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Preliminary Efficacy of INCB123667 (CDK2 Inhibition) With Bevacizumab in Recurrent Epithelial Ovarian Cancer (rEOC)

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Disclosures

- **Lorusso:** Consultant – *Novartis, PharmaMar.* Advisory board and invited speaker – *AstraZeneca, Clovis Oncology, Corcept, Genmab, GSK, Immunogen, MSD, Seagen, Sutro.* Coordinator for ENGOT trial with institutional support – *Clovis Oncology, Corcept, Genmab, MSD, Immunogen*. Received grant for founding academic trial – *Clovis Oncology, GSK, MSD*

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Introduction

- The CDK2/Cyclin E1 complex is crucial for cell-cycle progression and DNA replication[1]
- Cyclin E1 overexpression identifies a poor prognostic subgroup of patients with OC who derive less benefit from SoC therapies and have a high unmet need for new treatments[2-7]
- INCB123667 is a novel, selective, oral small-molecule CDK2 inhibitor
- INCB123667 monotherapy (50 mg bid) demonstrated a manageable safety profile and an ORR of 31% in patients with PROC treated in an ongoing phase 1 study (NCT05238922)[8]
- Combination treatment with INCB123667 + bevacizumab in a *CCNE1*-amplified OC model resulted in enhanced inhibition of tumour growth compared with either agent alone[9]

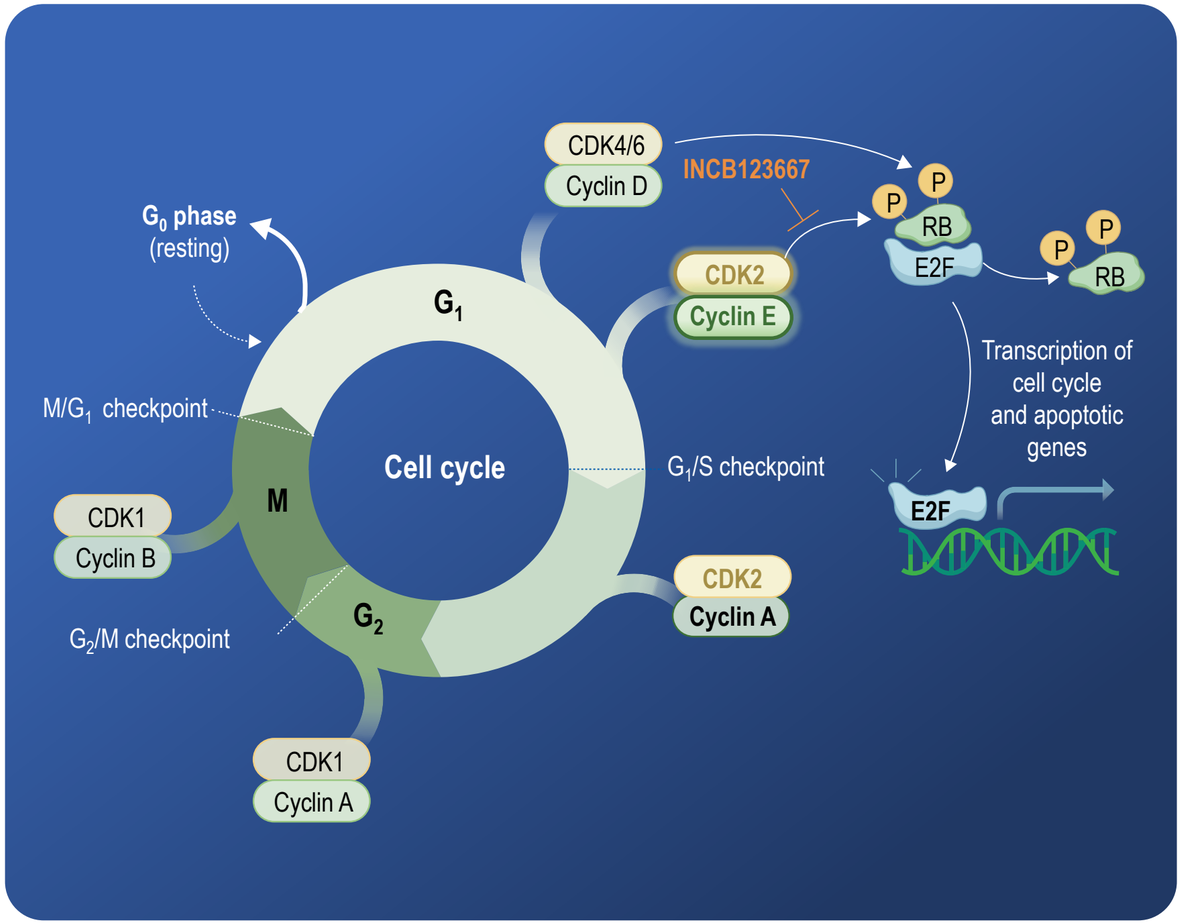


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bid, twice a day; CDK, cyclin-dependent kinase; OC, ovarian cancer; ORR, objective response rate; PROC, platinum-resistant or platinum-refractory ovarian cancer; RB, retinoblastoma protein; SoC, standard of care.

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Study Design

- INCB123667 is being evaluated in combination with anticancer therapies in a phase 1, open-label, multicentre, dose escalation and dose expansion study (NCT05238922) in patients with advanced solid tumours
- Here, we report preliminary phase 1 efficacy and safety data from patients with PROC who received INCB123667 + bevacizumab

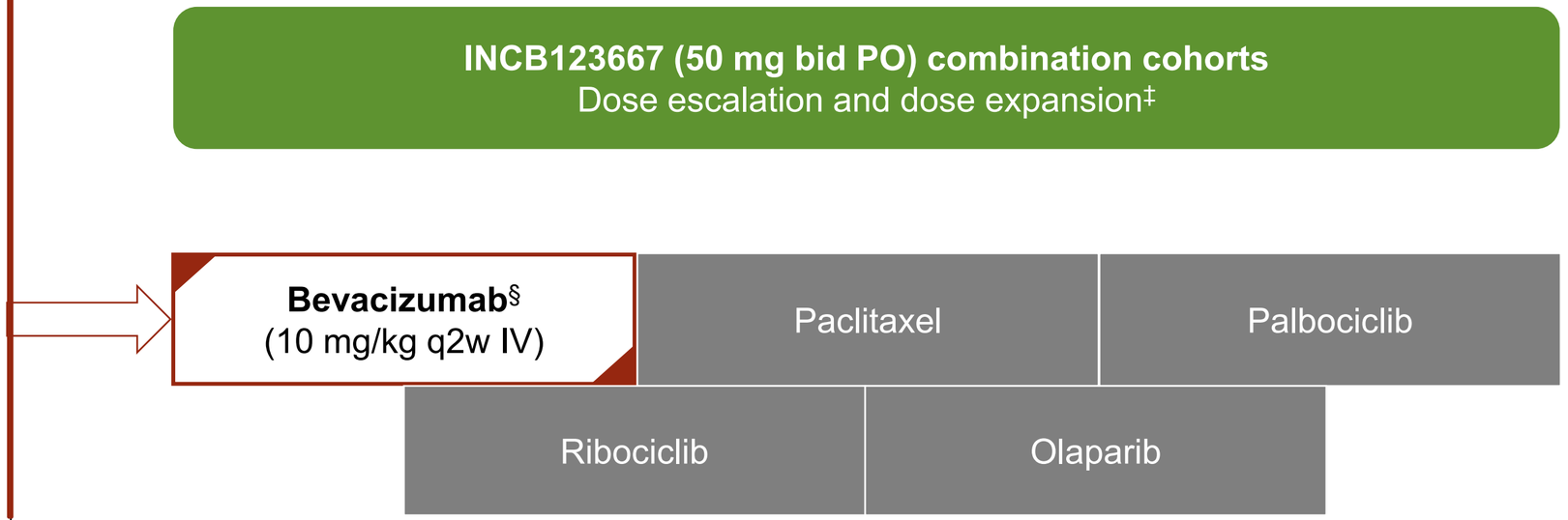
Key Eligibility Criteria

Dose Escalation
- Any advanced/metastatic solid tumour*
- Progressed on or ineligible/intolerant to SoC
- *CCNE1* amp not mandatory but preferred

Dose Expansion
- Advanced/metastatic epithelial ovarian, fallopian, or primary peritoneal carcinoma
- Prior first-line platinum-taxane chemotherapy
- *CCNE1* amp or cyclin E1 overexpression required†
- Number of prior lines of therapy was not limited

Primary Endpoints
- Safety and tolerability
- DLTs

Secondary Endpoints
- ORR, DCR, DOR
- PK



*Dose escalation tumours were HR+/HER2− breast cancer (regardless of *CCNE1* mutation/cyclin E1 overexpression status) or other solid tumours (documented *CCNE1* amp/cyclin E1 overexpression preferred but not mandatory). †*CCNE1* amp determined by a qualified local laboratory or cyclin E1 overexpression determined by central laboratory (CLIA assay). ‡Dose escalation started 1 dose level below the highest dose demonstrated to be safe in the monotherapy part of the study for INCB123667 combinations with bevacizumab, olaparib and paclitaxel, and 2 dose levels below the highest dose demonstrated to be safe for the monotherapy part of the study for INCB123667 combinations with palbociclib and ribociclib.[1] All patients with PROC were treated with INCB123667 50 mg bid + bevacizumab 10 mg/kg q2w IV in dose escalation/expansion. §Continuous 28-day cycles. Bevacizumab is administered until disease progression, unacceptable toxicity or 15 months of treatment have been received.

1. Lorusso D, et al. ESMO 2025. Presentation 974P.

amp, amplification; bid, twice a day; CLIA, chemiluminescent immunoassay; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; HR, hormone receptor; IV, intravenously; ORR, objective response rate; PK, pharmacokinetics; PO, orally; PROC, platinum-resistant or platinum-refractory ovarian cancer; q2w, every 2 weeks; SoC, standard of care.

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Baseline Disease Characteristics

	Total (N=23)
Patient and Disease Characteristics*	
Age, median (range), years	60 (45, 78)
ECOG PS, n (%)	
0	17 (73.9)
1	6 (26.1)
Tumour histology, n (%)	
Serous	18 (78.3)
High-grade serous	14/18 (77.8)
Clear cell	3 (13.0)
Mucinous	1 (4.3)
Carcinosarcoma	1 (4.3)
Primary platinum-free interval, n (%)	
<3 months	2 (8.7)
3-6 months	5 (21.7)
>6 months	16 (69.6)
Last platinum-free interval ≤6 months, n (%)	23 (100)

	Total (N=23)
Prior Therapies*	
Number of prior lines of therapy, n (%)	
1-2	8 (34.8)
3	5 (21.7)
≥4	10 (43.5)
Prior bevacizumab, n (%)	19 (82.6)
Prior PARPi, n (%)	15 (65.2)
PD during PARPi treatment	14/15 (93.3)
Biomarkers*	
Cyclin E1 overexpression,† n (%)	20 (87.0)
CCNE1 amplification‡	7/20 (35.0)
CCNE1 amplification not detected‡	13/20 (65.0)
Cyclin E1 expression unknown,§ n (%)	3 (13.0)
CCNE1 amplification‡	1/3 (33.3)
CCNE1 amplification not detected‡	2/3 (66.7)
HRD positive	7 (30.4)
BRCA mutation	7/7 (100)
HRD negative	5 (21.7)
HRD unknown	11 (47.8)

Data cutoff: July 30, 2026.

*Including patients with PROC who received INCB123667 50 mg bid orally + bevacizumab 10 mg/kg q2w intravenously in dose escalation (n=3) and dose expansion (n=20). †Data derived from NeoGenomics, August 24, 2026. ‡CCNE amplification status was based on a local test result (n=5) and where not available or not amplified locally, on the central test result using cell-free DNA. §Due to sample quantity not sufficient for analysis.

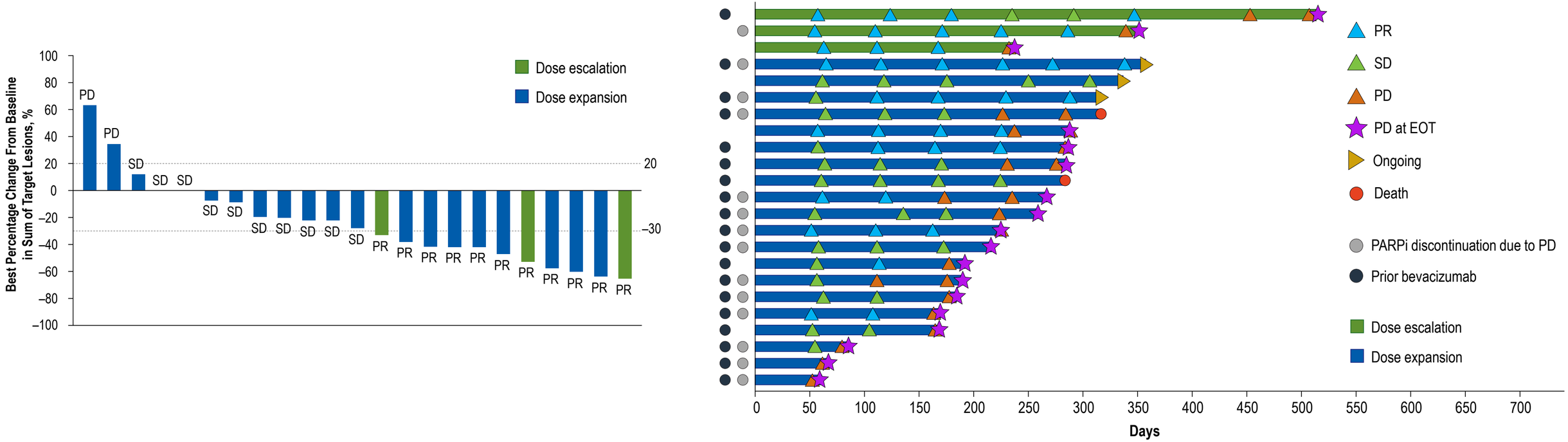
bid, twice a day; *BRCA*, breast cancer gene; ECOG PS, European Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; PROC, platinum-resistant or platinum-refractory ovarian cancer; q2w, every 2 weeks.

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Preliminary Efficacy in PROC

- Median follow-up was 7.4 months
- ORR 48% (95% CI: 27, 69); confirmed ORR 43% (95% CI: 23, 66) — 10 of 11 patients had a confirmed response
  - Prior PD with PARPi (n=14): ORR 43% (95% CI: 18, 71)
  - Prior bevacizumab (n=19): ORR 42% (95% CI: 20, 67); confirmed ORR 37% (95% CI: 16, 62)
- DCR 91% (95% CI: 72, 99)
- Median DOR 5.7 months (95% CI: 3.7, 9.4); median PFS 7.4 months (95% CI: 5.7, 9.3)



*Including RECIST-evaluable patients with PROC who received INCB123667 50 mg bid orally + bevacizumab 10 mg/kg q2w intravenously in dose escalation and dose expansion. RECIST-evaluable patients had a baseline scan and met at least 1 of the following criteria: ≥1 postbaseline scan, ≥63 days of treatment or study discontinuation.
bid, twice a day; CI, confidence interval; DCR, disease control rate; DOR, duration of response; EOT, end of treatment; ORR, objective response rate; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PR, partial response; PROC, platinum-resistant or platinum-refractory ovarian cancer; RECIST, Response Evaluation Criteria In Solid Tumours; SD, stable disease; q2w, every 2 weeks.

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Safety Outcomes

- The median (range) duration of exposure was 7.6 (1.9, 16.9) months for INCB123667 + bevacizumab
- Any-grade INCB123667-related TEAEs occurred in 23 (100%) patients
  - 18 (78%) had a bevacizumab-related TEAE
- Grade 3 treatment-related AEs occurred in 12 (52%) patients
- Grade 4 treatment-related AEs occurred in 1 patient (thrombocytopenia)
- Grade 5 TEAE occurred in 1 patient (sepsis, not considered to be related to treatment)
- SAEs occurred in 4 patients (17%) and were treatment-related in 1 patient (4%)
  - SAEs were colitis, constipation, intestinal obstruction*, sepsis, and small intestinal obstruction (n=1 each)
- No patients discontinued INCB123667 due to TEAEs
- 2 patients discontinued bevacizumab due to TEAEs (fistula and proteinuria, n=1 each)

Any-Grade TEAEs,† n (%)	Total (N=23)
Anaemia	16 (69.6)
Constipation	11 (47.8)
Neutropenia	11 (47.8)
Nausea	10 (43.5)
Hypertension	9 (39.1)
Thrombocytopenia	9 (39.1)
Abdominal pain	7 (30.4)
Leukopenia	7 (30.4)
Proteinuria	7 (30.4)
Vomiting	7 (30.4)
Arthralgia	6 (26.1)
Asthenia	6 (26.1)
Oedema, peripheral	6 (26.1)
Diarrhoea	5 (21.7)
Hypercholesterolaemia	5 (21.7)

Grade 3 TEAEs,‡ n (%)	Total (N=23)
Proteinuria	5 (21.7)
Intestinal obstruction	3 (13.0)
Neutropenia	3 (13.0)
Asthenia	2 (8.7)
Fatigue	2 (8.7)
GGT increased	2 (8.7)
Leukopenia	2 (8.7)

†Occurring in ≥5 patients.
‡Other grade 3 TEAEs occurring in 1 patient: abdominal pain, anaemia, blood alkaline phosphatase increased, colitis, constipation, diarrhoea, hyperamylasaemia, hyperbilirubinaemia, hypercholesterolaemia, hyperlipasaemia, hypertension, hypertriglyceridaemia, hypoalbuminaemia, hypokalaemia, hyponatraemia, nausea, oedema peripheral, pain in extremity, peripheral sensory neuropathy, sepsis, small intestinal obstruction, thrombocytopenia, vomiting.

*Related to INCB123667.
AE, adverse event; GGT, gamma-glutamyltransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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Conclusions

- INCB123667, a novel, selective, oral small-molecule CDK2 inhibitor, in combination with bevacizumab showed promising antitumour activity in heavily pretreated patients with PROC and cyclin E1-overexpression
  - Preliminary results report an ORR of 48%, a DCR of 91%, a median DOR of 5.7 months, and a median PFS of 7.4 months
- INCB123667 + bevacizumab was well tolerated and TEAEs were manageable
  - The most common TEAEs were anaemia (70%), constipation (48%) and neutropenia (48%), which were mostly low grade
  - No patients discontinued INCB123667 due to TEAEs; 2 patients discontinued bevacizumab
- A phase 3 study of INCB123667 + bevacizumab vs bevacizumab alone as first-line maintenance therapy in patients with EOC with cyclin E1 overexpression will commence in 2026 (MAESTRA3; NCT07797283)

DCR, disease control rate; DOR, duration of response; EOC, epithelial ovarian cancer; ORR, objective response rate; PFS, progression-free survival; PROC, platinum-resistant or platinum-refractory ovarian cancer; TEAE, treatment-emergent adverse event.

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