Preliminary Clinical Data from Ongoing Phase II Study with Enhancer of Zeste Homolog 2 (EZH2) Inhibitor CPI-0209 in Patients with Advanced Solid Tumors or Hematologic Malignancies

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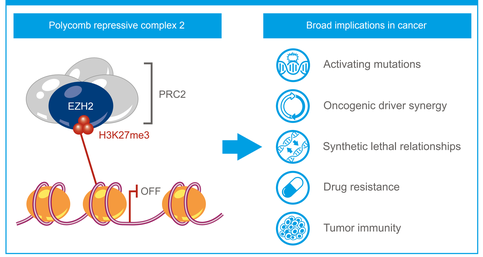
Background

- The histone methyltransferase enhancer of zeste homolog 2 (EZH2) is the enzymatic catalytic subunit of the polycomb repressive complex 2 (PRC2) that alters gene expression via trimethylation of lysine 27 on histone 3 (H3K27me3)[1–3] (**Figure 1**)
- Emerging evidence suggests that EZH2 is overexpressed in many cancer types and has a pivotal role in disease progression[1–3]

Figure 1. EZH2 function and potential role in tumorigenesis



EZH2, enhancer of zeste homolog 2; H3K27me3, trimethylation of histone H3 lysine 27; PRC2, polycomb repressive complex 2.

- Moreover, tumors that harbor mutations in epigenetic genes, such as *ARID1A* and *BAP1*, appear to be highly sensitive to EZH2 inhibition[1]
- CPI-0209 is a second-generation, oral, small molecule, selective inhibitor of EZH2 and EZH1 that has demonstrated extended on-target residence time with increased potency compared with first-generation EZH2 inhibitors in preclinical studies[4,5]
  - It has shown significant antitumor effects with a dose-dependent decrease in tumor H3K27me3 levels
  - Increased activity was observed in *ARID1A* mutant models of bladder, endometrial and ovarian cancer models treated with CPI-0209
- The Phase I dose-escalation part of the ongoing Phase I/II study (NCT04104776), which is evaluating CPI-0209 in advanced solid tumors and lymphomas, selected a recommended Phase II dose (RP2D) of 350 mg (ASCO 2021[5], also see updated results in poster PB068[6] at this congress)

Objective

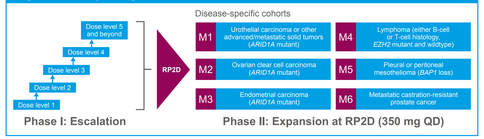
- To report preliminary results from the ongoing Phase II expansion study, which aims to evaluate the antitumor activity and safety of CPI-0209 as monotherapy across multiple tumor types

Methods

Study design

- The Phase II part comprises treatment with CPI-0209 at the RP2D in six disease-specific cohorts (**Figure 2**)
- Patients in Cohorts M1, M2, M3, M5, and M6 will be enrolled at 10 to 29 patients per cohort, using a Simon 2-stage design
  - Extension from stage 1 (n=10) to stage 2 (plus n=19) enrollment requires at least one confirmed partial response (PR) or complete response (CR) in stage 1
- Cohort M4 will enroll 10 patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) and 10 patients with diffuse large B cell lymphoma (DLBCL), including at least five patients with documented germinal-center B-cell-like DLBCL (GCB-DLBCL) with at least one EZH2 hotspot mutation
- Patients will receive CPI-0209 350 mg orally QD continuously in 4-week cycles (28 days) and be monitored for hematological adverse events with complete blood count checks on C1D10, C1D15, and C1D22

Figure 2. Study design



EZH2, enhancer of zeste homolog 2; QD, once daily; RP2D, recommended Phase II dose (as monotherapy).

Eligibility criteria

Key inclusion criteria

- All eligible patients are aged ≥18 years with a life expectancy of ≥12 weeks, ECOG PS 0–1, and adequate bone marrow, renal, and liver function
- Patients in the M1, M2, M3, and M5 cohorts have histologically or cytologically confirmed progressive tumors with known *ARID1A* mutation/BAP1 loss and measurable as per RECIST 1.1 criteria
- Patients in the M2 and M3 cohort include those who received ≥1 line of platinum-based chemotherapy and had progressive disease on other standard-of-care treatments
- The M4 cohort includes patients ineligible for hematopoietic cell transplantation, with refractory/relapsed or progressive PTCL or DLBCL
  - In PTCL, patients had neither CR after first-line therapy nor PR after second-line therapy or beyond
  - In DLBCL, patients had relapsed or refractory disease with ≥2 prior therapy lines, and were not considered candidates to receive chimeric antigen receptor-T cell (CAR-T) therapy
- Patients in the M6 cohort had metastatic disease with progression during prior therapies (at least one androgen receptor signaling inhibitor and at least one taxane-based therapy; patients known to possess a homologous recombination repair (HRR) mutation must have been treated with prior PARP inhibitor therapy), and baseline testosterone ≤50 ng/dL (≤2.0 nM) with surgical or ongoing medical castration maintained

Key exclusion criteria

- Patients with various known medical conditions, prior allogeneic hematopoietic cell transplant or various anticancer treatments within applicable timeframes prior to study treatment were excluded

Table 1. Key study objectives and endpoint

Objectives	Study endpoints
Primary	
Antitumor activity of CPI-0209	ORR (CR+PR) as assessed by the investigator according to: • RECIST 1.1 for solid tumors including peritoneal mesothelioma • 2014 Lugano criteria for lymphoma • modified RECIST 1.1 for pleural mesothelioma • PCWG3 criteria for prostate cancer
Secondary	
Safety, tolerability and preliminary efficacy of CPI-0209	• OS • PFS, DoR, and TTR • AEs and changes in laboratory values • DCR (best overall response of CR, PR, or SD) • ORR per GCIG-defined CA-125 response criteria (ovarian cancer)
PK/PD profile of CPI-0209*	PK and PD parameters
Exploratory	
Characterization of PD biomarkers to explore the association with PK, safety, and response*	Changes in H3K27me3 levels*
Identification of cancer-associated mutations, genetic alterations, or protein- or RNA-based signatures	• RNA- and/or protein-based changes* • Genomic, immunophenotypic, transcriptomic, proteomic, other molecular features, and tumor biopsies at baseline and on treatment
Evaluation of NCI (PRO-CTCAE) patient-reported outcomes	• PRO version of PRO-CTCAE questionnaire

*Characterization in tumor and/or peripheral tissues.
AE, adverse event; GCIG, Gynecologic Cancer Intergroup; CR, complete response; DCR, disease control rate; DoR, duration of response; H3K27me3, trimethylation of histone H3 lysine 27; NCI (PRO-CTCAE), National Cancer Institute Patient Reported Outcome-Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PRO, patient-reported outcome; SD, stable disease; TTR, time to response.

- Additional exclusion criteria for the M6 cohort include:
  - Bone-only disease without nodal disease and no evidence of visceral spread
  - Prior treatment with first-generation androgen receptor antagonists ≤4 weeks of study treatment, 5α reductase inhibitors, ketoconazole, estrogens, or progesterones ≤2 weeks of study treatment

Study endpoints

- Objectives and key endpoints for the Phase II expansion part of the study are shown in **Table 1**

Results

Patients

- As of 16 July 2022, 52 patients were enrolled in the Phase II expansion study
  - 51 patients (98%) received at least one dose of study drug (safety analysis set) **(Table 2)**
  - 34 patients (65%) received at least one dose of study drug and had at least one post-baseline tumor assessment (efficacy evaluable patients)
  - No cohort had yet completed stage 1 of the 2-stage design

Table 2. Baseline demographics and disease characteristics (safety analysis set)

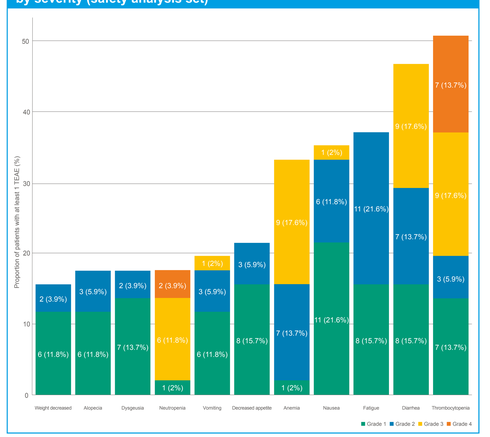
Total (N)	51
Age in years, mean (SD)	64.8 (11.25)
Sex	
Male/female, n (%)	28 (55)/23 (45)
Race and ethnicity*	
White	44 (86)
Black or African American	2 (4)
Asian	2 (4)
Hispanic or Latino	2 (4)
Other/not reported	3 (6)
Time in years since initial diagnosis, mean (SD)	4.2 (3.55)
Median follow-up, months (95% CI)	3.48 (2.1, NE)
Cohort, n (%)	
M1: Urothelial carcinoma or other advanced metastatic solid tumor (*ARID1A* mutant)	5 (10)
M2: Ovarian clear cell carcinoma (*ARID1A* mutant)	10 (20)
M3: Endometrial carcinoma (*ARID1A* mutant)	5 (10)
M4: Lymphoma (either B-cell or T-cell histology, EZH2 mutant and wildtype)	11 (22)
M5: Pleural or peritoneal mesothelioma (*BAP1* loss)	10 (20)
M6: Metastatic castration-resistant prostate cancer	10 (20)
Prior lines of therapies, n (%)	
1	12 (24)
2	13 (25)
3	8 (16)
>3	18 (35)

Date of data-cut: July 16, 2022. *More than one category possible per patient.
CI, confidence interval; EZH2, enhancer of zeste homolog 2; SD, standard deviation.

Safety

- The majority of the most frequently reported treatment-emergent adverse events (TEAEs) were Grade 1 or 2; Grade 3 or higher events were cytopenias, diarrhea, vomiting and nausea **(Figure 3)**
- 42 patients (82.4%) experienced at least one TEAE assessed by the investigator as possibly related to CPI-0209
  - TEAEs considered possibly related to CPI-0209 in ≥15% of patients were thrombocytopenia (47.1%), diarrhea (37.3%), nausea (29.4%), anemia (27.5%), fatigue (25.5%), neutropenia (17.6%), dysgeusia (17.6%), alopecia (15.7%), and vomiting (15.7%)
- 18 patients (35.3%) experienced at least one serious TEAE
  - Serious TEAEs reported in ≥2 patients were thrombocytopenia (7.8%), diarrhea (5.9%), respiratory failure (3.9%), and anemia (3.9%)
  - Serious AEs considered by the sponsor to be related to CPI-0209 were thrombocytopenia (7.8%), anemia (3.9%), and diarrhea (3.9%)
- One patient (2.0%) experienced a Grade 5 TEAE of respiratory failure, not attributed to CPI-0209; four other deaths were reported (two patients in M2, and one each in M4 and M5), all due to progressive disease and not attributed to CPI-0209

Figure 3. Most frequently reported TEAEs (occurring in ≥15% of patients) by severity (safety analysis set)



Date of data-cut: July 16, 2022.
TEAE, treatment-emergent adverse event.

- 16 patients (31.4%) reported TEAEs leading to CPI-0209 dose reduction
  - Thrombocytopenia (17.6%), anemia (11.8%), and diarrhea (5.9%) were reported in ≥2 patients
- 33 patients (64.7%) reported TEAEs leading to CPI-0209 dose interruptions
  - Reported in ≥2 patients: thrombocytopenia (27.5%), diarrhea (19.6%), anemia (13.7%), neutropenia (7.8%), nausea (5.9%), fatigue (3.9%), weight decreased (3.9%), and decreased appetite (3.9%)
- Seven patients (13.7%) reported TEAEs leading to CPI-0209 discontinuation
  - Respiratory failure (3.9%), anemia, thrombocytopenia, diarrhea, nausea, upper gastrointestinal hemorrhage, vomiting, fatigue, rash pustular, and pleuritic pain (2.0% each)

Efficacy

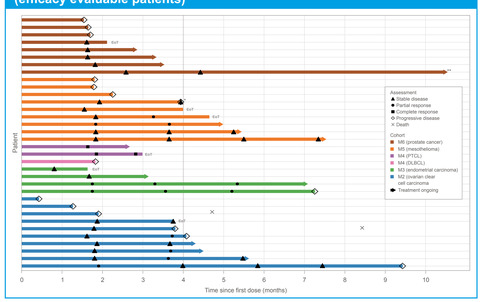
- Treatment duration and response assessment by cancer cohort per patient with at least one post-baseline tumor assessment (efficacy evaluable patients) are shown in **Figure 4**
- Preliminary responses observed by the data cut-off date of July 16, 2022 are shown in **Table 3**
- Updated observations based on preliminary data (as of September 15, 2022) occurring after the data cut-off date (July 16, 2022):
  - One confirmed PR in the M2 cohort (confirmatory assessment of previously unconfirmed PR)
  - One confirmed CR in the M3 cohort (updated classification from previously PR)

Table 3. Best unconfirmed response by cancer cohort

Category, n (%)	Urothelial* (M1) (N=5)	Ovarian (M2) (N=10)	Endometrial (M3) (N=5)	Lymphoma (M4) (N=11)	Mesothelioma (M5) (N=10)	Prostate (M6) (N=10)	Overall total Phase II (N=51)
Efficacy evaluable	0	10 (100)	4 (80.0)	3 (27.3)	9 (90.0)	8 (80.0)	34 (66.7)
Complete response	0	0	0	2 (66.7)	0	0	2 (5.9)
Partial response	0	4 (40.0)	2† (40.0)	0	2 (22.2)	0	8 (23.5)
Stable disease	0	3 (30.0)	2 (40.0)	0	4 (44.4)	5 (62.5)	14 (41.2)
Progressive disease	0	3 (30.0)	0	1 (33.3)	3 (33.3)	3 (37.5)	10 (29.4)

Date of data-cut: July 16, 2022.
*Or other advanced metastatic *ARID1A* mutant solid tumor; †One partial response in M3 cohort was later updated to complete response.

Figure 4. Treatment duration and response assessment by cancer cohort (efficacy evaluable patients)



Date of data-cut: July 16, 2022. One partial response in M3 cohort was later updated to complete response.
*At the time of the data-cut, the study site had entered both SD and PD, but has subsequently reclassified the visit assessment to SD.
**At the time of the data cut, after completion of 5 treatment cycles, patient was discontinued from the treatment but not yet captured in the case report form.
EoT, end of treatment.

Summary

- The safety profile of CPI-0209 is consistent with the known mechanism of action of EZH2 inhibition, preclinical toxicology and Phase I observations for this compound
- These preliminary data in heavily pre-treated patients with multiple tumor types, including those with *ARID1A* alterations or *BAP1* loss, support ongoing investigation of CPI-0209 treatment
- Recruitment and data generation are ongoing
  - Following the confirmed PR observed in each of the ovarian clear cell (M2), endometrial (M3), and mesothelioma (M5) cohorts, these cohorts are eligible for stage 2 expansion

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Disclosures

CPI-0209 is an investigational new drug and has not been approved by any regulatory authority.

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