Disclaimer: The following information is fictional and is only intended for the purposes of illustrating key concepts for results data entry in the Protocol Registration System (PRS).

Example Dose Escalation Study Design

(A Dose Escalation Study of Ender-G in Adults with Cancer)

Methods

Study Design

This single-group open label dose-escalation study of Ender-G enrolled patients with various cancer types from a single academic medical center in Bethesda, Maryland, in the United States. All participants were informed about the study and potential risks and required to provide written informed consent prior to undergoing study-related procedures.

A traditional 3 + 3 dose escalation design[1] was implemented. Successive cohorts of participants (3 participants /cohort) were each started on a fixed dose of Ender-G. The protocol specified 100 mg/m^2 of Ender-G twice a day administered intravenously, for the first cohort. Successive cohorts were given doses of 125 and 150 mg/m^2 twice a day.

Dose escalation continued until dose-limiting toxicities (DLTs, see *Primary Endpoint*) were observed in >33% of the participants. If no DLTs were observed for 8 weeks after administration of Ender-G, a new cohort was enrolled at the next planned dose level. If DLTs were observed in one participant in the cohort, another three participants were treated with the same dose level. The maximum-tolerated dose (MTD) was defined as one dose level below the dose in which DLTs were observed in >33% of the participants. In other words, if DLTs were observed in at least 2 of 3 participants, the MTD was determined to be the dose administered to the previous cohort. Similarly, in a cohort of 6 participants, 3 of the 6 participants would have to experience DLTs to determine the MTD.

Toxicities were graded using the Common Toxicity Criteria Version 3.0 (CTC 3.0)[2] If the CTC 3.0 did not apply to an adverse event, it was graded as mild, moderate, or severe. DLT was defined as any CTC 3.0 Grade 3 or 4 adverse event determined to be related to Ender-G.

Health status assessments, including physical exams, complete blood chemistry, and urinalysis were conducted at weeks 1, 2, 4, and 8.

The protocol and informed consent documents were reviewed and approved by the hospital human subjects review board and the study was performed in accordance with the Declaration of Helsinki.

Patient Eligibility

Adults over 21 years of age with clinically confirmed cancer were eligible for the study. Other inclusion criteria included (1) clinically significant electrocardiogram (ECG) abnormalities, (2) White blood cell (WBC) count ≤ 2,000/mm^3, and (3) a World Health Organization (WHO) performance status < 3. Patients receiving enzyme-inducing anticonvulsants, steroids, or other experimental drugs were excluded. Patients with a history of migraines were also excluded.

Study Objectives

The primary aim of the study was to establish the MTD of Ender-G in participants with cancer.

The secondary outcomes were pharmacokinetic and safety measures of Ender-G in participants with cancer.

Results

Disposition of Participants

A total of 15 participants were enrolled between January and April 2009 for three dose levels (Figure 1). The last visit of the final participant for assessment of the primary and secondary outcomes was in June 2009. Participant characteristics are listed in Table 1.

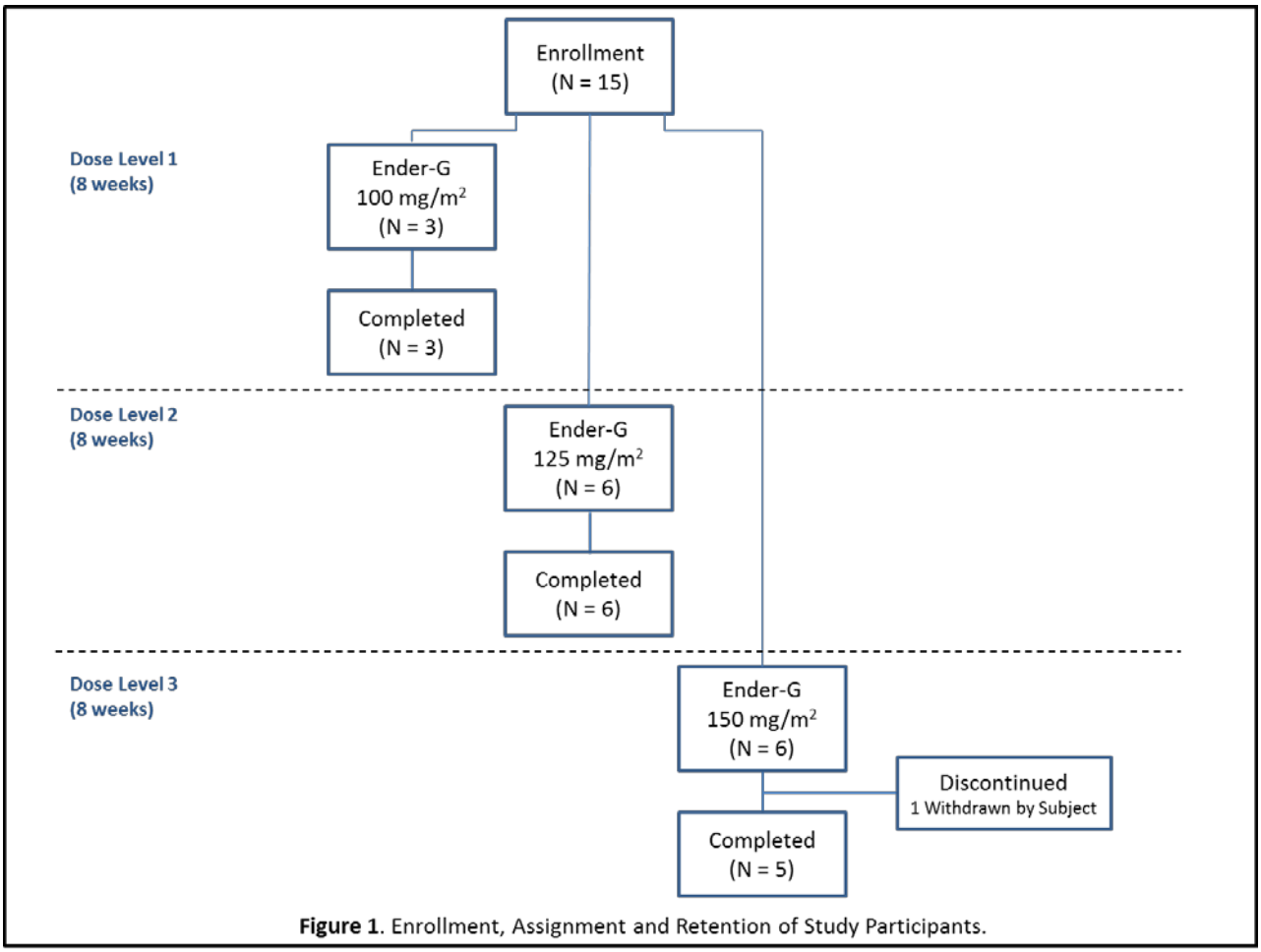

Figure 1. Enrollment, Assignment and Retention of Study Participants.

Outcomes

Primary Endpoint

In order to determine the primary endpoint, MTD, the number of participants who experienced DLTs over an 8-week period were assessed at each dose level. A DLT was any Grade 3 or 4 adverse event (AE) using the Common Toxicity Criteria Version 3.0 (CTC 3.0) that was possibly drug-related. CTE 3.0 Grade 3 is a severe AE and Grade 4 is a life-threatening or disabling AE. Such events interfere with activities of daily living and include: skin toxicity, diarrhea or antidiarrheal therapy, vomiting at same grade for >4 days despite aggressive antiemetic therapy, central nervous system, lung or renal toxicity or elevation of liver transaminases or bilirubin lasting more than 1 week. The Maximum Tolerated Dose (MTD) is defined as the dose level below the dose at which > 33% of participants experienced a DLT. The MTD analysis population consisted of all participants who received at least one dose of Ender-G.

No DLTs were observed by participants receiving the 100 mg/m^2 dose level. One participant experienced a DLT among the three participants receiving 125 mg/m^2 (Grade 4 vomiting), thus three more participants were added to the cohort of which none experienced a DLT. One participant experienced a DLT among the three participants receiving 150 mg/m^2 (Grade 4 vomiting), thus three more participants were added to the cohort of which two experienced a DLT (Grade 3 renal toxicity and Grade 4 diarrhea). Three DLTs in 3/6 participants (50%) at the 150 mg/m^2 dose established the MTD as 125 mg/m^2.

Table 1. Baseline Demographics and Disease Characteristics of Participants

CHARACTERISTIC	ALL TREATED PARTICIPANTS N = 15
Age, years, median (full range)	67 (36–82)
Sex, n (%)	
Female	7 (46.7)
Male	8 (43.3)
WHO performance status [a], n (%)	
0	5 (33.3)
1	7 (46.7)
2	3 (20.0)
Tumor type, n (%)	
NSCLC [b]	5 (33.3)
Prostate	5 (33.3)
Ovary	5 (33.3)
Number of prior chemotherapy regimens, n (%)	
1	4 (26.7)
2	2 (13.3)
3	2 (13.3)
≥4	7 (46.7)

[a] World Health Organization (WHO) performance status is measured on a scale from 0 to 5, with 0 = Asymptomatic (Fully active, able to carry on all predisease activities without restriction); 1 = Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work); 2 = Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours); 3 = Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours); 4 = Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair); and 5 = Death
[b] *NSCLC* non-small-cell lung cancer

Secondary Endpoints

Blood samples were obtained for pharmacokinetic analysis of Ender-G prior to the initial dose on day 1 and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 16, 24, 36, 48 and 72 hours post-dose. Plasma concentrations were determined using a validated high-pressure liquid chromatography method. Measurements included maximum observed plasma concentration of Ender-G (Cmax), time to maximum observed plasma concentration of Ender-G (Tmax), and area under the concentration-time curve from 0 to 72 hours post-dose.

The safety of Ender-G was summarized by the number of participants experiencing any adverse event(s), serious and non-serious, which were collected by systematic assessment using terms from the CTC 3.0. All participants in all 3 cohorts experienced at least one non-serious adverse event. Serious adverse events were considered to be Grade 3 or 4.

The results of the pharmacokinetic analysis are presented in Table 2 and the summary of adverse events is in Table 3.

References

1. Le Tourneau C, Lee JJ, and Siu LL. (2009) "Dose escalation methods in phase I cancer clinical trials." *J Natl Cancer Inst* 101(10): 708-20.
2. http://ctep.cancer.gov/protocolDevelopment/electronic.applications/docs/ctcaev3.pdf
3. Oken MM, et al. (1982) "Toxicity and response criteria of the Eastern Cooperative Oncology Group." *Am J Clin Oncol* 5(6): 649-55.

Table 2. Pharmacokinetic Parameters for Each Cohort

Cohort	Dose (mg/m^2)	No. of Participants	C_{max}[a] (mcg/ml)	AUC_{0-72}[b] (mcg*h/ml)	t_{max}[c] hours
1	100	3	0.535 (119)	7.41 (7.8)	5 (4 to 5)
2	125	6	1.10 (75)	18.1 (12.7)	5 (5 to 6)
3	150	6	1.58 (102)	18.8 (14.3)	5 (2 to 5)

[a] Geometric Mean (% gCV)
[b] Mean (Standard Deviation)
[c] Median (Full Range)

Table 3a. Participants with Grade 1 or 2 Adverse Events

ADVERSE EVENT	COHORT 1 100 MG/M^2 N = 3	COHORT 2 125 MG/M^2 N = 6	COHORT 3 150 MG/M^2 N = 6
Nausea	3	3	3
Diarrhea	1	3	2
Vomiting	1	3	5
Fatigue	1	2	6
Rash	1	3	5
Anorexia	3	1	4
Pain in extremity	2	2	4
Cough	2	2	4
Chills	2	1	3
Pyrexia	2	1	3
Headache	2	1	3
Dry skin	2	1	3
Pruritus	2	1	3

Table 3b. Participants with Grade 3 or 4 Adverse Events

ADVERSE EVENT	COHORT 1 100 MG/M^2 N = 3	COHORT 2 125 MG/M^2 N = 6	COHORT 3 150 MG/M^2 N = 6
Diarrhea[+]	0	0	1
Renal toxicity[*]	0	0	1
Vomiting[+]	0	1	1

[+] Grade 4
* Grade 3