Abstract #3583:

Results of a Completed Phase 1 Trial of CBL0137 Administered Intravenously (IV) to Patients with Advanced Solid Tumors

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Background

CBL0137 is a novel small molecule that intercalates DNA, interfering with histone/DNA binding. Consequent trapping of histone chaperone FACT leads to inhibition of pro-cancerous transcriptional factors, MYC, NF-kB, HSF1, and HIF1α, and activation of p53 and IFN response[1-3] (Fig. 1). CBL0137 shows broad nonclinical antitumor activity.

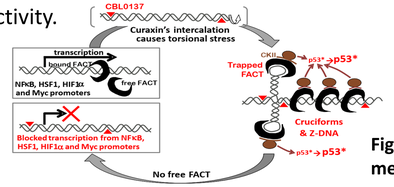


Fig.1 Curaxin CBL0137 mechanism of action.

Methods

This dose-ranging study assessed the CBL0137 maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D), and CBL0137 safety, pharmacokinetics (PK), and efficacy in adults with advanced, treatment-refractory solid tumors. CBL0137 was administered IV on Days 1, 8, and 15 of repeated 28-day cycles until progressive disease (PD) or unacceptable toxicity. Doses were escalated using a 3+3 design based on Cycle 1 dose-limiting toxicities (DLTs). PK samples were obtained through 168 hours after Day 1. Efficacy was evaluated every 8 weeks.

Results

The study enrolled 83 patients (pts) across 17 dose levels from 10 to 700 mg/m^2/infusion (Table 1). Pt characteristics included:

- Males / Females, n (%): 49 (59) / 34 (41);
- Median [range] age: 64 [33-85] years;
- ECOG performance status 0 / 1, n (%): 32 (39) / 51 (61).

The most common cancers included colorectal, prostate, glioblastoma, liver, non-small cell lung, as well as other cancers (Table 2).

Table 1. Dose levels

Cohort	Dose level, mg/m^2	n
1	10	5
2	20	3
3	30	4
4	40	3
5	60	3
6	80	4
7	100	3
8	120	6
9	150	5
10	180	4
11	240	9
12	320	7
13	400	12
14a	540	4
15	700	7
14b	650	2
14c	600	2

Table 2. Pts distribution by cancer types

Cancer Type	n (%)
Colorectal cancer	23 (27.7)
Prostate cancer	7 (8.4)
Glioblastoma	6 (7.2)
Hepatocellular carcinoma	6 (7.2)
Non-small cell lung cancer	5 (6.0)
Anal cancer	4 (4.8)
Bladder cancer	4 (4.8)
Endometrial cancer	4 (4.8)
Esophageal cancer	4 (4.8)
Intestinal cancer	3 (3.6)
Meningioma	3 (3.6)
Pancreatic cancer	3 (3.6)
Ovarian cancer	2 (2.4)
Others (1 each of ameloblastoma, biliary cancer, breast cancer, cervical cancer, melanoma, peritoneal cancer, sarcoma, small-cell lung cancer, thymoma)	9 (10.8)

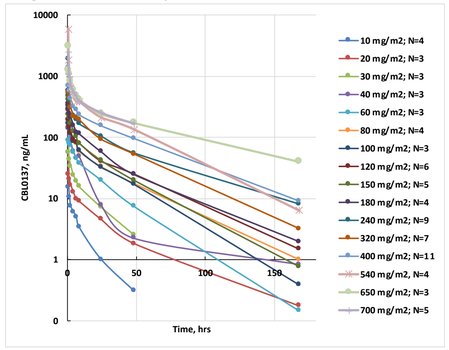
Safety

Durations of therapy ranged from 1 to 722 days (24 months). Cycle 1 DLTs [n grade (Gr) type] were observed at 240 mg/m^2 (1 Gr 3 photosensitivity), 400 mg/m^2 (1 Gr 3 anemia), 700 mg/m^2 (1 Gr 4 thrombocytopenia, 1 Gr 4 neutropenia/ Gr 4 thrombocytopenia), and 650 mg/m^2 (1 Gr 3 thrombocytopenia, 1 Gr 4 neutropenia/Gr 3 thrombocytopenia). The most common Gr 1-2 / 3-4 adverse events were fatigue (28% / 10%); nausea (30% / 1%); photosensitivity (19% / 5%), anemia (12% / 12%). Nausea and vomiting were successfully prevented with dexamethasone/serotonin antagonists. Photosensitization was effectively managed with sun protection. Peripheral venous thrombosis required central vein infusion in subjects with glioblastoma.

Pharmacokinetics

PK data showed dose-proportional increases in plasma CBL0137 area under the concentration-time curve (AUC), a high mean (range) volume of distribution (Vd) of 1,030 (655-1460) L/m^2 consistent with extensive tissue distribution and DNA intercalation, and an average mean (range) half-life ($t_{1/2}$) of 24.7 (10.3-40.7) hours without dose dependence.

Fig. 2. Mean CBL0137 plasma concentration-time curves



Conclusions:

CBL0137 administered IV was generally well tolerated with manageable toxicities. The MTD and RP2D were estimated at 540 mg/m^2 due to myelosuppressive DLTs. PK were predictable. Preliminary evidence of antitumor activity supports Phase 2 testing.

Efficacy

The best response was stable disease (SD). Out of 48 pts evaluable for response, 18 (37.5%) had SD: 2 pts with liver cancer had tumor control for 9 and 24 months and a maximum tumor regression of 10%; 2 pts with prostate cancer had tumor regressions by 11% and 22%; 1 pt with uterine cancer had a 20% tumor regression (Fig. 3, 4).

Fig. 3. Duration of IV CBL0137 Therapy by Dose Level and Subject

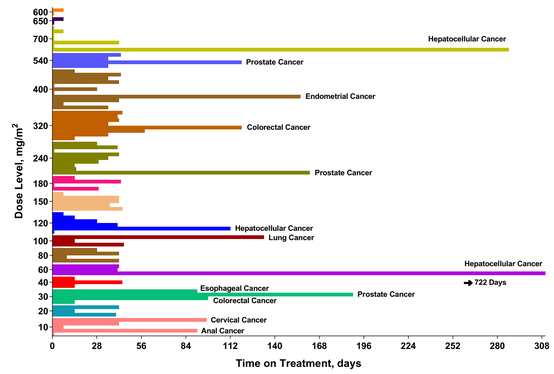
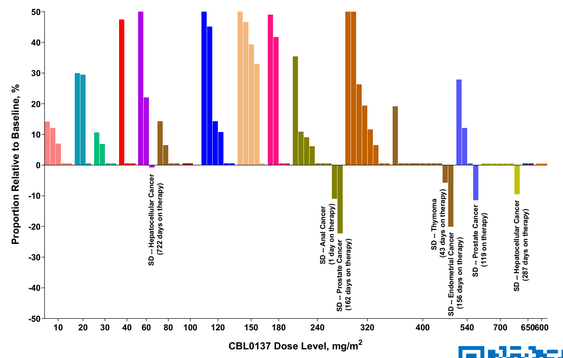


Fig. 4. Best On-Study Change in Tumor Dimensions by IV CBL0137 Dose Level and Subject



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References

1. Gasparian AV, et al. Sci Transl Med. 2011; 3(95):95ra74.
2. Leonova K, et al. eLife 2018;7:e30842.
3. Kantidze OL, et al. Nat Commun. 2019; 10(1):1441.

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