ME-143, a novel inhibitor of tumor-specific NADH oxidase (tNOX): Results from a first-in-human phase I study

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Background

- ME-143 is a next generation isoflavone-derived compound from a class of molecules that bind at low nanomolar concentrations to a tumor specific, splice variant form of NADH oxidase, referred to as tNOX
- Binding to tNOX alters the ceramide-S1P equilibrium in the plasma membrane causing a loss in AKT phosphorylation at Ser473 resulting in broad caspase activation and prompt apoptosis [see Figure 1]

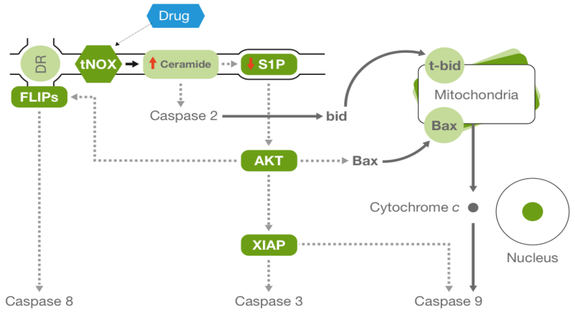


Figure 1

- Phenoxodiol, the first generation molecule in this class, administered either weekly IV bolus or by 7 day continuous IV administration, resulted in stable disease as the best response observed [reference 1,2]
- Based on favorable preclinical interactions, the phase II program for Phenoxodiol was executed exclusively in combination with cytotoxic chemotherapies
- Kelly et al. reported an objective response rate of 19% with another 56% of patients achieving stable disease when Phenoxodiol was administered weekly IV in combination with cisplatin in patients with platinum-resistant ovarian cancer [reference 3]
- A small phase III study involving 141 patients was subsequently conducted comparing weekly carboplatin + an oral formulation of Phenoxodiol to weekly carboplatin + placebo. The combined overall response rate was < 1% [data not published]. The lack of efficacy was thought related to poor bioavailability of active (unconjugated) Phenoxodiol when administered orally
- Intravenous ME-143 was selected for clinical development based on:
  - a similar mechanism of action as Phenoxodiol
  - the apparent clinical activity of IV Phenoxodiol when combined with platinum analogues
  - significantly greater *in vitro* potency compared to Phenoxodiol (see Table 1)

	Breast (SK-BR-3)	Melanoma (MM200)	Lung (NIC-H460)	Ovarian (CP70)	Prostate (PC3)
Phenoxodiol	16.95 μM	9.88 μM	4.4 μM	4.1 μM	6.46 μM
ME-143	0.07 μM	0.53 μM	0.58 μM	0.28 μM	0.27 μM

Table 1

- The importance of combination therapy is demonstrated in the xenograft study shown in Figure 2. Utilizing the A549 NSCLC model, only the combination of weekly i.p. ME-143 and cisplatin resulted in statistically significant tumor cell growth inhibition

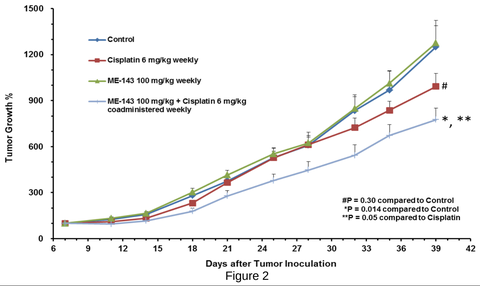


Figure 2

Methods

- A 3+3 dose escalation design was utilized
- 4 dose cohorts: 2.5, 5, 10, and 20mg/kg
- ME-143, formulated in 30% Captisol®, was administered IV over 30 minutes, weekly times 3, followed by a 1 week break, and then continuous weekly dosing until progressive disease (PD) or unacceptable toxicity
- Standard eligibility criteria were utilized including age ≥ 18 years, the diagnosis of a solid tumor with no standard treatment options, ECOG PS < 2, adequate organ function, and a normal QTc interval
- Dense PK sampling was performed at 0, 5, 10, 20, 30 60, 90, 120, 180, 240, 300, 360 minutes and 24 hours post-infusion day 1 and 15 of the first treatment cycle
- A DLT was defined as a NCI CTCAE v4.0 ≥ grade 3 judged by the investigator as possibly, probably or definitely related to study drug
- Tumor assessments were required at least every 12 weeks and scored according to RECIST v1.1.

Results

- Between September 16, 2011 and April 25, 2012, 15 patients were enrolled in this study. Selected demographic and baseline characteristics are shown in Table 2

Cohort/Patient		Age	Gender	Diagnosis	Number of Prior Therapies
1 2.5 mg/kg	1	68	F	Colorectal	2
	2	74	M	Colorectal	5
	3	65	M	Colorectal	4
2 5 mg/kg	4	75	F	Colorectal	2
	5	82	F	Endometrial	7
	6	66	F	Colorectal	5
3 10 mg/kg	7	48	F	Small Cell Lung	3
	8	65	F	Pancreas	5
	9	70	F	Endometrial	2
4 20 mg/kg	10	60	F	Colorectal	3
	11	44	F	Anal	4
	12	48	M	Cholangiocarcinoma	1
	13	20	M	Sarcoma	4
	14	80	F	Head and Neck	3
	15	68	M	Colorectal	7

Table 2

Treatment Emergent Adverse Events (AE)
(number of patients experiencing an event)

	Dosing Cohort								All AE, All Grades n=15	≥ Grade 3	
	2.5 mg/kg n=3		5.0 mg/kg n=3		10 mg/kg n=3		20 mg/kg n=7				
Adverse Event Preferred Term	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4		Related	Not related
Fatigue	3	.	1	.	.	.	2	.	6	.	.
Anemia	.	.	1	.	.	.	2	.	3	.	.
Diarrhea	2	.	1	.	.	.	.	.	3	.	.
Nausea	1	.	1	.	.	.	1	.	3	.	.
Anxiety	1	.	.	.	.	.	1	.	2	.	.
Back Pain	.	.	.	.	1	.	1	.	2	.	.
Cough	2	.	.	.	.	.	.	.	2	.	.
Dyspnea Exertional	1	.	1	.	.	.	.	.	2	.	.
Headache	1	.	1	.	.	.	.	.	2	.	.
Pneumonia	.	2	.	.	.	.	.	.	2	.	2
Asthenia	.	.	1	.	.	.	.	.	1	.	.
Confusional State	1	.	.	.	.	.	.	.	1	.	.
Constipation	1	.	.	.	.	.	.	.	1	.	.
Decreased Appetite	.	.	1	.	.	.	.	.	1	.	.
Dysphagia	.	.	.	.	.	.	1	.	1	.	.
Dyspnea	.	.	.	.	1	.	.	.	1	.	.
Dysuria	.	.	.	.	.	.	1	.	1	.	.
Edema Peripheral	.	.	.	.	1	.	.	.	1	.	.
Electrocardiogram QT Prolonged	.	.	1	.	.	.	.	.	1	.	.
Elevated Alkaline Phosphatase	.	.	.	.	.	.	.	1	1	.	1
Facial Pain	.	.	.	.	.	.	1	.	1	.	.
Fall	.	.	.	.	1	.	.	.	1	.	.
Hypertension	.	.	1	.	.	.	.	.	1	.	.
Hyponatremia	.	.	.	.	.	.	.	1	1	.	1
Hypoxia	1	.	.	.	.	.	.	.	1	.	.
Infusion Reaction	.	.	.	.	.	.	.	1	1	1	.
Muscle Twitching	.	.	.	.	.	.	1	.	1	.	.
Neuropathy Peripheral	.	.	.	.	.	.	1	.	1	.	.
Oral Herpes	.	.	1	.	.	.	.	.	1	.	.
Pain	.	.	1	.	.	.	.	.	1	.	.
Paranasal Sinus Hypersecretion	.	.	.	.	.	.	1	.	1	.	.
Productive Cough	.	.	.	.	1	.	.	.	1	.	.
Respiratory Tract Congestion	.	.	1	.	.	.	.	.	1	.	.
Supraventricular Tachycardia	.	.	.	.	.	.	1	.	1	.	1
Visual Impairment	1	.	.	.	.	.	.	.	1	.	.
Vomiting	1	.	.	.	.	.	.	.	1	.	.
Wheezing	1	.	.	.	.	.	.	.	1	.	.

Treatment Emergent Adverse Events Possibly, Probably, or Definitely Related to ME-143
(number of patients experiencing an event)

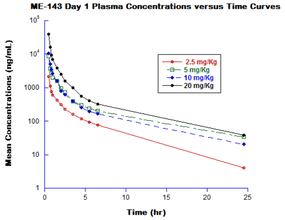
	Dosing Cohort			
	2.5 mg/kg n=3	5.0 mg/kg n=3	10.0 mg/kg n=3	20.0 mg/kg n=6
All Grades	2*	1**	0	0
≥ Grade 3	0	0	0	1***

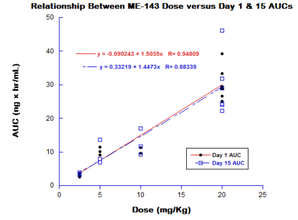
*Patient 1: Fatigue, Constipation, Confusional State; Patient 2: Fatigue, Diarrhea, Nausea, Vomiting.
**Electrocardiogram QT prolonged, Fatigue, Pain, Decreased appetite, Nausea, Diarrhea.
***Infusion Reaction, Patient 1: Grade 2 infusion reaction noted in 3 minutes following the start of the 7th infusion. Infusion interrupted, standard medications administered, infusion was restarted and completed without further issues. Prior to the 8th treatment, pre-treatment with palonosetron and dexamethasone was given. A Grade 4 infusion reaction occurred within 2 minutes of treatment initiation. The patient experienced an anaphylactic reaction and was hospitalized. Treatment was immediately and permanently discontinued.

Pharmacokinetic Results

	C_{max} (mg/mL)	$T_{1/2}$ (hr)*	AUC ∞ (mg*hr/mL)	CL (L/hr)
2.5mg/kg, Day 1	2.18	4.12	2.96	69.73
2.5 mg/kg, Day 15	3.55	4.36	3.57	56.18
5.0 mg/kg, Day 1	8.62	6.95	10.27	37.30
5.0 mg/kg, Day 15	8.94	5.12	9.47	41.32
10.0 mg/kg, Day 1	10.77	5.54	10.42	58.96
10.0 mg/kg, Day 15	17.61	4.89	12.62	59.41
20.0 mg/kg, Day 1	40.13	5.47	30.15	60.42
20.0 mg/kg, Day 15	37.48	5.64	29.61	61.43

*Harmonic Mean





Clinical Outcomes

- 15 patients have discontinued study treatment; 14 due to PD and 1 due to AE
- Median time on treatment was 50 days
- Best response was stable disease in 1 patient at 106 days

Conclusions

- ME-143 was generally well tolerated at all dose levels up to 20 mg/kg on a weekly dosing schedule with the exception of a single, severe infusion reaction
- Maximum Tolerated Dose (MTD) was defined as 20 mg/kg
- Pharmacokinetics demonstrated a linear relationship between dose and both C_{max} and AUC at day 1 and 15, with a harmonic mean $t_{1/2}$ of 5.4 hours (day 1) and 5.1 hours (day 15)
- The estimated AUC of the MTD, ~30 μg*hr/mL, is approximately 30 times higher than the exposure achieved with Phenoxodiol in the phase II study of Phenoxodiol plus cisplatin in refractory ovarian cancer
- The AUC also exceeded the target level determined from preclinical studies ($AUC_{t\text{-}0}$ ~10 μg*hr/mL)
- Phase II development is planned in combination with cytotoxic therapy

References

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