Updated Findings and Biomarker Analysis from the Ongoing Phase I Study of Enhancer of Zeste Homolog 2 (EZH2) Inhibitor CPI-0209 in Patients with Advanced Solid Tumors

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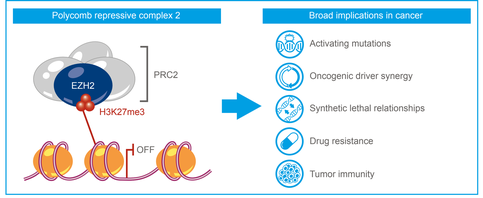
Background

- Enhancer of zeste homolog 2 (EZH2), an enzymatic catalytic subunit of polycomb repressive complex 2 (PRC2), mediates gene expression via trimethylation of lysine 27 in histone H3 (H3K27me3)[1]
  - EZH2 also regulates gene expression through PRC2-dependent non-histone protein methylation and PRC2-independent gene transactivation[1]
- Various EZH2-related oncogenic mechanisms are important in cancer development[1] **(Figure 1)**
- Preclinical models have shown that tumors harboring *ARID1A* and *BAP1* mutations are likely to be sensitive to EZH2 inhibition, suggesting that EZH2 may be a promising target for cancer treatment[2–4]

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.

- CPI-0209 is a second-generation, oral, small molecule, selective inhibitor of EZH2 and EZH1 that has demonstrated a significant reduction in global H3K27me3 levels and tumor growth inhibition in several preclinical models[5]
- CPI-0209 has a longer residence time than first-generation EZH2 inhibitors, contributing to its increased potency in preclinical assays[5]
- This ongoing Phase I/II open-label study (NCT04104776) is investigating the safety, tolerability, and clinical activity of CPI-0209 in patients with multiple types of advanced solid tumors or hematologic malignancies
  - A recommended Phase II dose of CPI-0209 as monotherapy was chosen as 350 mg once daily (QD), as previously reported[6] (primary objective of the Phase I dose-escalation part of the study)

Objective

- To provide updated results for the secondary objectives of the Phase I study, which were to determine the safety, tolerability and preliminary clinical activity of CPI-0209 as monotherapy in patients with advanced tumors

Methods

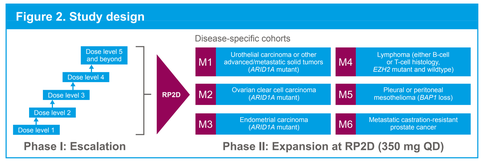
Study design

- Six clinical sites in the US enrolled patients for Phase I, with a planned treatment duration of 3–6 months and an 18-month enrollment period
- The maximum tolerated dose (MTD) of CPI-0209 was determined using a 3+3 dose escalation design **(Figure 2)**

Dosing and dose escalation

- Patients received oral CPI-0209 QD in continuous 4-week (28-day) cycles with a starting dose of 50 mg
- The CPI-0209 dose was escalated between dose levels by ≤100% unless at least one treatment-related Grade 2 adverse event (AE) occurred, after which the dose was escalated by ≤40%
- If one dose-limiting toxicity (DLT) was reported, an additional three patients were enrolled at that dose; one additional DLT at that level would define it as the non-tolerated dose
- The MTD was defined as the dose level immediately below the non-tolerated dose
- No intra-patient dose escalation was allowed

Figure 2. Study design



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

Eligibility criteria

- Eligible patients were aged ≥18 years with histologically or cytologically confirmed locally advanced (unresectable) or metastatic tumors (solid tumors or lymphoma), with one of the following:
  - Prior relapse after or progression through standard therapy
  - Disease with no standard effective therapy
- Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–1
- Those with prior allogeneic hematopoietic cell transplant or various anticancer treatments within applicable timeframes prior to study treatment, uncontrolled active or chronic infections, concurrent malignancies, suspected active or known history of pneumonitis or interstitial lung disease, or cardiovascular disease were excluded

Study endpoints

- The primary endpoint was the assessment of DLTs
- Secondary endpoints included the assessment of AEs (CTCAE classification), pharmacokinetic and pharmacodynamic parameters, objective response rate, progression-free survival, duration of response, disease control rate (DCR; the proportion of patients with a best overall response of complete response, partial response [PR], or stable disease), and time to response
- Exploratory endpoints included characterization of pharmacodynamic biomarkers to explore the association with pharmacokinetics, safety, and response, changes in H3K27me3 levels in tumor or peripheral tissues, and identification of cancer-associated mutations, genetic alterations, or protein- or RNA-based signatures in tumor biopsies at baseline and during treatment

Results

Patients

- As of July 16, 2022, 41 patients had been enrolled in the Phase I study and comprised the safety analysis set **(Table 1)**

Table 1. Patient disposition

	N (%)
Enrolled	41 (100)
Treated	41 (100)
Ongoing	1 (2.4)
Discontinued	40 (97.6)
Reason for treatment discontinuation	
Progressive disease	34 (82.9)
Death	3 (7.3)
Adverse event	3 (7.3)
Median follow-up, months (95% CI)	2.07 (1.84–3.58)
Analysis set	N (%)
Safety analysis set	41 (100)
Efficacy analysis set*	39 (95.1)
CPI-0209 dose	N (%)
50 mg	4 (9.8)
100 mg	6 (14.6)
137.5 mg	6 (14.6)
187.5 mg	6 (14.6)
225 mg	7 (17.1)
275 mg	4 (9.8)
375 mg	8 (19.5)
Total	41 (100)

*Two patients (on 375 mg) had no post-baseline tumor assessment. The safety analysis set is defined as all patients who received any amount of the study drug. The efficacy analysis set is defined as all patients who received the study drug and had at least one post-baseline tumor assessment.
CI, confidence interval.

- The mean age of enrolled patients was 63.9 years, 24 (59%) were female, and 28 (68%) were treated with ≥3 prior lines of therapy **(Table 2)**

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

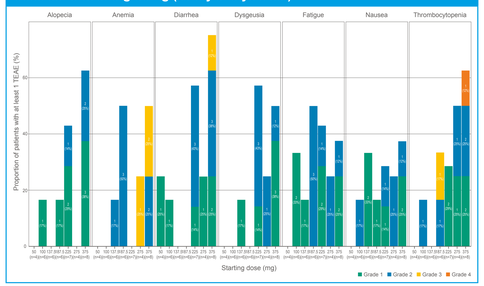
Total, N (%)	41 (100)
Age in years, mean (SD)	63.9 (10.9)
Sex	
Male/female, n (%)	17 (41)/24 (59)
Time in years since initial diagnosis, mean (SD)	5.1 (5.44)
Cancer type, n (%)	
Mesothelioma	6 (15)
Pancreatic cancer	6 (15)
Ovarian cancer	5 (12)
Breast cancer	5 (12)
Colon cancer	5 (12)
Endometrial cancer	2 (5)
Leiomyosarcoma	2 (5)
Other*	10 (24)
Prior lines of therapy, n (%)	
1	4 (10)
2	9 (22)
3	12 (29)
>3	16 (39)

*Other cancer includes bladder cancer, clear cell adenocarcinoma, dedifferentiated carcinoma, cholangiocarcinoma, urethral adenocarcinoma, high-grade carcinoma, gastric cancer, melanoma, prostate cancer, and tonsil carcinoma.

Safety

- One DLT (Grade 4 thrombocytopenia) was experienced by a patient in the 375 mg dose cohort; further dose escalation was not considered for the selection of the RP2D, based on available PK data and observed dose-dependent thrombocytopenia events. Formal MTD was not reached
- 39/41 patients (95.1%) reported at least one treatment-emergent adverse event (TEAE), while 19 patients (46.3%) reported at least one Grade ≥3 TEAE
- The most frequently reported TEAEs (≥15% of patients) by dose cohorts and grading are shown in Figure 3. Most of these events were Grade 1 or 2; Grade ≥3 events were cytopenia, diarrhea, and nausea

Figure 3. TEAEs occurring in ≥15% of the patients in the overall population by dose cohorts and grading (safety analysis set)



Data cut-off date July 16, 2022
TEAE, treatment-emergent adverse event.

- 30/41 patients (73.2%) experienced TEAEs considered possibly related to CPI-0209 by the investigator, with at least one Grade ≥3 TEAE in five patients (12.2%): 1/6 (16.7%) in the 187.5 mg dose cohort and 4/8 (50.0%) in the 375 mg cohort
- The most common (≥10% of patients) hematologic TEAEs considered possibly related to CPI-0209 were thrombocytopenia (29.3%, Grade ≥3: 4.9%) and anemia (12.2%, Grade ≥3: 4.9%). The most common non-hematologic TEAEs considered possibly related were diarrhea (31.7%, Grade ≥3: 2.4%), fatigue (26.8%, Grade ≥ 3: 0%), nausea (24.4%, Grade ≥3: 2.4%), dysgeusia (24.4%, Grade ≥3: 0%), alopecia (22.0%, Grade ≥3: 0%)
- 13/41 patients (31.7%) had dose modifications (drug interruption or dose reduction) due to TEAEs
- 6/41 patients (14.6%) discontinued due to TEAEs, and three of these events were considered possibly related to CPI-0209 by the investigator (dysgeusia in one and hemolysis in two patients)
- 15/41 patients (36.6%) experienced at least one serious TEAE, of whom three patients (7.3%, all in the 375 mg cohort) had at least one serious TEAE considered possibly related to treatment (anemia in two patients and hemolysis in one patient)
- 3/41 patients (7.3%) experienced Grade 4 TEAEs, including the DLT experienced by one patient in the 375 mg dose cohort (Grade 4 thrombocytopenia). One patient in the 137.5 mg cohort and one in the 275 mg cohort had lipase increase and lung infection, respectively, which were assessed as being unrelated to the study drug
- One patient in the 375 mg cohort had a Grade 5 fatal event, considered unrelated to CPI-0209

Molecular diagnosis and biomarkers

- At study entry, 15 patients had *ARID1A* alterations; these were detected based on local or central tissue next-generation sequencing (NGS), or central cell-free (cf) DNA NGS **(Table 4)**
  - 10 patients had *ARID1A* mutations detected by cfDNA
  - 12 patients had *ARID1A* alterations identified by either local or central tissue NGS

Table 4. *ARID1A* mutations detected by NGS analysis in cfDNA or tumor tissue

Dose (mg)	Primary diagnosis	Local tissue NGS	Central tissue NGS	Central cfDNA NGS	Central IHC H-score
50	Colon cancer	Unknown	Unknown	p.Q594Sfs*25	97
50	Colon cancer	Unknown	Unknown	p.P111S	250
100	Cholangiocarcinoma	T1150fs*11	p.T1150Pfs*11	p.T1150Pfs*11	0
137.5	Breast cancer	Unknown	p.490L	p.490L	215
137.5	Gastric cancer	S11fs*91	ND	ND	130
225	Bladder cancer	Unknown	p.H1858Pfs*25	ND	270
225	Mesothelioma	p.R1323C	p.R1323C	p.R1323C	90
225	Ovarian cancer	Q2115*	p.Q2115*	p.Q2115*	60
225	Ovarian cancer	T118fs*275	Unknown	p.T118Rfs*275	Unknown
225	Recurrent clear endometrial cancer	N1216fs	ND	p.D1219Hfs*4	210
275	Clear cell ovarian cancer	Q546fs	Unknown	ND	Unknown
275	Pancreatic cancer	Unknown	ND	DEL	160
375	Endometrial cancer†	*ARID1A* mutant (no detail)	p.A162Rfs*238	ND	70
375	Ovarian cancer	*ARID1A* mutant (no detail)	p.Y1233Lfs*4	p.Y1233Lfs*4	105
375	Clear cell ovarian cancer	*ARID1A* mutant (no detail)	Unknown	ND	13

†This patient experienced a partial response; see efficacy results.
DEL, deletion; IHC, immunohistochemistry; ND, *ARID1A* mutation not detected; NGS, next-generation sequencing; Unknown, assay unable to be carried out due to insufficient sample or poor sample quality.

- All patients with mesothelioma had *BAP1* alteration/loss detected by local tissue NGS and immunohistochemistry (IHC) or central NGS/IHC **(Table 5)**

Table 5. *BAP1* mutations detected by NGS analysis in cfDNA or tumor tissue

Dose (mg)	Primary diagnosis	Local tissue NGS & IHC	Central tissue NGS	Central cfDNA NGS	Central IHC H-score
100	Mesothelioma	Unknown	ND	ND	45
187.5	Mesothelioma	**NGS:** ND	ND	ND	140
225	Mesothelioma†	**NGS:** *BAP1* loss + DEL **IHC:** loss	ND	ND	1
225	Mesothelioma	**NGS:** *BAP1* loss	Insufficient DNA	ND	4
275	Mesothelioma	**NGS:** ND **IHC:** loss	p.G194R	ND	25
375	Mesothelioma	**NGS:** p.L49Qfs*18 **IHC:** loss	p.L49Qfs*18	p.L49Qfs*18	0

†This patient experienced a partial response; see efficacy results.
IHC, immunohistochemistry; ND, *BAP1* alteration not detected; NGS, next-generation sequencing; unknown, assay unable to be carried out due to insufficient sample or poor sample quality.

Efficacy

- A DCR of 66.7% was reported in the 375 mg cohort (n=6), 25.0% in 275 mg cohort (n=4), 71.4% in the 225 mg cohort (n=7), 33.3% in the 187.5 mg cohort (n=6), 50% in the 100 mg cohort (n=6), and 25.0% in the 50 mg cohort (n=4); no responses were reported in the 137.5 mg cohort (n=6)
- PR as the best response was achieved in two patients
  - One patient in the 225 mg cohort with mesothelioma and *BAP1* loss confirmed by both local (NGS and IHC) and central (IHC) testing (case presented at ASCO 2021,[5] remained on study until Cycle 10 [progressive disease])
  - In the 375 mg cohort, a 47-year-old patient with Stage IV endometrial cancer and *ARID1A* mutation (prior brachytherapy and two lines of platinum-based regimen) had a PR after 9 cycles and remained on study treatment at 21 months **(Figure 4)**

Figure 4. Treatment response with CPI-0209 in a patient with endometrial carcinoma with *ARID1A* mutation detected by central testing

Summary

- The updated safety results for CPI-0209 are consistent with previous reports;[6] TEAEs were manageable
- *ARID1A* mutations were detected across multiple tumor types
  - One patient with endometrial cancer with *ARID1A* mutation had a PR and remained on study treatment for at least 21 months
- *BAP1* alterations were detected in all patients with mesothelioma
  - One patient had a confirmed PR
- These initial results support patient selection based on *ARID1A* and *BAP1* in the Phase II expansion study, as we continue to explore the extent to which these mutations confer sensitivity to EZH2 inhibition
- Given these Phase I findings, the Phase II expansion study will continue to evaluate the antitumor activity and safety of CPI-0209 across selected tumor types; preliminary Phase II data are reported in poster PB079 at this congress[7]

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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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References

1. Duan R, et al. J Hematol Oncol 2020;13(1):104.
2. LaFave LM, et al. Nat Med 2015;21(11):1344–9.
3. Biter BG, et al. Nat Med 2015;21(3):231–8.
4. Yamada L, et al. Gastric Cancer 2021;24(1):60–71.
5. Keller, PJ et al. [Abstract] Clin Cancer Res 2020;26(15_Suppl): A18
6. Lakhani NJ, et al. [Abstract] J Clin Oncol 2021;39(15_Suppl): 3104
7. Kindler H, et al. ENA 2022. Poster PB079

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