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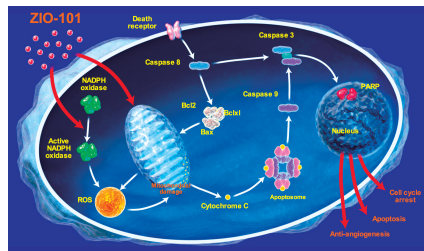
ZIO-101 (S-dimethylarsino-glutathione): Phase 1/2 Trials in Advanced/Progressive Multiple Myeloma

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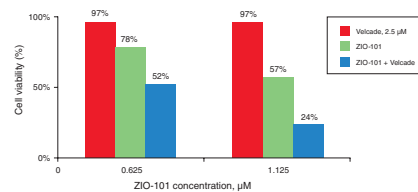
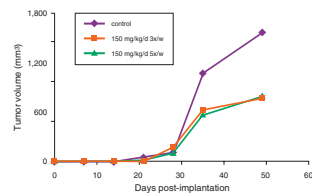
Background

ZIO-101 (S-dimethylarsino-glutathione), a novel organic arsenic, has a multifaceted mechanism of action mediated by disrupted mitochondrial function, increased reactive oxygen species (ROS) production, modified signal transduction, and anti-angiogenesis. ZIO-101 is active against multiple *in vitro* and animal cancer models.



ZIO-101 is active in LAGk-1B multiple myeloma xenografts.

In preclinical myeloma studies, ZIO-101 has demonstrated both *in vitro* and *in vivo* activity. In *in vivo* studies in SCID mice with human myeloma xenografts (LAGk-1B tumor model), two schedules of administration were evaluated.



ZIO-101 and bortezomib synergize in cytotoxic activity in MM RPMI cells. RPMI 8226 multiple myeloma cells were cultured with ZIO-101, Velcade® (bortezomib), or the combination of both drugs at indicated concentrations for 72 hours. Number of viable cells were determined using CellTiterGlo™ assay and are expressed as percentage of controls (DMSO).

Objectives

Two studies are ongoing to evaluate different treatment schedules in patients with advanced/progressive myeloma

- Phase 1/2 study: daily x 5/week, every 4 weeks
 - Phase 2 portion: to determine preliminary efficacy and safety profile
- Phase 2 study: twice weekly for 3 weeks, every 4 weeks
 - To determine preliminary efficacy and safety profile

Study Design

- Two Phase 2 trials were conducted using an open-label, 2-stage design to evaluate the following schedules:
 - 300 mg/m² for 5 consecutive days, every 4 weeks
 - 420 mg/m² twice weekly for 3 weeks, every 4 weeks
- Therapy was continued in all patients until toxicity, myeloma progression, or 6 cycles were completed

Patient Selection

Included

- Progressive multiple myeloma
- ≥2 prior therapies
- Myeloma-related paraprotein in serum and/or urine (Phase 2 only)
- ECOG performance score ≤2
- Adequate bone marrow, liver, and renal function

Excluded

- NYHA functional class ≥3, myocardial infarction ≤6 mo, or uncontrolled cardiac arrhythmia other than asymptomatic atrial fibrillation; QTc ≥450 msec; AV block ≥Grade 2, or LBBB
- Uncontrolled infection
- Chemotherapy, radiation therapy, or immune therapy for ≥3 weeks (≥6 w for nitrosoureas and ≥8 weeks for systemic radiotherapy)
- Arsenic allergy
- Prior seizures ≥Grade 3 in NCI-CTCAE v.3 criteria

Outcome

Efficacy

- EBMT response criteria
- Evaluable for efficacy: ≥2 cycles; 4-week follow-up after 2nd cycle

Safety

- NCI-CTCAE v.3 criteria

Results

- At 300 mg/m² for 5 consecutive days, every 4 weeks
 - 14 patients treated
- At 420 mg/m² twice weekly for 3 weeks, every 4 weeks
 - 3 patients treated

Baseline Characteristics

Dose	300 mg/m ²	420 mg/m ²
Schedule q 4 weeks	Daily x 5	Twice weekly for 3 wks
Sex	(n=14)	(n=3)
Male	10	1
Female	4	2
Age		
Years (range)	66 (37 to 80)	66 (49 to 72)
Prior therapies		
Median (range)	7 (2 to 14)	8 (7 to 9)
Prior regimen (% of patients)		
Steroid	93	100
Bortezomib	71	100
Melphalan	79	100
Thalidomide	71	100
Lenalidomide	50	33
Other	93	100

Preliminary Efficacy

Dose	300 mg/m ²	420 mg/m ²
Schedule q 4 weeks	Daily x 5	Twice weekly for 3 wks
	(n=14)**	(n=3)
Evaluable for Efficacy*	10	0
Best Response		
SD	4	0
PD	6	0

SD—stable disease PD—progression of disease
*To be evaluable for efficacy, patients must have received at least 2 cycles of ZIO-101.
** 3 patients ongoing

Safety

- ZIO-101 was well tolerated
- In both schedules, common AEs included nausea, vomiting, fatigue, and infusion site pain (only in patients dosed via peripheral line)
- No clinically relevant QTc prolongation, bone marrow suppression, or neuropathy observed with either schedule

Grade 3 or 4 Adverse Events

Dosing regimen	300 mg/m ² x 5 days x q 4 weeks (n=13)	420 mg/m ² twice/week for 3 weeks q 4 weeks (n=3)
Patients with at least one ≥Grade 3 AE	8	1
System organ class / preferred term		
Blood and lymphatic system disorders		
Anaemia	0	1
Neutropenia	1	0
Thrombocytopenia	1	0
Cardiac disorders		
Cardiac failure congestive	0	1
Gastrointestinal disorders		
Abdominal pain	0	1
Aphthous stomatitis	1	0
Constipation	1	0
General disorders		
Asthenia	1	0
Chest pain	1	0
Fatigue	2	0
Injury, poisoning, and procedural complications		
Contusion	1	0
Investigations		
Blood lactate dehydrogenase increased	1	0
Blood urea increased	1	0
Sinus tachycardia	1	0
Metabolism and nutrition disorders		
Hyperkalaemia	1	0
Hypocalcaemia	1	0
Hypokalaemia	1	0
Musculoskeletal and connective tissue disorders		
Pain in extremity	1	0
Psychiatric disorders		
Confusional state	2	0
Respiratory, thoracic and mediastinal disorders		
Pulmonary haemorrhage	1	0
Vascular disorders		
Vaginal haemorrhage	0	1

Conclusion

- Both ZIO-101 dosing schedules have been well tolerated
- Common adverse events included nausea, vomiting and fatigue
- No clinically significant bone marrow suppression or clinically relevant QTc prolongation
- Clinical activity in the form of prolonged disease stabilization observed in the daily x 5 schedule
- Patient accrual continues