A Phase I, Multicenter, Open-label, Dose-Escalation, Safety, Pharmacodynamic and Pharmacokinetic Study of GZ17-6.02 Given Orally on a Daily Schedule in Patients with Advanced Solid Tumors Or Lymphoma

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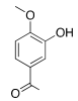
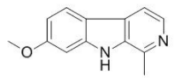
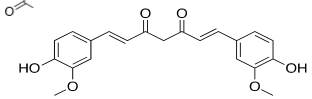
GZ17-6.02 Description

Natural products have been extensively used and researched in oncology. However the advent of targeted therapeutics have resulted in a decrease of natural product research.

GZ17-6.02 is combination of 3 fully synthetic naturally occurring molecules.

Isovanillin 

Harmine 

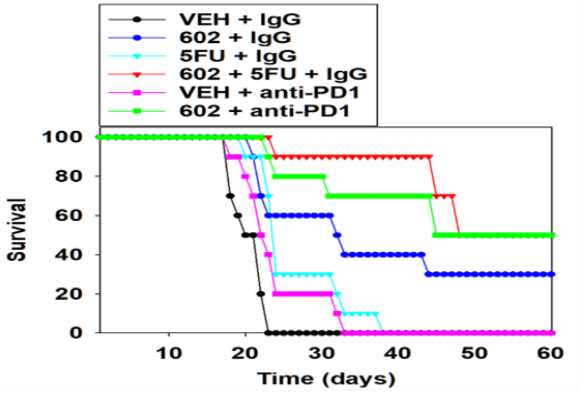
Curcumin 

A standardized ratio of 77% Isovanillin, 13% Harmine, and 10% Curcumin was determined to be the optimal ratio from preclinical studies.

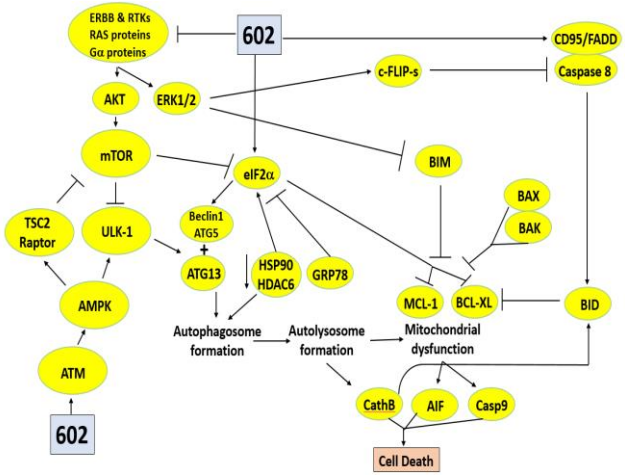
GZ17-6.02 was observed to affect various signaling pathways preclinically. Further evaluation determined these molecules gain synergistic effect by modulating super enhancers.

Preclinical data demonstrates GZ17-6.02's ability to enhance efficacy of other SoC agents, including fluoropyrimidines, IO agents, and cyclin-dependent kinase inhibitors (data on file).

An in vivo model demonstrates GZ17-6.02's ability to enhance biological effect when combined with other therapeutics in a CT26 murine CRC model as illustrated in the figure below.



GZ17-6.02 Mechanism of Action



GZ17-6.02 affects multiple signaling pathways and biological pathways. These data when paired with RNA chipseq data demonstrate GZ17-6.02's effect on super enhancers and the subsequent downstream effects.

Patients and Methods

- Patients with solid tumors were enrolled to receive GZ17-6.02 (QD or BID) on a continuous dosing schedule.
- Primary Objectives: To evaluate the safety and tolerability of GZ17-6.02 by determination of the MTD, DLT, and RP2D. Secondary Objectives: assessment of PK and antitumor activity.
- Main Inclusion Criteria: informed consent, > 18y.o., ECOG-PS 0-1, adequate organ function, pathologically confirmed diagnosis of advanced solid tumors or lymphoma, albumin >3 g/dL.
- Dose-escalation was dependent on <33% of patients in a cohort experiencing DLT during cycle 1 (28 days). Dose was increased by predetermined dose in single patient cohorts, followed by a "3+3" design.
- PK was assessed during cycle 1 in each patient.
- PD assessment determined by standard imaging studies including PET.
- NCT #03775525. Sponsor: Genzada Pharmaceuticals.

DOSING SCHEDULE

Cohort 1[1]	675mg QD	1 patient
Cohort 2	300mq QD	3 patients
Cohort 3	150mg BID	3 patients
Cohort 4	225mg BID	6 patients
Cohort 5	375mg BID	6 patients
Cohort 6	450mg BID	6 patients
Cohort 7	375mg BID	11 patients

1. Patient 001 experienced G3 dizziness leading to the more conservative dosing regimen.

Results

Total Population

Consented[1]	53
Dosed	38
Evaluable DLT	33
Female	21/33 (64%)
Mean Age	63.85 (39-86)
ECOG 0:1	14:19

1. Includes screen failures.

Tumor Type

NSCLC	7 (21%)
Ovarian	5 (15%)
Colorectal	4 (12%)
Sarcoma	2 (6%)
Other	15 (45%)

Prior Systemic Treatment

Mean	4.03	Range	1 - 10

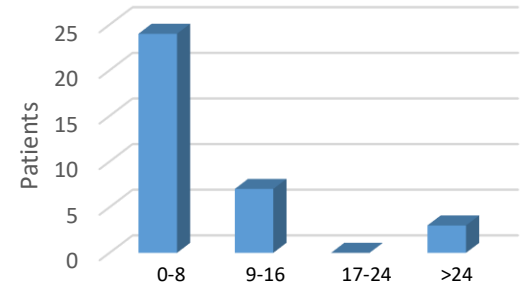
Adverse Events on Treatment

All Grade ≥3 AEs	33	Definitely Related Grade ≥3 AEs	2
Related Grade ≥3 AEs	12	Probably Related Grade ≥3 AEs	0
Related Grade ≥4 AEs	None	Possibly Related Grade ≥3 AEs	10

- Grade ≥3 AEs occurred in 8 patients, none were SAEs
- 3 patients with Grade ≥3 AEs were dosed above the MTD
- 4 instances of Grade ≥3 ALT and AST elevation occurred in the same patient

Data represented is not fully reconciled as the trial is ongoing but are an accurate representation at the time of publication.

Time on Treatment (Weeks)



- **One Partial Response (PR) was observed in a patient with NSCLC with one additional minor response in a patient with uveal melanoma**

Discussion

- 33 patients have been treated in 6 dosage levels (QD and BID schedule). The drug was overall well tolerated: DLTs included reversible transaminitis and transient dizziness. Most common AEs were reversible transaminitis, fatigue, dizziness, constipation, nausea, and vomiting.
- GZ17-6.02 was administered with Peptamen®.
- While biological effect was observed, PK analysis largely demonstrated levels of the 3 active pharmaceutical ingredients (APIs) to be below levels of quantification. PK assay optimization to further identify and evaluate PK characteristics will occur in future studies.
- Further clinical evaluation of GZ17-6.02 with SoC therapeutics is planned.

Conclusions

- 375mg BID was determined to be the MTD and the monotherapy R2PD
- GZ17-6.02 was well tolerated with manageable, reversible AEs.
- Further evaluation of PK parameters is ongoing.
- Various dosing strategies evaluating mono and combination therapy applications to occur in future phase Ib studies.

Acknowledgements

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- Dr. Mita has no conflicts of interest to declare
- Please email questions to info@genzada.com