Safety and Tolerability of INCB123667, a Selective CDK2 Inhibitor, in Patients With Advanced Solid Tumors: A Phase 1 Study

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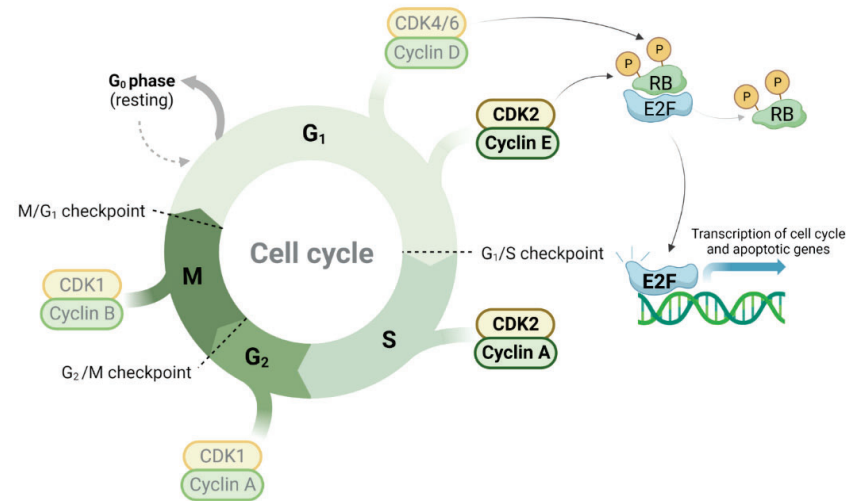
Abstract #5348

DECLARATION OF INTERESTS

- **Matteo Simonelli**: Consulting or Advisory Role – Bristol-Myers Squibb, GSK, Incyte, Sanofi, Servier

Introduction

- CDK2/cyclin E is crucial for cell cycle progression and DNA replication

- Cancer cells with *CCNE1* amplification/cyclin E1 overexpression are dependent on CDK2[1]

- *CCNE1* amplification and cyclin E1 overexpression are prevalent in multiple tumor types, including gynecologic malignancies,[2,3] and are associated with poor clinical outcomes[3]

  - In ovarian cancer, approximately 12% are *CCNE1* amplified[3] and 50% overexpress cyclin E1[2,4]

- INCB123667 is a highly selective CDK2 inhibitor that showed antitumor activity in preclinical models[5]
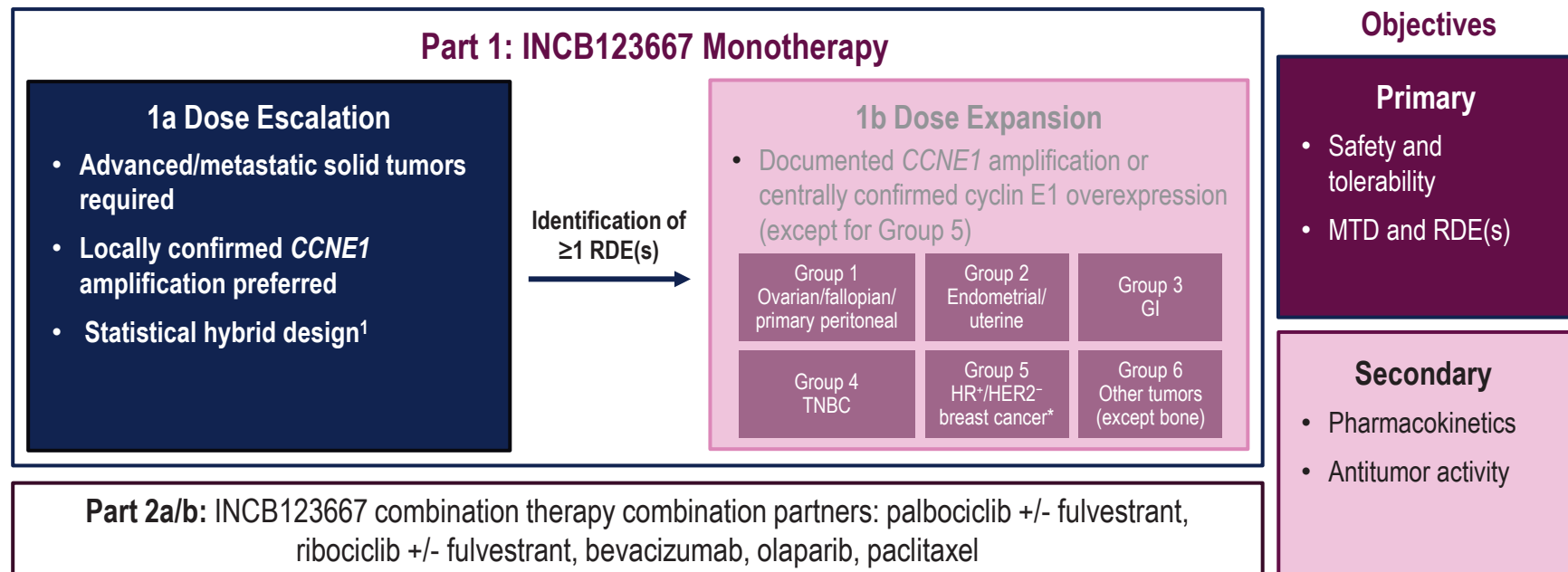
Role of CDK2/Cyclin E Complex in the Cell Cycle

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1. Etemadmoghadam D, et al. *Clin Cancer Res*. 2013;19(21):5960-5971. 2. Gorski JW et al. *Diagnostics (Basel)*. 2020;10(5):279. 3. Chan AM, et al. *J Pathol Clin Res*. 2020;6(4):252-262. 4. MSK-IMPACT panel data from AACR Genie v16 public database. 5. Chand S, et al. *Cancer Res*. 2023;83(7_Supplement):1143. CDK2, cyclin-dependent kinase 2; CCNE1, cyclin E1.

Study Design and Objectives

- Phase 1, open-label, multicenter study (NCT05238922)

Part 1: INCB123667 Monotherapy

1a Dose Escalation

- **Advanced/metastatic solid tumors required**
- **Locally confirmed *CCNE1* amplification preferred**
- **Statistical hybrid design[1]**

Identification of ≥1 RDE(s) →

1b Dose Expansion

- Documented *CCNE1* amplification or centrally confirmed cyclin E1 overexpression (except for Group 5)

Group 1 Ovarian/fallopian/ primary peritoneal	Group 2 Endometrial/ uterine	Group 3 GI
Group 4 TNBC	Group 5 HR+/HER2− breast cancer*	Group 6 Other tumors (except bone)

Part 2a/b: INCB123667 combination therapy combination partners: palbociclib +/- fulvestrant, ribociclib +/- fulvestrant, bevacizumab, olaparib, paclitaxel

Objectives

Primary

- Safety and tolerability
- MTD and RDE(s)

Secondary

- Pharmacokinetics
- Antitumor activity

*With progression on/intolerance of a CDK4/6 inhibitor.
1. Liao JJZ et al. *Int J Cancer.* 2022.1:151(9):1602-1610.
CCNE1, cyclin E1 gene; ECOG PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; MTD, maximum-tolerated dose; PO, orally; qd, once daily; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

Patient Disposition and Characteristics

- 7 dose levels were explored using qd and bid schedules and total daily dose ranging from 50 to 150 mg

- 61 patients (73%) discontinued treatment, most commonly due to disease progression (80%)

Part 1a Dose Escalation Patient Demographics and Clinical Characteristics

	Total (N=84)
Age, median (range), years	60 (18-77)
Female, n (%)	67 (79.8)
Race, n (%)	
White	60 (71.4)
Black	1 (1.2)
Asian	7 (8.3)
Not reported/unknown/missing	16 (19.0)
ECOG PS status, n (%)	
0	55 (65.5)
1	29 (34.5)
Cancer type	
Ovarian cancer	45 (53.6)
Breast cancer	10 (11.9)
GI malignancy	8 (9.5)
Endometrial cancer	3 (3.6)
Others	18 (21.4)
Number of prior lines of systemic therapy, median (range)	4 (1-15)

Data cutoff: July 15, 2024

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Safety Summary

- 82 patients (98%) experienced TEAEs
  - 2 patients (2.4%) discontinued INCB123667 due to TEAEs (vomiting and asthenia)
  - Less than 10% of patients had dose reduction due to TEAEs
  - A total daily dose up to 125 mg is well tolerated

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)	7 (36.8)	11 (44.0)	5 (83.3)	1 (25.0)	39 (46.4)
Serious TEAEs	2 (40.0)	4 (21.1)	2 (33.3)	2 (10.5)	7 (28.0)	1 (16.7)	1 (25.0)	19 (22.6)
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

Data cutoff: July 15, 2024
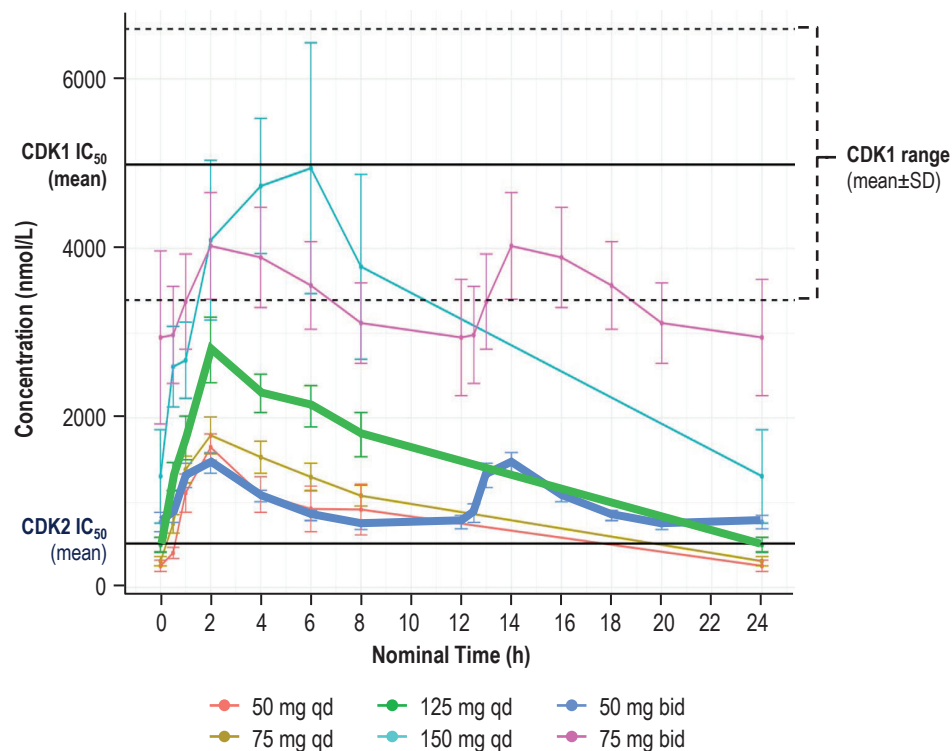
Most Common TRAEs

- The most common hematologic TRAEs were thrombocytopenia (35%), anemia (30%), and neutropenia (26%)

- The most common non-hematologic TRAEs were nausea (42%), fatigue (23%), and vomiting (17%)

- Grade ≥3 TRAEs occurred in 23 patients (27%), most commonly thrombocytopenia (13%), neutropenia (8%), and anemia (7%)

Part 1a Dose Escalation TRAEs

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 intermittent* (n=4)	Total (N=84)
Any-grade TRAEs	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 TRAEs	1 (20.0)	4 (21.1)	4 (66.7)	2 (10.5)	7 (28.0)	5 (83.3)	0	23 (27.4)

Data cutoff: July 15, 2024

Preliminary Pharmacokinetics/Pharmacodynamics Analyses

- Optimal exposure coverage of CDK2 inhibition was observed with 50 mg bid and 125 mg qd, while 75 mg bid and 150 mg qd reached CDK1 off-target range

- During Part 1a Dose Escalation, 39 out of 48 patients who had ctDNA measurements at C1D1 and C2D1 had reductions in ctDNA*

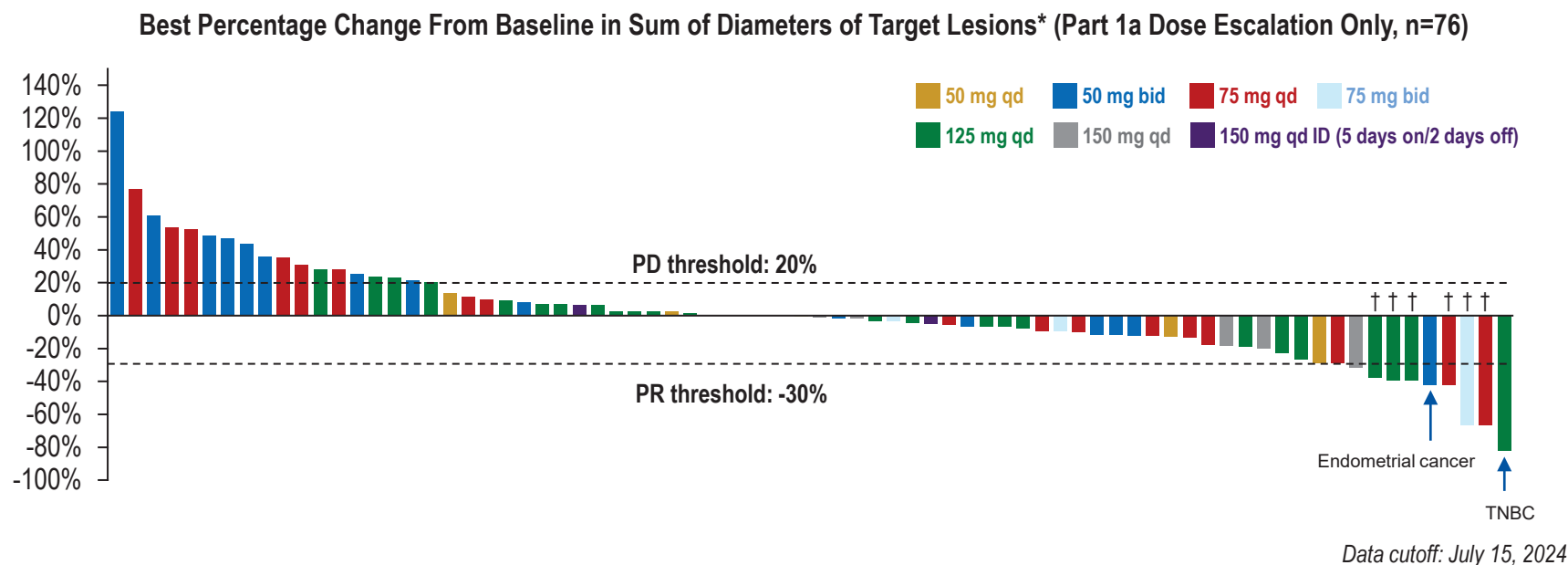 - Decreases in ctDNA were enriched in cyclin E IHC-positive patients

Note: C1D8 PK data were collected from 0-8 h for bid and from 0-24 h for qd. Pre-dose samples for bid were used again at the 12-h time point. For bid, data after the first dose were plotted between 0-12 h and then again from 12-24 h to replicate the profile after the second dose. 50 mg qd (n=5); 50 mg bid (n=19); 75 mg bid (n=6); 75 mg qd (n=19); 125 mg qd (n=20); 150 mg qd (n=5). Mean ± SD CDK2 IC_{50} = 570 ± 468 (n=66); Mean ± SD CDK1 IC_{50} = 5488 ± 1759 (n=6) (whole blood assay).
*Copy number burden estimated by PredicineSCORE™.
bid, twice daily; C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; CDK1, cyclin-dependent kinase 1; CDK2 cyclin-dependent kinase 2; ctDNA, circulating tumor DNA; IC_{50}, half-maximal inhibitory concentration; IHC, immunohistochemistry; qd, once daily; SD, standard deviation.
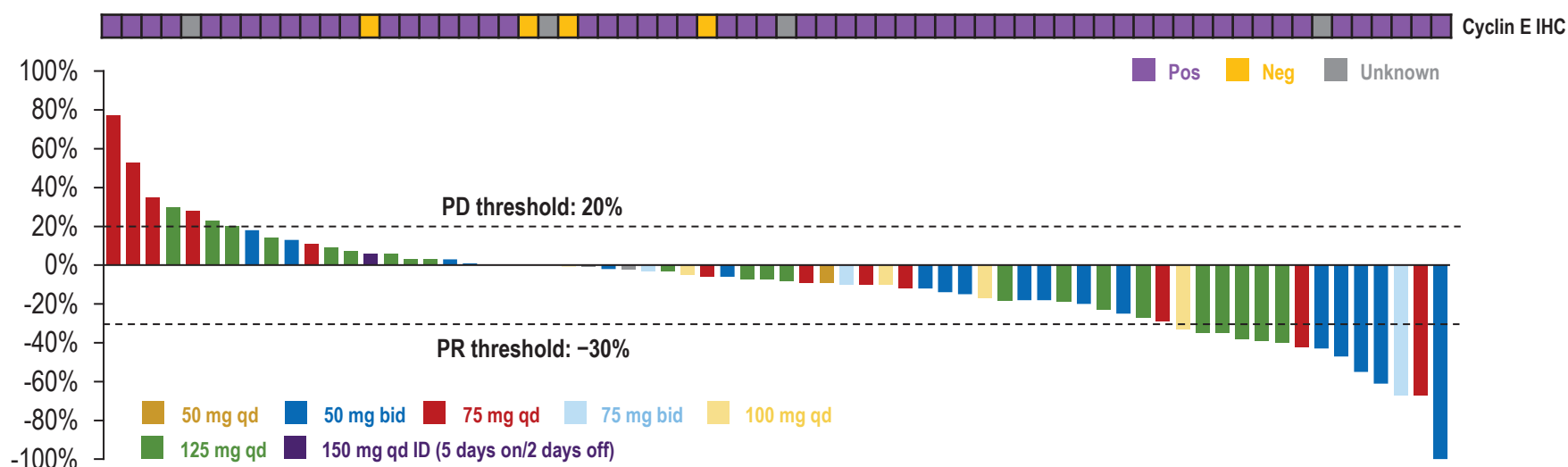
Preliminary Efficacy

- Of the 76 patients from **Part 1a Dose Escalation** who were evaluable for response per RECIST V1.1, 8 PRs were observed (ovarian cancer, n=6; endometrial and TNBC, n=1 each), 40 patients had SD

Best Percentage Change From Baseline in Sum of Diameters of Target Lesions* (Part 1a Dose Escalation Only, n=76)

Legend:
- 50 mg qd
- 50 mg bid
- 75 mg qd
- 75 mg bid
- 125 mg qd
- 150 mg qd
- 150 mg qd ID (5 days on/2 days off)

PD threshold: 20%

PR threshold: -30%

Endometrial cancer

TNBC

Data cutoff: July 15, 2024

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Preliminary Efficacy: Ovarian Cancer (Parts 1a & 1b)

- Of the 68 patients with **ovarian cancer from Parts 1a and 1b Dose Escalation and Expansion** who were evaluable for response per RECIST V1.1
  - 2 had CRs, 12 had PRs, and 38 had SD

Best Percentage Change From Baseline in Sum of Diameters of Target Lesions* (Ovarian Cancer Part 1a & 1b, n=68)

Cyclin E IHC

Pos   Neg   Unknown

PD threshold: 20%

PR threshold: −30%

50 mg qd   50 mg bid   75 mg qd   75 mg bid   100 mg qd
125 mg qd   150 mg qd ID (5 days on/2 days off)

Data cutoff: July 15, 2024

Conclusions

- The CDK2 inhibitor INCB123667 was generally well tolerated in patients with advanced/metastatic solid tumors up to a total daily dose of 125 mg

- The most common TRAEs were nausea, thrombocytopenia, and anemia

- Preliminary antitumor activity and decreases in ctDNA were observed across a range of doses and regimens, especially in ovarian cancer

- 50 mg bid and 125 mg qd doses showed good tolerability and were selected for ongoing expansion

- Evaluation of INCB123667 in combination therapy with selected anticancer therapies is ongoing

Acknowledgments

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presentation, scan code.