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EZH2/EZH1 inhibitor tulmimetostat (CPI-0209) in patients with advanced solid tumors or hematologic malignancies: Preliminary Phase II results

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OBJECTIVE

To report updated preliminary Phase II results with the investigational EZH2/EZH1 inhibitor tulmimetostat as monotherapy in multiple advanced malignancies

SUMMARY

> Among the solid tumor cohorts, the ovarian (M2), endometrial (M3) and mesothelioma (M5) cohorts have achieved eligibility for Stage 2 expansion following confirmed responses to tulmimetostat monotherapy

> Complete and partial responses have also been observed in the lymphoma (M4) cohort, which is using a single-stage enrollment design

> The safety profile of tulmimetostat is consistent with the mechanism of EZH2 inhibition, and the majority of the most common TEAEs are Grade 1 or 2

> These preliminary findings in heavily pretreated patients with multiple tumor types, including tumors with *ARID1A* alterations or *BAP1* loss, support ongoing investigation of dual EZH2/EZH1 inhibitor tulmimetostat

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Tulmimetostat is an investigational product and has not been approved by any regulatory authority.

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BACKGROUND

> Epigenetic regulation by EZH2 is involved in several tumorigenic contexts, including tumors with *ARID1A* mutations or *BAP1* loss[1]

> Tulmimetostat (CPI-0209), a next-generation, oral, dual EZH2/EZH1 inhibitor under investigation, has demonstrated improved on-target residence times, lower clearance rates (owing to no induction of CYP3A activity), and more potent anti-tumor activity versus 1st generation EZH2 inhibitors in preclinical studies[2,3]

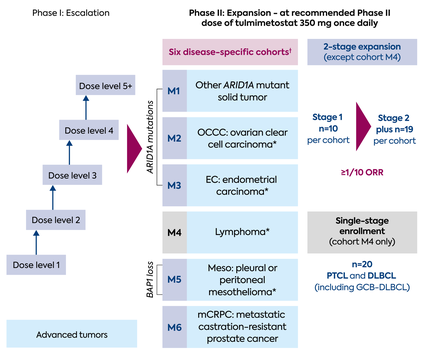
> This ongoing Phase I/II study (NCT04104776)[4] is evaluating the anti-tumor activity and safety of tulmimetostat in advanced solid tumors and lymphomas
- Phase I results[2,5] supported a recommended Phase II dose of 350 mg once daily
- Preliminary Phase II results from July 2022 were previously presented[6]

METHODS

> The Phase II expansion is evaluating tulmimetostat 350 mg in a continuous once-daily dose in six cohorts by tumor types (**Figure 1**)
- The Simon 2-stage study design requires one objective response in Stage 1 (n=10 patients) for expansion to Stage 2 (plus n=19)
- Cohort M4 (lymphoma) is using single-stage enrollment

> The study is enrolling adult patients with disease that has progressed on applicable prior lines of treatments, and that meets other tumor-specific inclusion criteria as listed on ClinicalTrials.gov[4]

Figure 1. Study Design



*Histologically or cytologically confirmed progressive tumor. †Patients in all cohorts have progressive disease with applicable prior lines of therapy.
CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal-center B-cell-like; ORR, objective response rate; PR, partial response; PTCL, peripheral T-cell lymphoma.

RESULTS

> As of February 14, 2023:
- 81 patients received ≥1 dose of tulmimetostat (**safety analysis set**)
- 75 patients also had ≥1 post-baseline response assessment or discontinued the treatment prior to their first post-baseline assessment for any reason (**efficacy evaluable set**)

> 55 patients discontinued treatment (progressive disease, n=37; adverse events [AEs], n=9; patient withdrawal, n=5; physician decision, n=3; and other, n=1), and 26 were ongoing on treatment

> All cohorts completed Stage 1 enrollment

> Median age overall was 65.0 years (range 34–88); baseline characteristics and median treatment duration in the safety analysis set are shown in **Table 1**

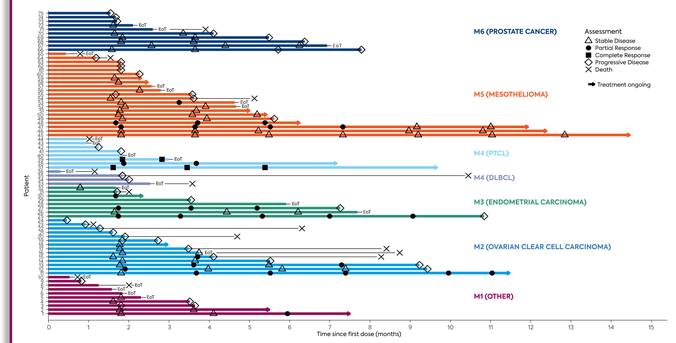
RESULTS (CONTINUED)

Table 1. Baseline characteristics and median treatment duration (safety analysis set)

		M1 Other	M2 OCCC	M3 EC	M4 Lymph	M5 Meso	M6 mCRPC	Overall
Patients, N		12	14	10	12	23	10	81
Median time since diagnosis, years (range)		1.4 (0–5.0)	3.5 (0.6–8.8)	3.2 (0.6–6.6)	3.3 (0.6–7.6)	2.2 (0.6–7.0)	6.7 (1.2–19.6)	2.8 (0–19.6)
Lines of prior cancer therapy, n (%)	1	0	4 (28.6)	2 (20.0)	0	5 (21.7)	0	11 (13.6)
	2	6 (50.0)	2 (14.3)	3 (30.0)	4 (33.3)	9 (39.1)	2 (20.0)	26 (32.1)
	≥3	5 (41.7)	8 (57.1)	5 (50.0)	8 (66.7)	6 (26.1)	8 (80.0)	40 (49.4)
	ND	1 (8.3)	0	0	0	3 (13.0)	0	4 (4.9)
ECOG performance status, n (%)	0	2 (16.7)	6 (42.9)	4 (40.0)	2 (16.7)	12 (52.2)	1 (10.0)	27 (33.3)
	1	10 (83.3)	8 (57.1)	6 (60.0)	10 (83.3)	11 (47.8)	9 (90.0)	54 (66.7)
Median treatment duration, days (range)		36.0 (15–229)	70.5 (2–350)	60.5 (19–336)	62.5 (3–295)	78.0 (2–428)	92.0 (8–232)	57.0 (2–438)

EC, endometrial carcinoma; ECOG, Eastern Cooperative Oncology Group; Lymph, lymphoma; mCRPC, metastatic-castration-resistant prostate cancer; Meso, pleural or peritoneal mesothelioma; ND, not defined; OCCC, ovarian clear cell carcinoma.

Figure 3. Treatment duration and response assessment



Efficacy evaluable set. DLBCL, diffuse large B-cell lymphoma; EoT, end of treatment; PTCL, peripheral T-cell lymphoma.

Efficacy

> Best confirmed responses (**Table 2**) show that three of the five cohorts using the Simon 2-stage design have achieved eligibility for Stage 2 expansion (M2: OCCC, M3: EC, and M5: Meso)
- In cohort M1 (other *ARID1A* mutant solid tumor), one patient has a currently unconfirmed partial response (PR)
- In cohort M4 (lymphoma), which uses single-stage enrollment, two patients have had a best response of complete response (CR), and one patient with PR (all with peripheral T-cell lymphoma)
- In cohort M6: mCRPC, the best response was stable disease (in six patients) and Stage 2 will not commence

> The best percentage changes in target lesion diameter from baseline for patients in the solid tumor cohorts are shown in **Figure 2**

> Treatment duration and response assessments for patients in the efficacy evaluable set for all cohorts are shown in **Figure 3**

Table 2. Best responses

		M1 Other	M2 OCCC	M3 EC	M4 Lymph	M5 Meso	M6 mCRPC
Efficacy evaluable, N		10	14	8	12	21	10
Best confirmed response*, n	Complete response	0	0	0	2	0	0
	Partial response	0	1	2	1	2	0
	Stable disease	4	7	2	0	11	6
Best response (confirmed or unconfirmed)*, n	Complete response	0	0	0	2	0	0
	Partial response	1	4	3	1	3	0
	Stable disease	3	4	1	0	10	6
No response, n	Progressive disease	2	6	2	4	6	3
	Not evaluable	0	0	1‡	0	0	0
	Discontinued†	4	0	1	5	2	1

*Per RECIST 1.1 or modified RECIST 1.1 as applicable except in M4 (2014 Lugano criteria[7], in which confirmation is not required). †Discontinued treatment without a response assessment. ‡Patient had stable disease assessment prior to the required 28 days. EC, endometrial carcinoma; Lymph, lymphoma; mCRPC, metastatic-castration-resistant prostate cancer; Meso, pleural or peritoneal mesothelioma; OCCC, ovarian clear cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours.

Safety

> In the safety analysis set, 80 patients (98.8%) had ≥1 treatment-emergent AE (TEAE)
- 30 patients (37.0%) had ≥1 serious TEAE
- 53 patients (65.4%) had ≥1 Grade 3 or higher TEAE

> TEAEs considered at least possibly related to tulmimetostat occurred in 74 patients (91.4%)
- 12 (14.8%) patients had ≥1 possibly related serious TEAE
- 39 (48.1%) patients had ≥1 Grade 3 or higher TEAE considered at least possibly related to tulmimetostat
- The most frequent TEAEs considered at least possibly related to tulmimetostat were thrombocytopenia and diarrhea (**Table 3**, **Figure 4**)

> A total of 63 patients (77.8%) experienced TEAEs leading to dose modifications, 31 (38.3%) to dose reductions, and 57 (70.4%) to dose interruptions

> A total of nine patients (11.1%) discontinued treatment and 14 (17.3%) discontinued the study owing to TEAEs
- Five (6.2%) discontinuations were considered at least possibly related to tulmimetostat

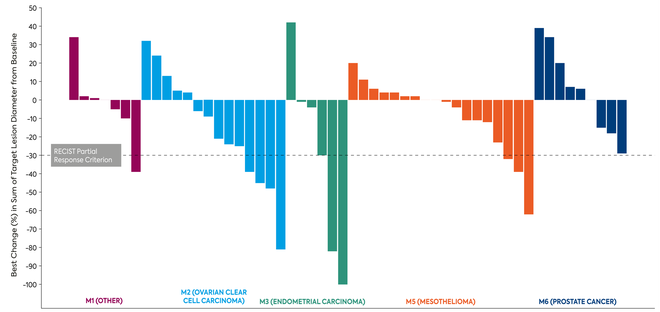
> Five (6.2%) patients died due to TEAEs, none considered related to tulmimetostat

Table 3. Most frequently reported TEAEs* considered at least possibly related to tulmimetostat

Preferred Term	Any grade	Grade ≥3
Thrombocytopenia	41 (50.6)	20 (24.7)
Diarrhea	37 (45.7)	9 (11.1)
Anemia	29 (35.8)	12 (14.8)
Nausea	27 (33.3)	1 (1.2)
Fatigue	26 (32.1)	0
Alopecia	22 (27.2)	1 (1.2)
Dysgeusia	20 (24.7)	0
Vomiting	18 (22.2)	1 (1.2)
Decreased appetite	12 (14.8)	1 (1.2)
Neutropenia	13 (16.0)	11 (13.6)
Weight decreased	10 (12.3)	0

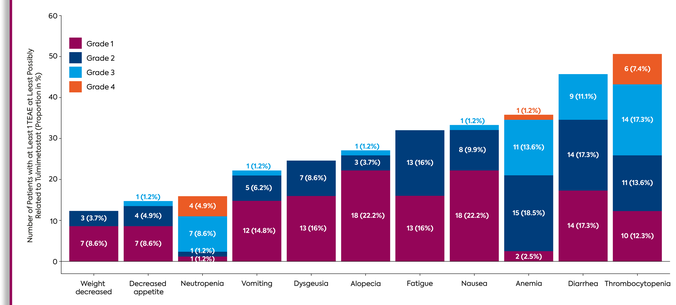
*Occurring in ≥10% of patients. Data are N (%) patients in the safety analysis set.
TEAE, treatment-emergent adverse event.

Figure 2. Best percentage change



Efficacy evaluable set (patients with at least one valid post-baseline tumor assessment). RECIST, Response Evaluation Criteria in Solid Tumours.

Figure 4. Most common TEAEs (occurring in ≥10% of patients), considered at least possibly related to tulmimetostat, by severity



Safety analysis set. TEAE, treatment-emergent adverse event.