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Example Dose Escalation Study Design***

This study has been completed.

Sponsor:	PRS Training
Collaborators:	
Information provided by (Responsible Party):	, National Library of Medicine (NLM)
ClinicalTrials.gov Identifier:	

Purpose

The primary aim of the study is to establish the maximum-tolerated dose (MTD) of Ender-G in participants with cancer. The secondary aims are to describe the pharmacokinetics of Ender-G and the toxic effects of Ender-G in participants with cancer.

Condition	Intervention	Phase
Cancer	Drug: Ender-G	Phase 1

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, N/A, Safety Study

Official Title: A Phase I Clinical Trial of Ender-G in Adults With Cancer

Further study details as provided by , National Library of Medicine (NLM):

Primary Outcome Measure:

- Maximum Tolerated Dose (MTD) of Ender-G [Time Frame: 40 weeks] [Designated as safety issue: Yes]

  MTD was determined by testing increasing doses up to 150 mg/m^2 twice a day via IV on dose escalation cohorts 1 to 3 with 3 to 6 participants each. MTD reflects the highest dose of drug that did not cause a Dose-Limiting Toxicity (DLT) in > 33% of participants. DLTs were defined as any Ender-G-related Common Toxicity Criteria Version 3.0 Grade 3 or 4 adverse events (reported in the subsequent

Primary Outcome Measure).

- Number of Participants Who Experienced Dose-Limiting Toxicities (DLTs) [Time Frame: Up to 8 Weeks per dose] [Designated as safety issue: Yes]
  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 Ender-G-related. CTE 3.0 Grade 3 is a severe AE and Grade 4 is a life-threatening or disabling AE. (e.g., 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) DLTs were collected to determine the Maximum-Tolerated Dose (MTD), which is defined as the dose level below the dose at which > 33% of participants experienced a DLT.

Secondary Outcome Measures:

- Maximum Observed Plasma Concentration of Ender-G (Cmax) [Time Frame: 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] [Designated as safety issue: No]
  Blood samples were obtained and plasma concentrations were determined using a validated high-pressure liquid chromatography method.

- Time to Maximum Observed Plasma Concentration of Ender-G (Tmax) [Time Frame: 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] [Designated as safety issue: No]
  Blood samples were obtained and plasma concentrations were determined using a validated high-pressure liquid chromatography method.

- Area Under the Concentration-Time Curve (AUC 0-72h) [Time Frame: 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] [Designated as safety issue: No]
  Blood samples were obtained and plasma concentrations were determined using a validated high-pressure liquid chromatography method.

- The Number of Participants Who Experienced Serious or Non-Serious Adverse Events [Time Frame: Up to 8 Weeks for each dosing cohort] [Designated as safety issue: Yes]
  A non-serious adverse event is any untoward medical occurrence. A serious adverse event is any adverse event that meets one or more of the following: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; requires intervention to prevent permanent impairment or damage. Specific Adverse Event terms are provided in the Adverse Event module.

Enrollment: 15
Study Start Date: January 2009
Study Completion Date: June 2009
Primary Completion Date: June 2009

Arms	Assigned Interventions
Experimental: Ender-G Dose Escalation A traditional 3 + 3 dose escalation design will be implemented. Successive cohorts of patients (3 participants/cohort) will each be started on a fixed dose of Ender G. If no DLTs are observed in the first 3 participants, then a new cohort will be enrolled at the next planned dose level. If 1 participant has a DLT, then 3 more will be enrolled at the same dose level. If ≤ 2 of 6 experience a DLT, then a new cohort will be enrolled at the next dose level. If ≥ 3 of 6 experience a DLT, then no new cohort will be enrolled. The protocol specifies 100 mg/m^2 twice a day, via intravenous catheter (IV), for the first cohort. Successive cohorts will be given doses of 125 and 150 mg/m^2 twice a day also via intravenous catheter (IV).	Drug: Ender-G 100, 125 or 150 mg/m^2 intravenous solution

This study will enroll patients with various cancer types from a single academic medical center in the United States. All participants will be 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 will be implemented. Successive cohorts of patients (3 participants/cohort) will each be started on a fixed dose of Ender-G. The protocol specifies 100 mg/m^2 twice a day, via intravenous catheter (IV), for the first cohort. Successive cohorts will be given doses of 125 and 150 mg/m^2 twice a day also via intravenous catheter (IV).

Dose escalation will continue until the maximum-tolerated dose (MTD), defined as the one dose level below the dose in which dose-limiting toxicities (DLTs) are observed in at least two participants within two cohorts of three participants (>33%) of the participants. If no DLTs are observed for 8 weeks after administration of Ender-G, a new cohort will be enrolled at the next planned dose level. If DLTs are observed in 2 of the three participants, the MTD will be determined to be the dose administered to the previous cohort. If DLTs are observed in one participant in the cohort, another three participants will be treated with the same dose level. In that case, 3 of the 6 participants would have to experience DLTs to determine the MTD.

Toxicities will be graded using the Common Toxicity Criteria Version 3.0 (CTC 3.0). If the CTC 3.0 does not apply to an adverse event, it will be graded as mild, moderate, or severe. DLT is defined as any Ender-G-related CTC 3.0 grade 3 or 4 adverse event.

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

Eligibility

Ages Eligible for Study: 21 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Clinically confirmed cancer
- Clinically significant electrocardiogram (ECG) abnormalities
- White blood cell (WBC) count ≤ 2,000/mm^3
- A World Health Organization (WHO) performance status < 3

Exclusion Criteria:

- Receiving enzyme-inducing anticonvulsants, steroids, or other experimental drugs
- History of migraines

Contacts and Locations

Locations

United States, Maryland

Bethesda, Maryland, United States

More Information

Responsible Party: , Information Research Specialist, National Library of Medicine (NLM)
Study ID Numbers: MTD-CA
Health Authority: United States: Food and Drug Administration

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Study Results

Participant Flow

Reporting Groups

	Description
Ender-G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G twice a day, via intravenous catheter (IV), for 8 weeks.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G twice a day, via intravenous catheter (IV), for 8 weeks.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G twice a day, via intravenous catheter (IV), for 8 weeks.

Cohort 1: Dose Level 1 (8 Weeks)

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
STARTED	3	0	0

COMPLETED	3	0	0
Not Completed	**0**	**0**	**0**

Cohort 2: Dose Level 2 (8 Weeks)

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
STARTED	0	6	0
COMPLETED	0	6	0
Not Completed	**0**	**0**	**0**

Cohort 3: Dose Level 3 (8 Weeks)

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
STARTED	0	0	6
COMPLETED	0	0	5
Not Completed	**0**	**0**	**1**
Withdrawal by Subject	0	0	1

Baseline Characteristics

Reporting Groups

	Description
All Participants	All participants who received at least 1 dose of Ender-G, either at 100 mg/m^2, 125 mg/m^2 or 150 mg/m^2 via IV.

Baseline Measures

	All Participants
Number of Participants	15
Age Continuous *[units: years]* *Median (Full Range)*	67 (36 to 82)
Gender, Male/Female *[units: participants]*	
Female	7

Male	8
Region of Enrollment	
[units: participants]	15
United States	
Study Specific Characteristic [WHO Performance Status] [1]	
[units: participants]	
0 (Asymptomatic)	5
1 (Symptomatic, but ambulatory)	7
2 (Symptomatic, <50% in bed)	3
Study Specific Characteristic [Cancer Type]	
[units: participants]	
Non-small-cell lung carcinoma (NSCLC)	5
Prostate	5
Ovary	5
Study Specific Characteristic [Number of Prior Chemotherapy Regimens]	
[units: participants]	
1	4
2	2
3	2
≥ 4	7

[1] World Health Organization (WHO) performance status:

- 0 = Asymptomatic (Fully active, able to carry out predisease activities without restriction)
- 1 = Symptomatic, but ambulatory (only physically strenuous activity restricted)
- 2 = Symptomatic, <50% in bed (Ambulatory, capable of all self care, unable to carry out any work activities. Up and about >50% of waking hours)
- 3 = Symptomatic, >50% in bed, but not bedbound (only limited self-care, confined to bed or chair >50% of waking hours)
- 4 = Bedbound (Completely disabled, no self-care, Totally confined to bed or chair)
- 5 = Death

Outcome Measures

1. Primary Outcome Measure:

Measure Title	**Maximum Tolerated Dose (MTD) of Ender-G**
Measure Description	MTD was determined by testing increasing doses up to 150 mg/m^2 twice a day via IV on dose escalation cohorts 1 to 3 with 3 to 6 participants each. MTD reflects the highest dose of drug that did not cause a Dose-Limiting Toxicity (DLT) in > 33% of participants. DLTs were defined as any Ender-G-related Common Toxicity Criteria Version 3.0 Grade 3 or 4 adverse events (reported in the subsequent Primary Outcome Measure).
Time Frame	40 weeks
Safety Issue?	Yes

Population Description -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

Reporting Groups

	Description
All Participants	All participants who received at least 1 dose of Ender-G, either at 100 mg/m^2, 125 mg/m^2 or 150 mg/m^2 via IV.

Measured Values

	All Participants
Number of Participants Analyzed	15
Maximum Tolerated Dose (MTD) of Ender-G *[units: mg/m^2]*	125

2. Primary Outcome Measure:

Measure Title	**Number of Participants Who Experienced Dose-Limiting Toxicities (DLTs)**
Measure Description	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 Ender-G-related. CTE 3.0 Grade 3 is a severe AE and Grade 4 is a life-threatening or disabling AE. (e.g., 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) DLTs were collected to determine the Maximum-Tolerated Dose (MTD), which is defined as the dose level below the dose at which > 33% of participants experienced a DLT.
Time Frame	Up to 8 Weeks per dose

Safety Issue?	Yes

Population Description -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

All participants who received at least one dose of Ender-G.

Reporting Groups

	Description
Ender-G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 8 weeks.

Measured Values

	Ender-G 100 mg/m^2	**Ender-G 125 mg/m^2**	**Ender-G 150 mg/m^2**
Number of Participants Analyzed	3	6	6
Number of Participants Who Experienced Dose-Limiting Toxicities (DLTs) *[units: participants]*	0	1	3

3. Secondary Outcome Measure:

Measure Title	**Maximum Observed Plasma Concentration of Ender-G (Cmax)**
Measure Description	Blood samples were obtained and plasma concentrations were determined using a validated high-pressure liquid chromatography method.
Time Frame	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
Safety Issue?	No

Population Description -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

Reporting Groups

	Description

Ender-G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 8 weeks.

Measured Values

	Ender-G 100 mg/m^2	**Ender-G 125 mg/m^2**	**Ender-G 150 mg/m^2**
Number of Participants Analyzed	3	6	6
Maximum Observed Plasma Concentration of Ender-G (Cmax)			
[units: mcg/mL]	0.535 (119%)	1.10 (75%)	1.58 (102%)
Geometric Mean (Geometric Coefficient of Variation)			

4. Secondary Outcome Measure:

Measure Title	**Time to Maximum Observed Plasma Concentration of Ender-G (Tmax)**
Measure Description	Blood samples were obtained and plasma concentrations were determined using a validated high-pressure liquid chromatography method.
Time Frame	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
Safety Issue?	No

Population Description -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

Reporting Groups

	Description
Ender-G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 8 weeks.

Measured Values

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
Number of Participants Analyzed	3	6	6
Time to Maximum Observed Plasma Concentration of Ender-G (Tmax) *[units: hours]* Median (Full Range)	5 (4 to 5)	5 (5 to 6)	5 (2 to 5)

5. Secondary Outcome Measure:

Measure Title	**Area Under the Concentration-Time Curve (AUC 0-72h)**
Measure Description	Blood samples were obtained and plasma concentrations were determined using a validated high-pressure liquid chromatography method.
Time Frame	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
Safety Issue?	No

Population Description -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

Reporting Groups

	Description
Ender-G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 8 weeks.

Measured Values

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
Number of Participants Analyzed	3	6	6
Area Under the Concentration-Time Curve (AUC 0-72h) *[units: mcg*h/mL]* Mean ± Standard Deviation	7.41 ± 7.8	18.1 ± 12.7	18.8 ± 14.3

6. Secondary Outcome Measure:

Measure Title	**The Number of Participants Who Experienced Serious or Non-Serious Adverse Events**
Measure Description	A non-serious adverse event is any untoward medical occurrence. A serious adverse event is any adverse event that meets one or more of the following: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; requires intervention to prevent permanent impairment or damage. Specific Adverse Event terms are provided in the Adverse Event module.
Time Frame	Up to 8 Weeks for each dosing cohort
Safety Issue?	Yes

Population Description -- *Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate:*

Reporting Groups

	Description
Ender G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 8 weeks.
Ender G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 8 weeks.

Measured Values

	Ender G 100 mg/m^2	**Ender G 125 mg/m^2**	**Ender G 150 mg/m^2**
Number of Participants Analyzed	3	6	6
The Number of Participants Who Experienced Serious or Non-Serious Adverse Events *[units: participants]*	3	6	6

Reported Adverse Events

Reporting Groups

Description

Ender-G 100 mg/m^2	Cohort 1: Participants were administered 100 mg/m^2 of Ender-G via IV twice a day for 8 weeks. A traditional 3 + 3 dose escalation design was implemented. Successive cohorts of patients were each started on a fixed dose of Ender-G. Dose escalation continued until the maximum-tolerated dose. If no dose-limiting toxicities were observed for 8 weeks after administration of Ender-G, a new cohort was enrolled at the next planned dose level.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 8 weeks. A traditional 3 + 3 dose escalation design was implemented. Successive cohorts of patients were each started on a fixed dose of Ender-G. Dose escalation continued until the maximum-tolerated dose. If no dose-limiting toxicities were observed for 8 weeks after administration of Ender-G, a new cohort was enrolled at the next planned dose level.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 8 weeks. A traditional 3 + 3 dose escalation design was implemented. Successive cohorts of patients were each started on a fixed dose of Ender-G. Dose escalation continued until the maximum-tolerated dose. If no dose-limiting toxicities were observed for 8 weeks after administration of Ender-G, a new cohort was enrolled at the next planned dose level.

Time Frame	Up to 8 weeks for each dosing cohort
Additional Description	

Serious Adverse Events

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
Total # participants affected/at risk	**0/3 (0%)**	**1/6 (16.67%)**	**3/6 (50%)**
Gastrointestinal disorders			
Diarrhea † A			
# participants affected/at risk	0/3 (0%)	0/6 (0%)	1/6 (16.67%)
Vomiting † A			
# participants affected/at risk	0/3 (0%)	1/6 (16.67%)	1/6 (16.67%)
Renal and urinary disorders			
Renal Toxicity † A			
# participants affected/at risk	0/3 (0%)	0/6 (0%)	1/6 (16.67%)

† Indicates events were collected by systematic assessment.

A Term from vocabulary, CTCAE (3.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Ender-G 100 mg/m^2	Ender-G 125 mg/m^2	Ender-G 150 mg/m^2
Total # participants affected/at risk	**3/3 (100%)**	**6/6 (100%)**	**6/6 (100%)**
Endocrine disorders			
Chills † A			
# participants affected/at risk	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Gastrointestinal disorders			
Diarrhea † A			
# participants affected/at risk	1/3 (33.33%)	3/6 (50%)	2/6 (33.33%)
Nausea † A			
# participants affected/at risk	3/3 (100%)	3/6 (50%)	3/6 (50%)
Vomiting † A			
# participants affected/at risk	1/3 (33.33%)	3/6 (50%)	5/6 (83.33%)
General disorders			
Fatigue † A			
# participants affected/at risk	1/3 (33.33%)	2/6 (33.33%)	6/6 (100%)
Immune system disorders			
Pyrexia † A			
# participants affected/at risk	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Musculoskeletal and connective tissue disorders			
Pain in Extremity † A			
# participants affected/at risk	2/3 (66.67%)	2/6 (33.33%)	4/6 (66.67%)
Nervous system disorders			
Headache † A			
# participants affected/at risk	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Psychiatric disorders			
Anorexia † A			

# participants affected/at risk	3/3 (100%)	1/6 (16.67%)	4/6 (66.67%)
Respiratory, thoracic and mediastinal disorders			
Cough † A			
# participants affected/at risk	2/3 (66.67%)	2/6 (33.33%)	4/6 (66.67%)
Skin and subcutaneous tissue disorders			
Dry Skin † A			
# participants affected/at risk	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Pruritus † A			
# participants affected/at risk	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Rash † A			
# participants affected/at risk	1/3 (33.33%)	3/6 (50%)	5/6 (83.33%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, CTCAE (3.0)

More Information

Certain Agreements:

All Principal Investigators ARE employed by the organization sponsoring the study.

Limitations and Caveats -- *Limitations of the study, such as early termination leading to small numbers of subjects analyzed and technical problems with measurement leading to unreliable or uninterpretable data:*

[Not specified.]

Results Point of Contact:

Name/Official Title: June Bug
Organization: PRS Training
Phone: 555-555-5555
Email: register@clinicaltrials.gov

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