Safety and Preliminary Efficacy From a Phase 1 Study of INCB123667, a Selective CDK2 Inhibitor, in Patients With Advanced Platinum-Resistant and Refractory Ovarian Cancer

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Key Takeaways

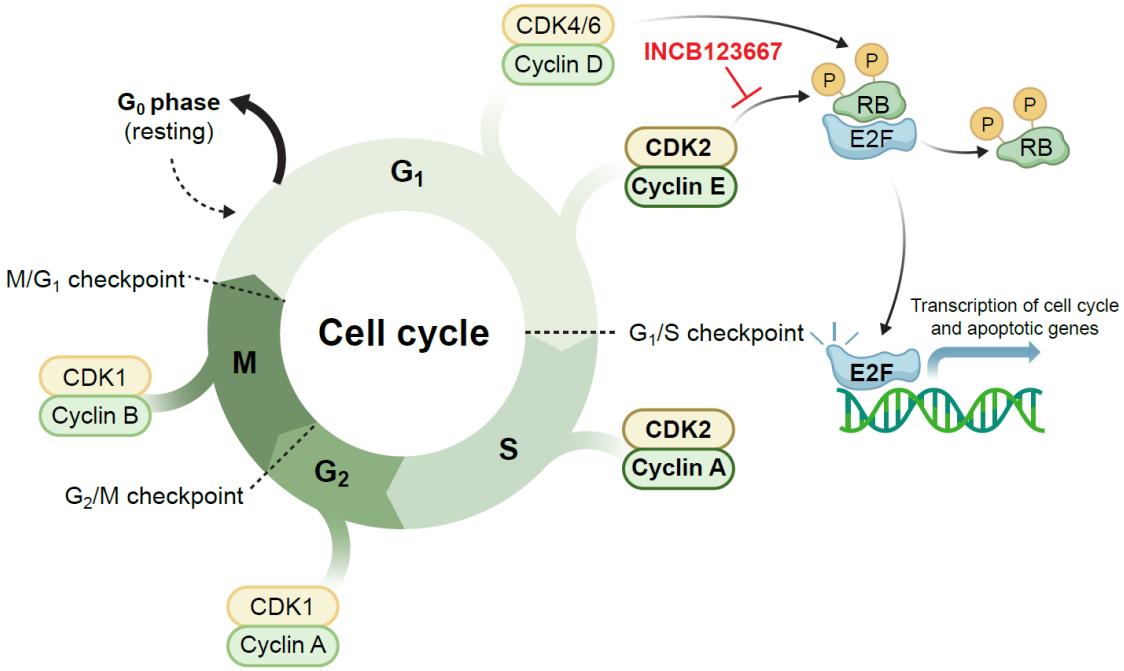
- In this phase 1 study in patients with heavily pretreated recurrent platinum-resistant or -refractory ovarian cancer, INCB123667 monotherapy at the dose of 100 mg daily reported an ORR of 33.3% with a median DOR of 3.6 months and median PFS of 5.3 months
  - All responder patients had cyclin E1 overexpression except 1 with unknown status
- INCB123667 showed manageable safety and tolerability
- These data provide a proof of concept in this difficult to treat population and support the advancement of INCB123667 into pivotal studies in patients with platinum-resistant ovarian cancer

DOR, duration of response; ORR, overall response rate; PFS, progression-free survival.

Introduction

- The cyclin-dependent kinase 2 (CDK2)/cyclin E1 (*CCNE1*) complex is crucial for DNA replication and cell cycle progession[1-4]
- *CCNE1* amplification or overexpression results in premature entry into S phase, leading to double-strand DNA breaks, stress replication forks, and genomic instability[5-8]
- *CCNE1* amplification and cyclin E1 overexpression is associated with poor prognosis[9]
- Approximately 50% of ovarian cancers overexpress cyclin E1[10,11]
- In this ongoing phase 1 study, INCB123667, a potent and selective CDK2 inhibitor, demonstrated manageable safety and preliminary efficacy in patients with advanced solid tumors (NCT05238922)[12]

Role of CDK2/Cyclin E Complex in the Cell Cycle



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CDK2, cyclin-dependent kinase 2; CCNE1, cyclin E1.

Study Design

Part 1A Dose Escalation (N=84)

- Advanced or metastatic solid tumors
- Disease progression on prior standard treatment
- Documented *CCNE1* amplification (local laboratory) was preferred but not mandatory
- ECOG PS 0 or 1

Part 1B Ovarian Cancer Cohort (N=45)

- Platinum-resistant or -refractory epithelial ovarian/fallopian/primary peritoneal carcinoma
- Up to 4 prior lines of systemic therapy
- *CCNE1* amplification (local laboratory) or central cyclin E1 overexpression
- ECOG PS 0 or 1

- Starting at 50 mg qd; escalated to
  - 50 mg bid
  - 75 mg qd/bid
  - 125 mg qd
  - 150 mg qd*

Identification of RDEs

- RDEs
  - 50 mg bid
  - 100 mg qd
  - 125 mg qd

Objectives

- Primary: Safety, tolerability, and determine MTD and RDEs of INB123667 monotherapy
- Secondary: Preliminary efficacy of INCB123667 as monotherapy in terms of ORR, DCR, and DOR
- Exploratory: Biomarkers that predict pharmacologic activity and/or correlate with clinical safety or efficacy

*Continuous or intermittent dosing.

bid, twice daily; CCNE1, cyclin E1; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; ORR, overall response rate; qd, daily; RDE, recommended dose for expansion.

Background

- INCB123667 showed manageable safety in doses up to 125 mg daily in dose escalation (Part 1A)[1]
- Based on the safety, PK and preliminary activity, 50 mg bid, 100 mg qd, and 125 mg qd were selected as recommended doses for expansion (RDEs) for the ovarian cancer cohort (Part 1B)

Part 1A Dose Escalation/Back Fill Safety Summary

n (%)*	50 mg qd (n=5)	50 mg bid (n=19)	75 mg bid (n=6)	75 mg qd (n=19)	125 mg qd (n=25)	150 mg qd (n=6)	150 mg qd ID† (n=4)	Total (N=84)
Any-grade TEAEs	5 (100.0)	18 (94.7)	6 (100.0)	18 (94.7)	25 (100.0)	6 (100.0)	4 (100.0)	82 (97.6)
Treatment-related TEAEs	4 (80.0)	14 (73.7)	6 (100.0)	15 (78.9)	25 (100.0)	6 (100.0)	4 (100.0)	74 (88.1)
Grade ≥3 TEAEs	2 (40.0)	9 (47.4)	4 (66.7)	8 (42.1)	10 (40.0)	5 (83.3)	2 (50.0)	40 (47.6)
Serious TEAEs	2 (40.0)	4 (21.1)	2 (33.3)	2 (10.5)	7 (28.0)	1 (16.7)	0 (0.0)	18 (21.4)
Any-cause fatal TEAEs	0	0	0	0	1 (4.0)	0	0	1 (1.2)
Discontinuation of INCB123667	0	0	1 (16.7)	0	0	1 (16.7)	0	2 (2.4)
DLTs	0	1 (hematologic)	4 (hematologic, neutropenic sepsis, vomiting)	0	0	2 (hematologic)	0	7

*n (event) for DLTs. †5 days on/2 days off.

1. Simonelli M, et al. *Ann Oncol*. 2024;35(Suppl 2):S482-S535.

bid, twice daily; DLT, dose-limiting toxicity; ID, intermittent dose; PK, pharmacokinetics; qd, once daily; TEAE, treatment-emergent adverse event.

Patients and Disease Characteristics

- 90 patients with ovarian cancer were enrolled and received INCB123667 (45 in Part 1A and 45 in Part 1B)
- As of the data cutoff (March 10, 2025), treatment was ongoing in 8 patients (8.9%)
- 82 patients (91.1%) discontinued, primarily for disease progression (n=70; 77.8%)
  - 3 patients (3.3%) discontinued for AEs
- **Here we report safety and efficacy data of Part 1B**

Baseline Characteristic	Total (N=90)
Age, median (range), years	62.0 (37.0-80.0)
≥65 years, n (%)	31 (34.4)
Race, n (%)	
White	64 (71.1)
Asian	8 (8.9)
Not reported/unknown/missing	18 (20.0)
ECOG PS, n (%)	
0	68 (75.6)
Histology, n (%)	
Serous	72 (80.0)
Clear cell	5 (5.6)
Endometrioid	1 (1.1)
Other*	12 (13.3)
Cyclin E1 overexpression,† n (%)	83 (92.2)
CCNE1 amplification,† n (%)	51 (56.7)
Prior systemic therapies, median (range)	4 (1-12)
Prior PARPi, n (%)	62 (68.9)
Prior bevacizumab, n (%)	69 (76.7)

*Mucinous, carcinosarcoma, neuroendocrine and adenocarcinoma-NOS.
†Overexpression as determined by central testing; CCNE1 amplification determined by either local results or central testing.
AE, adverse event; CCNE1, cyclin E1; ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; PARPi, poly-ADP ribose polymerase inhibitor.

Safety and Tolerability Summary (Part 1B)

- A manageable safety profile was observed in patients with ovarian cancer at the doses selected for expansion

TEAEs, n (%)	50 mg bid (n=16)	100 mg qd (n=14)	125 mg qd (n=15)	Total (N=45)
Any TEAE	15 (93.8)	14 (100.0)	15 (100.0)	44 (97.8)
Treatment-related TEAE	14 (87.5)	14 (100.0)	14 (93.3)	42 (93.3)
Serious TEAE	2 (12.5)	2 (14.3)	3 (20.0)	7 (15.6)
Grade ≥3 TEAE	4 (25.0)	4 (28.6)	8 (53.3)	16 (35.6)
Fatal TEAE	0 (0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to TEAEs	0 (0)	0 (0.0)	1 (6.7)*	1 (2.2)
Dose interruption owing to TEAEs	3 (18.8)	5 (35.7)	7 (46.7)	15 (33.3)
Dose reduction owing to TEAEs	0 (0)	0 (0.0)	3 (20.0)	3 (6.7)

*Discontinuation due to a TEAE of hepatic cytolysis.
bid, twice daily; qd, daily; TEAE, treatment-emergent adverse event.

Treatment-Emergent Adverse Events*

	50 mg bid (n=16)		100 mg qd (n=14)		125 mg qd (n=15)		Total (N=45)	
TEAEs, n (%)	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hematologic								
Anemia	7 (43.8)	1 (6.3)	5 (35.7)	1 (7.1)	5 (33.3)	0 (0)	17 (37.8)	2 (4.4)
Thrombocytopenia	7 (43.8)	0 (0)	5 (35.7)	0 (0)	4 (26.7)	0 (0)	16 (35.6)	0 (0)
Neutropenia	5 (31.3)	1 (6.3)	6 (42.9)	0 (0)	5 (33.3)	0 (0)	16 (35.6)	1 (2.2)
Non-hematologic								
Nausea	7 (43.8)	0 (0)	10 (71.4)	0 (0)	8 (53.3)	0 (0)	25 (55.6)	0 (0)
Constipation	5 (31.3)	0 (0)	5 (35.7)	0 (0)	8 (53.3)	0 (0)	18 (40.0)	0 (0)
Vomiting	2 (12.5)	0 (0)	4 (28.6)	0 (0)	8 (53.3)	0 (0)	14 (31.1)	0 (0)
Fatigue	3 (18.8)	1 (6.3)	3 (21.4)	0 (0)	8 (53.3)	1 (6.7)	14 (31.1)	2 (4.4)
Abdominal pain†	3 (18.8)	0 (0)	4 (28.6)	1 (7.1)	6 (40.0)	0 (0)	13 (28.9)	1 (2.2)
Intestinal obstruction	1 (6.3)	0 (0)	1 (7.1)	0 (0)	3 (20.0)	3 (20.0)	5 (11.1)	3 (6.7)

*Occurring in >20% of patients for any grade events or ≥5% of patients for grade ≥3 events.
†Includes preferred terms of abdominal pain, abdominal pain lower, and abdominal pain upper.
bid, twice daily; qd, daily; TEAE, treatment-emergent adverse event.

Efficacy (Part 1B)

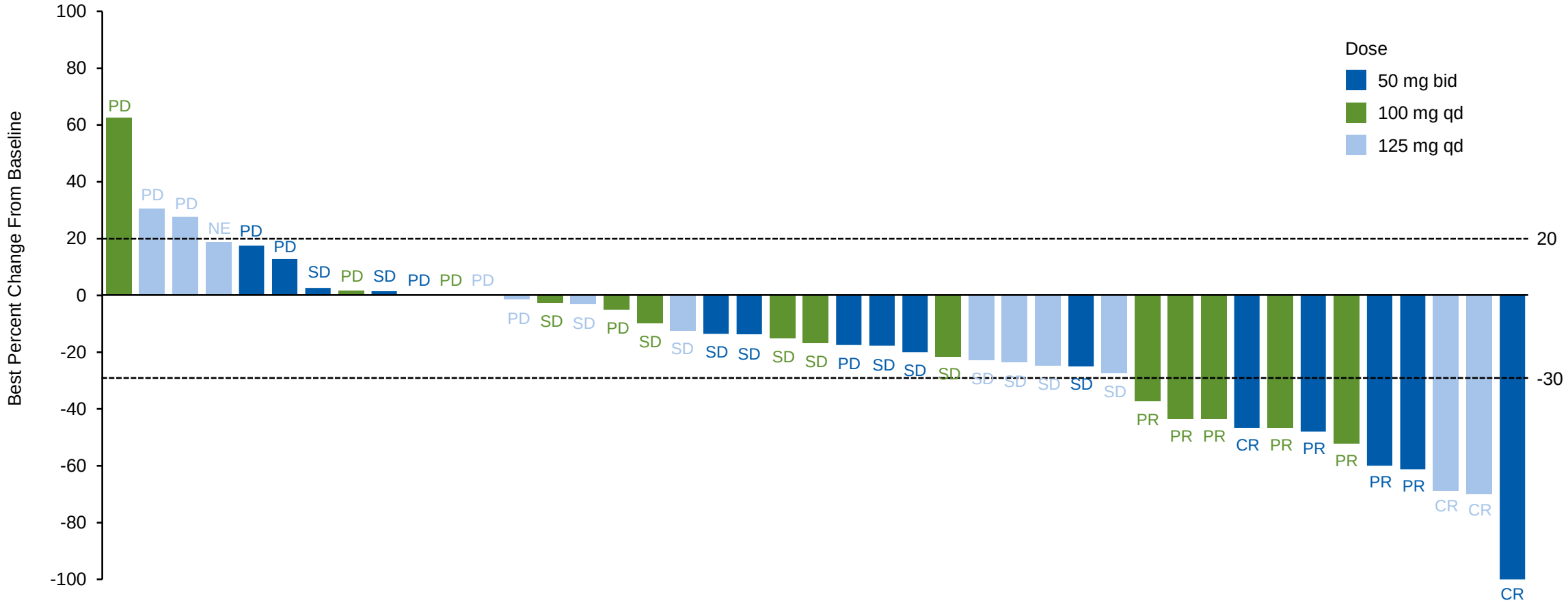
- Best response rate was achieved at 100 mg daily
  - In the combined dataset (50 mg bid and 100 mg qd), ORR was 33.3%, median DOR 3.6 months, and median PFS 5.3 months
- Cyclin E1 overexpression was noted in all but 1 responder (11/12), whose status was unknown due to limited tissue
- Responses were observed in patients with *CCNE1* amplification (7/29) and in patients without *CCNE1* amplification but with cyclin E1 overexpression (5/16)

Variable	50 mg bid (n=16)	100 mg qd (n=14)	125 mg qd (n=15)
Overall response rate, n (%) [95% CI]	5 (31.3) [11.0, 58.7]	5 (35.7) [12.8, 64.9]	2 (13.3) [1.7, 40.5]
Complete response	2 (12.5)	0 (0)	2 (13.3)
Partial response	3 (18.8)	5 (35.7)	0 (0)
Stable disease	7 (43.8)	5 (35.7)	6 (40.0)
Progressive disease	4 (25.0)	4 (28.6)	4 (26.7)
Not evaluable/missing, n (%)	0 (0)	0 (0)	3 (20.0)
Disease control rate, n (%) [95% CI]	12 (75.0) [47.6, 92.7]	10 (71.4) [41.9, 91.6]	8 (53.3) [26.6, 78.7]
Duration of response, median (95% CI), months	4.5 (1.7, NE)	3.6 (1.9, NE)	-
Progression-free survival, median (95% CI), months	5.5 (2.0, 7.3)	4.5 (2.0, 6.2)	5.4 (1.8, 9.0)

Median follow-up of 9.4 months.
bid; twice daily; CCNE1, cyclin E1; CI, confidence interval; DOR, duration of response; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; qd, daily.

Best Percent Change in Target Lesions From Baseline

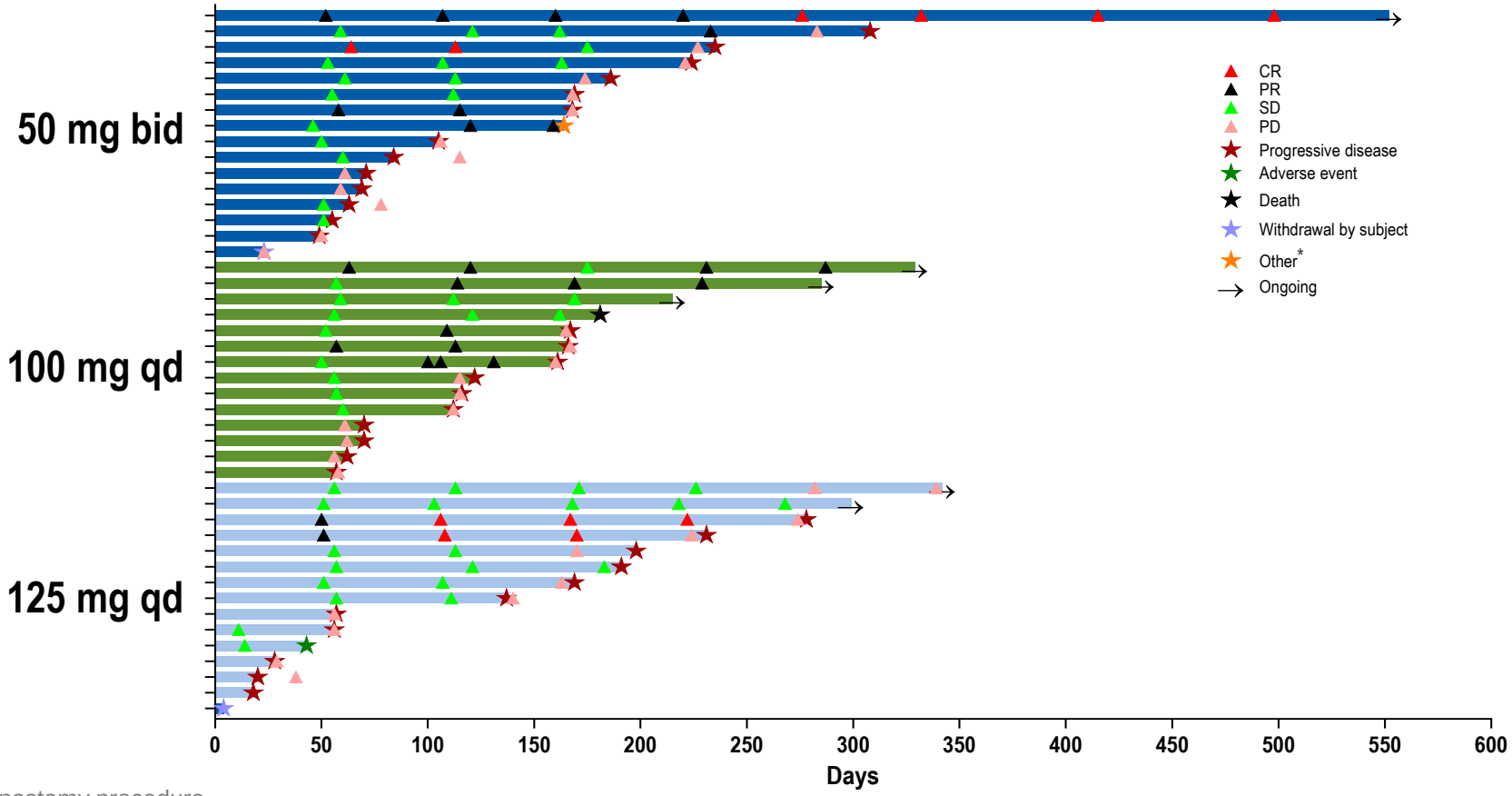
- Over 70% of patients had a reduction in tumor size compared with baseline



bid, twice daily; CR, complete response; PD, progressive disease; PR, partial response; qd, daily; SD, stable disease.

Duration of Treatment and Response

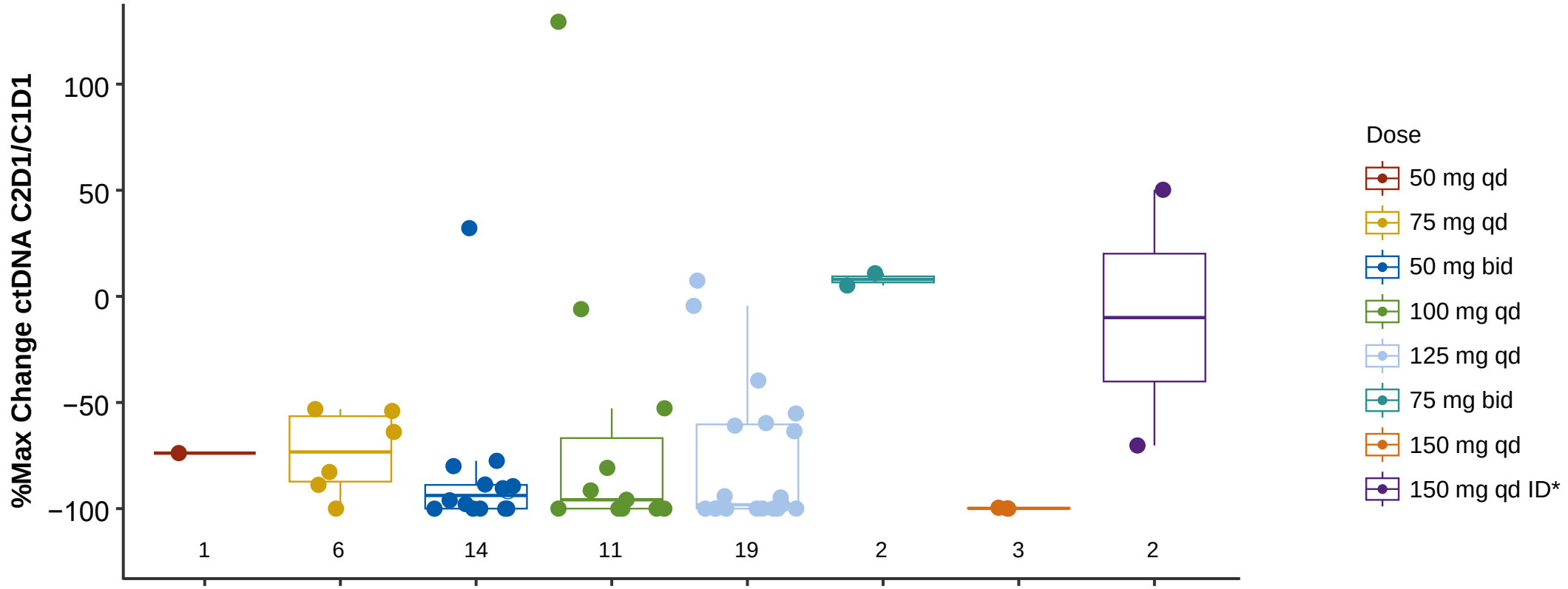
- Median duration of treatment (range) was 4.5 (0.1-18.1) months
- Median time to response (range) was 2.1 (1.6-7.7) months



*Sponsor decision after jejunostomy procedure.
bid, twice daily; CR, complete response; PD, progressive disease; PR, partial response; qd, daily; SD, stable disease.

Pharmacodynamics: ctDNA

- A decrease in ctDNA was observed on treatment (C2D1) compared with baseline (C1D1), consistent with the cell growth arrest mechanism of action of CDK2 inhibition



*5 days on/2 days off.
% max change in ctDNA determined by using PredicineSCORE™.
bid, twice daily; ctDNA, circulating tumor deoxyribonucleic acid; ID, intermittent dose; qd, daily.

Conclusions

- In patients with recurrent platinum-resistant or refractory ovarian cancer, single agent INCB123667 at the dose of 100 mg daily achieved
  - ORR of 33.3% (31.3% at 50 mg bid and 35.7% at 100 mg qd)
  - Median DOR of 3.6 months (4.5 months at 50 mg bid and 3.6 months at 100 mg qd)
  - Median PFS of 5.3 months (5.5 months at 50 mg bid and 4.5 months at 100 mg qd)
- All responders had cyclin E1 overexpression except 1 with unknown status
- INCB123667 showed manageable safety and tolerability
  - Most common TEAEs were hematologic and gastrointestinal, predominantly grade ≤2
  - Few (2.2%) patients discontinued due to TEAEs
- The observed safety, tolerability, and encouraging antitumor activity of single agent INCB123667 provides proof of concept and supports the advancement of INCB123667 into pivotal studies in patients with advanced or recurrent ovarian cancer

bid, twice daily; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival; qd, daily; TEAE, treatment-emergent adverse event.

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