Phase 1/2 First-in-Human (FIH) Study of CPI-0209, a Novel Small Molecule Inhibitor of Enhancer of Zeste Homolog 2 (EZH2) in Patients With Advanced Tumors

Poster # 3104

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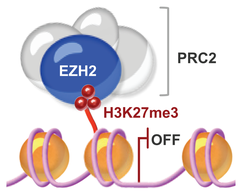
BACKGROUND

EZH2 "Writer" Activity Suppresses Gene Transcription

Polycomb Repressive Complex 2 (PRC2)



EZH2 trimethylates histone H3 at **lysine 27** and **suppresses transcription**

EZH2i – enhancer of zeste homolog 2 (EZH2) inhibitor

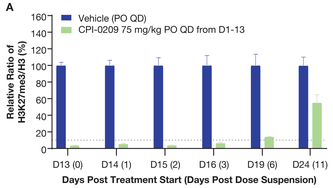
Broad Implications in Cancer

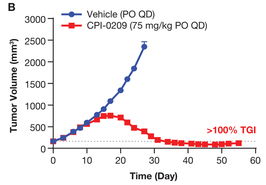
- **Activating mutations**
- **Oncogenic driver synergy**
- **Synthetic lethal relationships**
- **Drug resistance**
- **Tumor immunity**

CPI-0209: Durable and Complete Tumor Regression in Xenograft Model

H3K27me3 and Efficacy

HT1376 ARID1A Mutant Bladder Cancer Xenograft Model



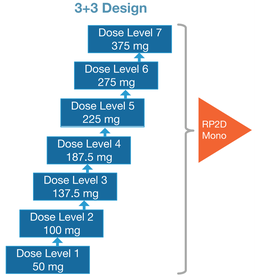


- Significant reduction (>90%) of global H3K27me3 levels
- Reduction of H3K27me3 maintained for days after dose suspension
- Tumor regression seen with 75 mg/kg QD dosing
- Long residence time
- Increased potency
- Sustained target engagement allows for QD dosing

STUDY DESIGN

Phase 1 – Escalation

Monotherapy – Advanced Tumor 3+3 Design



Phase 2 – Expansion at RP2D* (350 mg QD)

Monotherapy Disease-Specific Cohorts

M1	Urothelial Carcinoma (ARID1A mutant)	M4	Lymphoma (either B-cell or T-cell histology, EZH2 mutant and wildtype)
M2	Ovarian Clear Cell Carcinoma (ARID1A mutant)	M5	Pleural or Peritoneal Mesothelioma (BAP1 loss)
M3	Endometrial Carcinoma (ARID1A mutant)	M6	Metastatic Castration Resistant Prostate Cancer

*RP2D - recommended Phase 2 dose

- Phase 1 primary objective is to determine the maximum tolerated dose (MTD) and/or RP2D of CPI-0209 in patients with advanced tumors
- Phase 2 primary objective is to evaluate the antitumor activity of CPI-0209 in patients with selected tumors

RESULTS

Patient Disposition

	N (%)
Enrolled	41
Treated	40
Ongoing*	9 (22)
Discontinued	32 (78)
Reason for treatment discontinuation	
Progressive disease	31 (76)
Adverse event	1 (2)
Treatment duration (days) – median (min, max)	43 (1, 324)
Total number of cycles – median (min, max)	2 (1, 12)
Analysis Set	**N**
Safety Analysis Set	40
Efficacy Analysis Set	34

CPI-0209 Dose	N
50 mg	4
100 mg	6
137.5 mg	6
187.5 mg	6
225 mg	7
275 mg	4
375 mg*	8
Total	41

The Safety Analysis Set is defined as all patients who received any amount of study drug
The Efficacy Analysis Set is defined as all patients who received the study drug and had at least 1 post-baseline tumor assessment
*1 patient (375 mg) – treatment not started as of 09Mar21

Baseline Demographics and Disease Characteristics

Safety Analysis Set (N=40)

	Mean (SD) or n (%) or Median (Min, Max)
Total (N)	40
Age (years)	64 (11)
Gender	
Male/Female	17 (43)/23 (58)
Time since initial diagnosis (days)	925 (88, 9159)
Cancer Type	
Ovarian cancer	7 (18)
Mesothelioma*	6 (15)
Pancreatic cancer	6 (15)
Breast cancer	5 (13)
Colon cancer	5 (13)
Endometrial cancer	2 (5)
Leiomyosarcoma	2 (5)
Other†	7 (18)
Prior lines of cancer therapies	
1	3 (8)
2	9 (23)
3	12 (30)
>3	16 (40)

*4 mesothelioma patients had BAP1 loss
†Other – bladder cancer, cholangiocarcinoma, gastric cancer, melanoma, prostate cancer, tonsil carcinoma, and uterine carcinoma

Summary of Treatment Emergent Adverse Events

TEAEs†	All Grades N=40² n (%)	Grades ≥3 N=40² n (%)
Hematological Events		
Thrombocytopenia³	11 (28)	2 (5)
Anemia	8 (20)	2 (5)
Non-hematological Events		
Gastrointestinal Events		
Diarrhea	11 (28)	0
Nausea	9 (23)	0
Abdominal pain	6 (15)	2 (5)
Other Non-hematological Events		
Asthenic conditions⁴	11 (28)	0
Dysgeusia	8 (20)	0
Alopecia	6 (15)	0

†TEAEs of all grades that occurred in ≥15% of patients
‡Safety evaluable population: received at least 1 dose of study drug as of the data cut-off
³Includes TEAE platelet count decrease
⁴Includes TEAEs of fatigue and malaise

- CPI-0209 was generally well tolerated
- 37 pts (93%) reported at least 1 treatment-emergent adverse event (TEAE)
- 17 pts (43%) reported at least 1 ≥Grade 3 TEAE
  - Reported in ≥2 pts were thrombocytopenia, anemia, abdominal pain, pneumonia, amylase ↑, AST ↑, ALP ↑, pulmonary embolism, and back pain
- 1 dose-limiting toxicity (DLT) (Grade 4 thrombocytopenia) was reported by 1 pt from 375 mg dose cohort
- 9 pts (23%) reported TEAEs leading to CPI-0209 dose reduction or interruption
  - Grade 2 diarrhea (2) and Grade 3 anemia (1) were *related* TEAEs leading to dose interruption in 3 pts
- 4 pts (10%) reported TEAEs leading to CPI-0209 discontinuation
  - Grade 2 dysgeusia was the *related* TEAE leading to discontinuation in 2 pts
- 1 pt experienced Grade 5 TEAE (progressive malignant neoplasm)

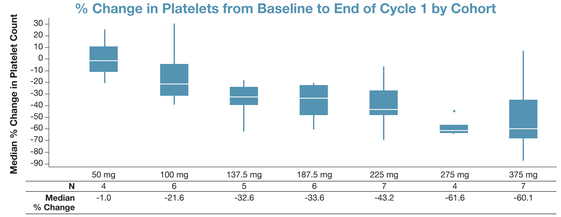
TEAEs Occurring in ≥15% Overall by Dose Cohorts

TEAEs	CPI-0209 50 mg (N=4)	CPI-0209 100 mg (N=6)	CPI-0209 137.5 mg (N=6)	CPI-0209 187.5 mg (N=6)	CPI-0209 225 mg (N=7)	CPI-0209 275 mg (N=4)	CPI-0209 375 mg (N=7)	Overall Total (N=40)
Total Patients with at least 1 TEAE	3 (75%)	6 (100%)	6 (100%)	6 (100%)	6 (86%)	4 (100%)	6 (86%)	37 (93%)
Total Number of TEAEs	8	26	27	52	44	30	37	224
Thrombocytopenia[1]	0	1 (17%)	0	2 (33%)	2 (29%)	2 (50%)	4 (57%)	11 (28%)
Diarrhea	1 (25%)	1 (17%)	0	1 (17%)	4 (57%)	1 (25%)	3 (43%)	11 (28%)
Asthenic conditions[2]	0	1 (17%)	1 (17%)	3 (50%)	4 (57%)	1 (25%)	1 (14%)	11 (28%)
Nausea	0	1 (17%)	2 (33%)	1 (17%)	2 (29%)	1 (25%)	2 (29%)	9 (23%)
Anemia	0	0	1 (17%)	3 (50%)	0	1 (25%)	3 (43%)	8 (20%)
Dysgeusia	0	0	1 (17%)	0	4 (57%)	1 (25%)	2 (29%)	8 (20%)
Abdominal pain	1 (25%)	1 (17%)	1 (17%)	2 (33%)	1 (14%)	0	0	6 (15%)
Alopecia	0	1 (17%)	0	1 (17%)	3 (43%)	0	1 (14%)	6 (15%)

[1]Includes TEAE thrombocytopenia and platelet count decrease
[2]Includes TEAEs of fatigue and malaise

Platelet Count Change

% Change in Platelets from Baseline to End of Cycle 1 by Cohort



	50 mg	100 mg	137.5 mg	187.5 mg	225 mg	275 mg	375 mg
N	4	6	5	6	7	4	7
Median % Change	-1.0	-21.6	-32.6	-33.6	-43.2	-61.6	-60.1

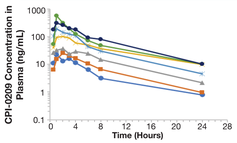
A dose dependent platelet count decrease was observed that was manageable and reversible

Summary of TEAEs by Dose Cohorts

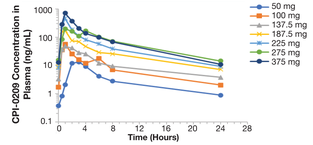
- 43% of pts had at least 1 ≥ Grade 3 TEAE; these occurred at 25% in dose-cohort 50 mg; 50% in 100 mg, 137.5 mg, and 187.5 mg; 75% in 275 mg, and 57% in 375 mg dose cohort
- 28% of pts had at least 1 serious AE; these occurred at 14% in 375 mg, 33% in 100 mg and 137.5 mg, 50% in 187.5 mg, and 75% in 275 mg; no pts in 50 mg and 225 mg had a serious AE
- 68% of pts had at least 1 TEAE considered possibly related to CPI-0209
  - TEAEs considered possibly related in more than 2 pts were anemia, diarrhea, nausea, vomiting, fatigue, platelet count decrease, dysgeusia, and alopecia
- 3 pts experienced Grade 4 TEAEs
  - Worsening lipase increased (137.5 mg), lung infection (275 mg), and thrombocytopenia (375 mg)

CPI-0209 Pharmacokinetics in Patients Exhibit Durable Exposure and Half-Life of ~8 hrs

Cycle 1 Day 1



Cycle 2 Day 1 (QD×28 Days)



- Plasma concentrations increase with increases in dose
- Estimated mean half-life ~8 hrs (range 4-11 hrs)
- Exposure is durable over time
  - Accumulation after 1 cycle ~10-50% across cohorts, consistent with estimated half-life
  - Trough concentrations are stable, no evidence for net autoinduction

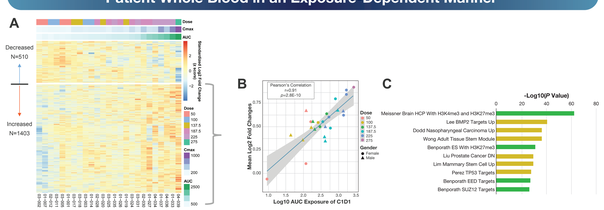
CPI-0209 Reduces H3K27me3 in Monocytes

CPI-0209 Impact on H3K27me3 in Monocytes in Patients

Change of H3K27me3/total H3 ratio at cycle 1 day 8 (C1D8) compared to baseline (C1D1)

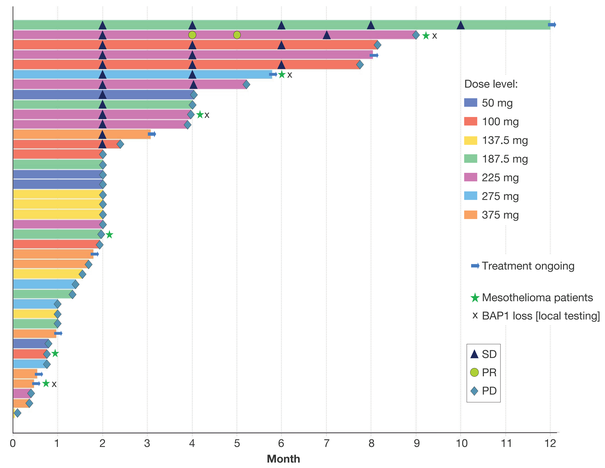
- Comprehensive target engagement was observed after 7 days of treatment within the first cycle at all dose levels in monocytes
- CPI-0209 reduces H3K27me3 over 90% in monocytes at doses ≥100 mg

CPI-0209 Increased the Expression of PRC2-Controlled Gene Sets in Patient Whole Blood in an Exposure-Dependent Manner

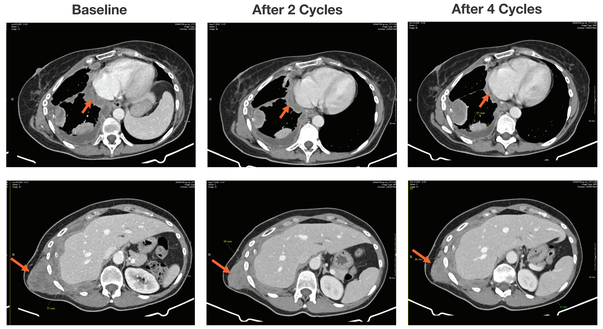


- RNAseq analysis of patient whole blood (Day 1 vs 22) identified expression changes on 1913 genes
  - 1403 up-regulated genes and 510 down-regulated genes
- Expression changes of CPI-0209 up-regulated genes correlate with exposure in plasma
- Up-regulated genes are mechanism-related: gene set enrichment analysis of up-regulated genes identified PRC2 related gene sets

Treatment Duration by Dose Level



Preliminary Evidence of CPI-0209 Activity in Mesothelioma With BAP1 Loss



- Diagnosed with biphasic mesothelioma BAP1 bi-allelic mutation and IHC negative
- Patient had rapid progression through 2 prior lines of therapy
- Partial response after 4 cycles (225 mg QD), confirmed at cycle 5

CONCLUSIONS

- Comprehensive target engagement as assessed by global reduction in H3K27me3 levels was observed within the first cycle after 7 days of treatment at all dose levels in monocytes
- CPI-0209 increased the expression of PRC2-controlled gene sets in whole blood in an exposure-dependent manner
- CPI-0209 pharmacokinetics in patients exhibit durable exposure and a half-life of ~8 hrs
- CPI-0209 showed a manageable safety profile with dose dependent thrombocytopenia
- There was 1 DLT in 375 mg cohort (Grade 4 thrombocytopenia)
- The MTD has not been reached. The RP2D was chosen as 350 mg QD based on collective safety assessments
- Of the 4 BAP1 loss mesothelioma patients, 1 patient had a durable PR and 2 had SD ≥2 months