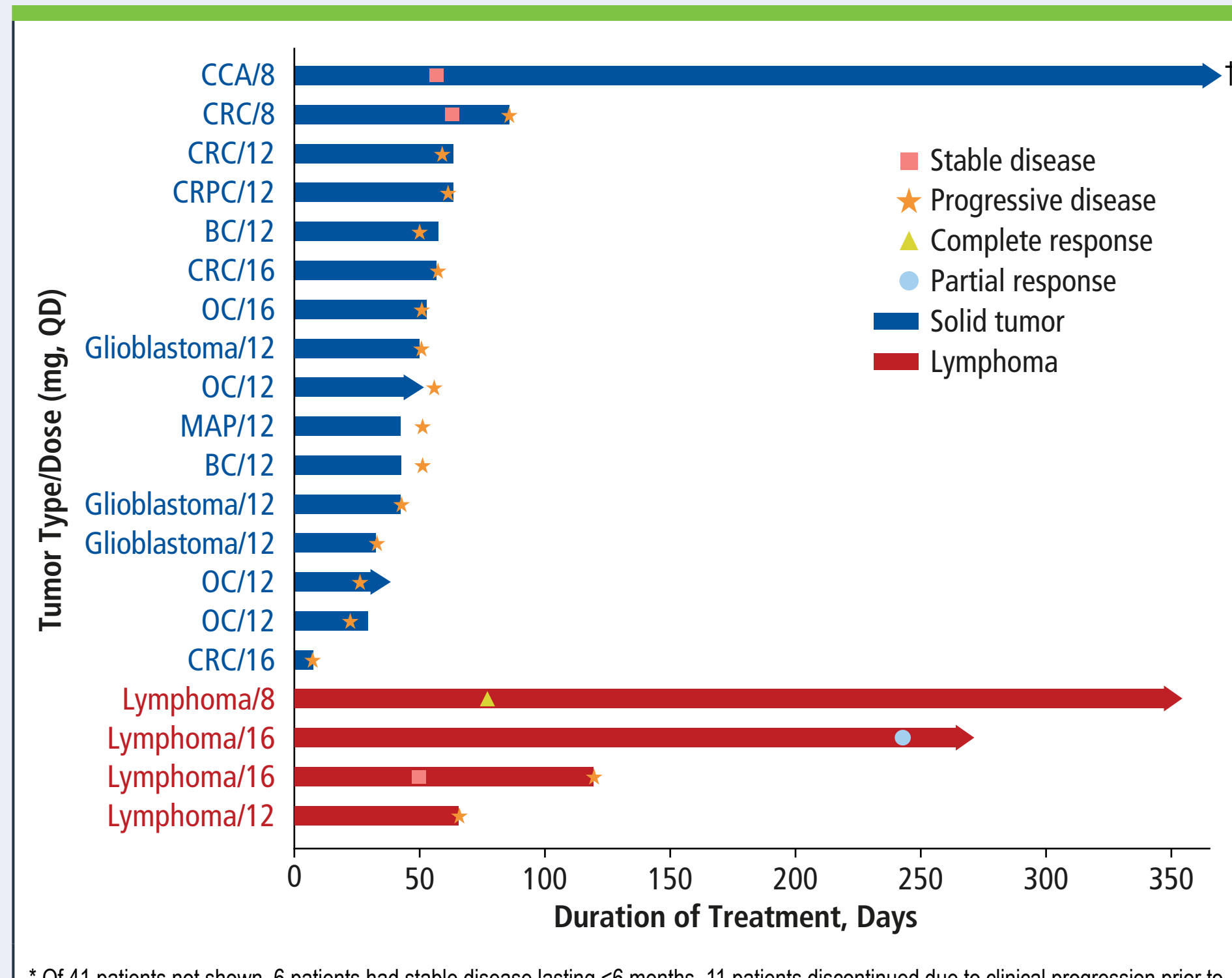
- Best response among evaluable patients is shown in Table 5

Table 5. Best Response\* (Parts 1 and 2)

Response, n (%)	Part 1		Part 2	
	Solid Tumors (n=13)	Lymphoma (n=3)	AML (n=4) MDS (n=1)	Solid Tumors (n=33) Lymphoma (n=7)
Objective response	0	2 (67)	0	0
Complete response	0	1 (33)	0	0
Partial response	0	1 (33)	0	0
Stable disease ≥6 months	1 (8)	0	0	0
Stable disease <6 months	2 (15)	1 (33)	0	3 (11) 2 (29)
Progressive disease	5 (38)	0	0	9 (27) 1 (14)
Not evaluable				
Clinical progression	3 (23)	0	0	8 (24) 0
Missing <sup>†</sup>	2 (15)	0	5 (100)	13 (39) 4 (57)

\*Assessed by RECIST v1.1 for solid tumors, the Lugano Classification for lymphoma, International Working Group Response Criteria for AML, International Working Group Response Criteria for MDS, and the modified Response Assessment in Neuro-Oncology (RANO) criteria for glioblastoma. <sup>†</sup>Missing response due to treatment discontinuation prior to first tumor response assessment (due to adverse events [n=5], death [n=2], withdrawal of consent [n=1], other reason [poor tolerance of drug, n=1]), or did not reach first tumor response assessment at data cutoff date (n=4), or overall assessment not provided by investigator (n=1). AML, acute myeloid leukemia; asc, escalation; exp, expansion; MDS, myelodysplastic syndrome; TG, treatment group.

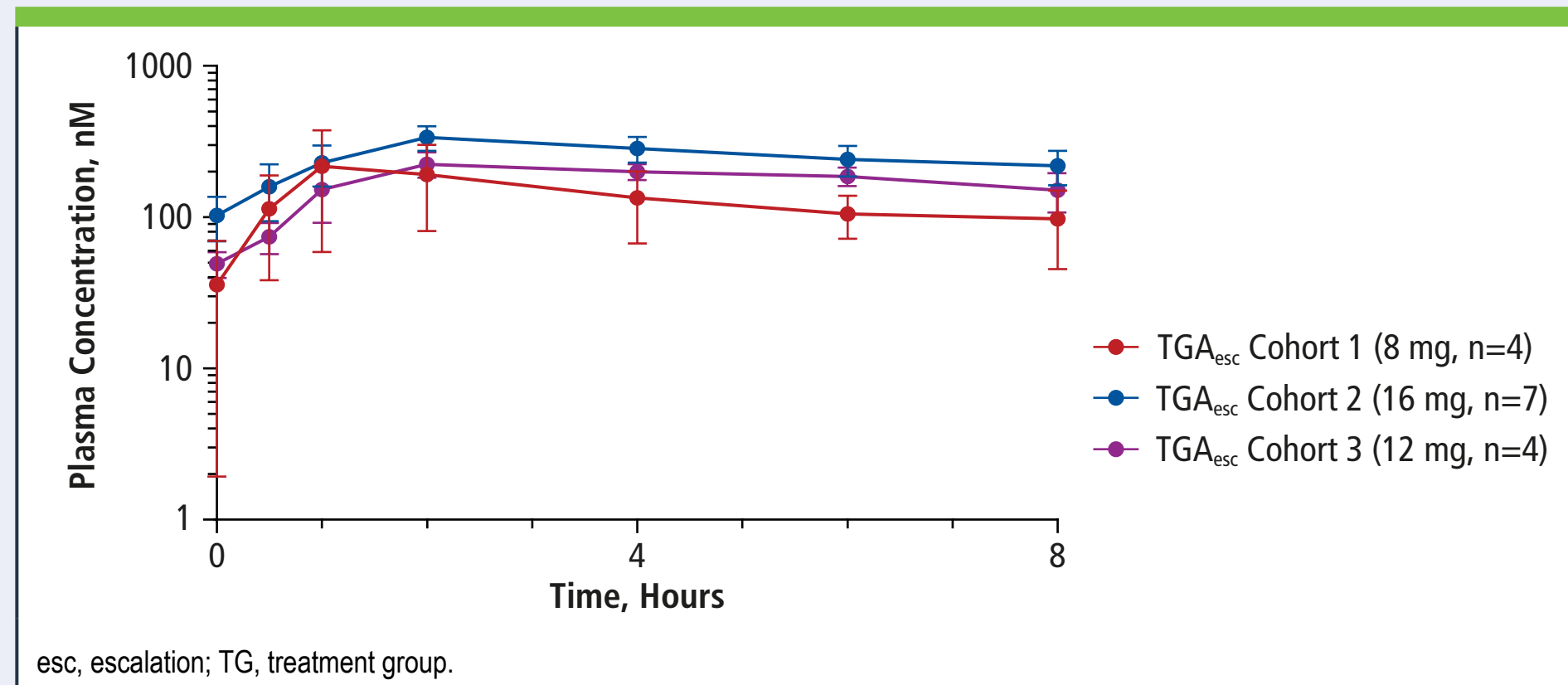
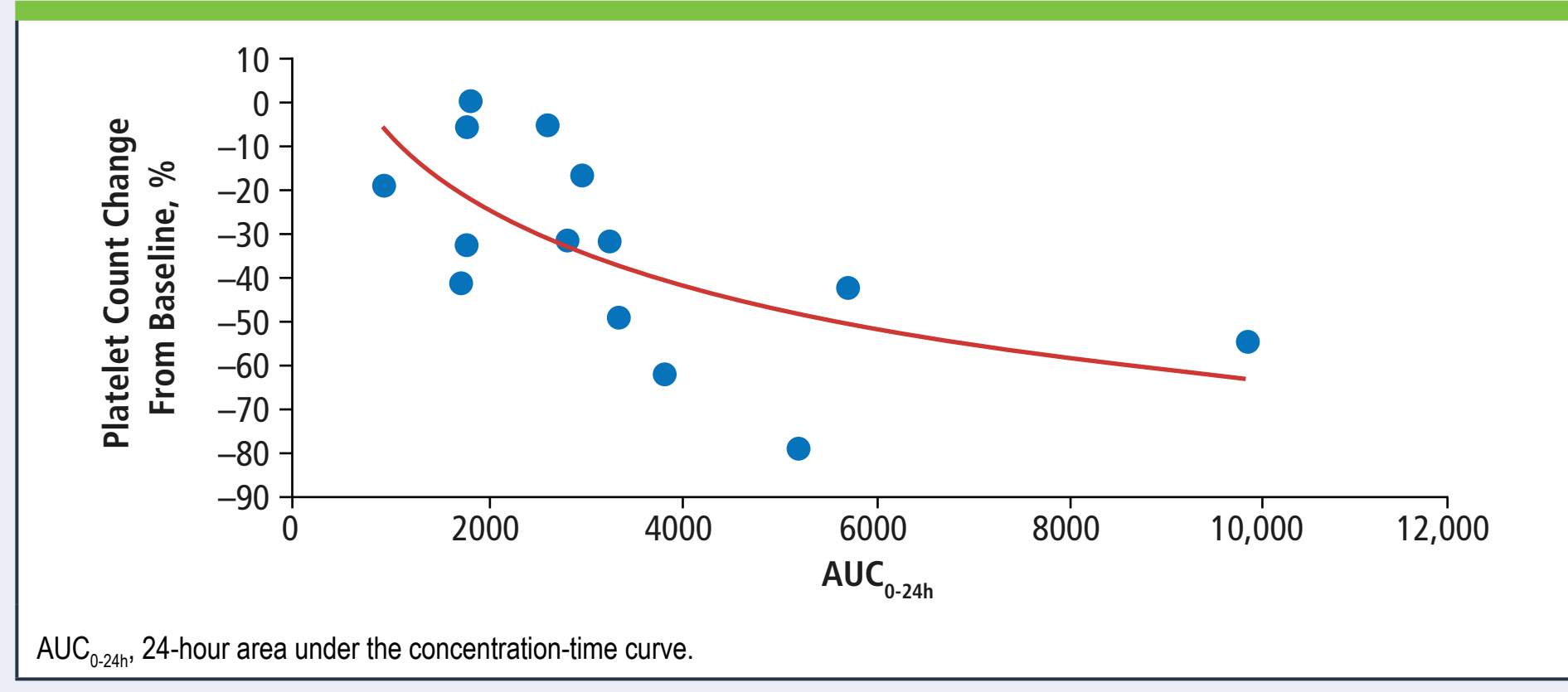
- One patient (8 mg QD) with heavily pretreated follicular lymphoma had a complete response (based on positron emission tomography [PET]) and a response that was ongoing as of the data cutoff date (DOR, 9 months)
- One patient (16 mg QD) with follicular lymphoma had a partial response (based on computed tomography [CT] and PET; 63.6% decrease in target lesion per RECIST v1.1), with a response that was ongoing as of the data cutoff date (DOR, 1 month)
- One patient (8 mg QD) with cholangiocarcinoma had stable disease (based on CT), with ongoing disease control at 12 months as of the data cutoff date
- Best percent change from baseline in target lesion size and best overall response are shown in Figure 4; duration of treatment and best overall response are shown in Figure 5

Figure 4. Best Percentage Change From Baseline in Target Lesion Size in Efficacy-Evaluable Patients (Part 1 TGA<sub>esc</sub> and Part 2 TGA<sub>exp</sub>)<sup>\*</sup>Figure 5. Duration of Treatment and Best Overall Response (Parts 1 and 2)<sup>\*</sup>

### PK and PD of INCB057643

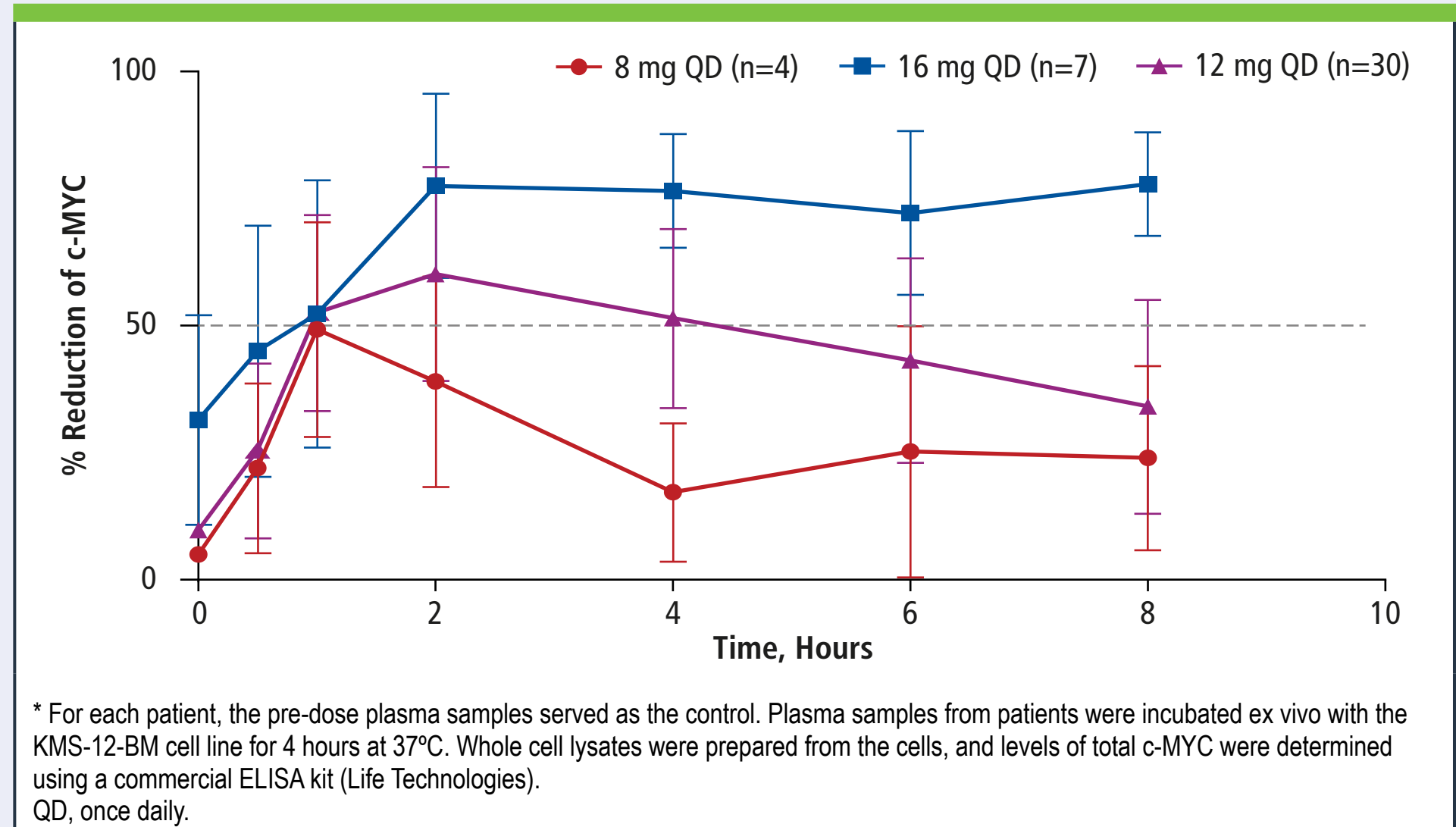
- INCB057643 had a low clearance and a long mean terminal elimination half-life of approximately 12–14 hours (Figure 6)
- INCB057643 exposure correlated with thrombocytopenia on an individual basis
  - Higher INCB057643 exposures were associated with greater decrease in platelet count percentage from baseline (Figure 7)

Figure 6. INCB057643 Plasma Concentration-Time Profiles, by Dose

Figure 7. Relationship Between Steady-State AUC<sub>0-24h</sub> and Maximum Percentage Decrease From Baseline in Platelet Count

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- Ex vivo PD assays showed reduction in *c-MYC* expression in spiked KMS-12-BM cells after incubation in patient plasma samples for 4 hours (Figure 8)
- The 12-mg dose met the target PD activity level (inhibition of *c-MYC* expression)
- PD results were generally consistent with PK

Figure 8. Percentage Reduction in *c-MYC* Expression Versus Time, by Dose and Regimen<sup>\*</sup>\*For each patient, the pre-dose plasma samples served as the control. Plasma samples from patients were incubated ex vivo with the KMS-12-BM cell line for 4 hours at 37°C. Whole cell lysates were prepared from the cells, and levels of total *c-MYC* were determined using a commercial ELISA kit (Life Technologies).

## Conclusions

- INCB057643, a potent small-molecule BET inhibitor, demonstrated a tolerable safety profile and preliminary activity in heavily pretreated patients with advanced malignancies
  - INR increase was the only dose-limiting toxicity reported
  - One patient each with follicular lymphoma achieved complete response and partial response as best response
- INCB057643 demonstrated a favorable PK/PD profile
  - A long mean terminal elimination half-life (~12–14 hours) and a moderate interpatient variability in oral clearance
  - Reduction in *c-MYC* expression (PD) correlated with PK
- Pharmacologic activity (objective tumor response) was seen at 8 mg QD, with target levels of *c-MYC* inhibition seen at 12 mg QD
  - 12 mg QD was selected as the dose for further evaluation
- Dose escalation and dose expansion are ongoing in Parts 1 and 2
- The protocol is being amended to allow evaluation of INCB057643 in combination with other antitumor agents

## Disclosures

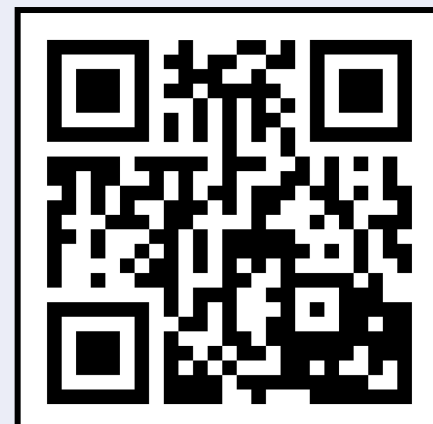
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