Dose Escalation Study Design Example (With Results)

This study has been completed.

Sponsor: PRS Results Training

Information provided by (Responsible Party): PRS Results Training

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

Full Text View

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: Allocation: N/A
Endpoint Classification: Safety Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase 1 Clinical Trial of Ender-G in Adults With Cancer

Further study details as provided by PRS Results Training

Primary Outcome Measure:

- Maximum Tolerated Dose (MTD) of Ender-G [Time Frame: Up to 8 weeks for each dosing cohort] [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 Terminology Criteria for Adverse Events Version 3.0 (CTCAE 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 for each dosing cohort] [Designated as safety issue: Yes]

  A DLT was any Grade 3 or 4 adverse event (AE) using the Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE 3.0) that was possibly Ender-G-related. CTCAE 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

Detailed Description

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, via intravenous catheter (IV), twice a day for 4 weeks for the first cohort. Successive cohorts will be given doses of 125 and 150 mg/m^2 twice a day.

Dose escalation will continue until the maximum-tolerated dose (MTD), defined as one dose level below the dose in which dose-limiting toxicities (DLTs) are observed in >33% of the participants (e.g., in at least 2 participants in a cohort of 3 or in at least 3 participants in a cohort of 6). If no DLTs are observed for 4 weeks after administration of the last dose 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 Terminology Criteria for Adverse Events Version 3.0 (CTCAE 3.0). If the CTCAE 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 CTCAE 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.

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

Eligibility

Ages Eligible for Study: 21 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Inclusion Criteria

- Clinically confirmed cancer
- A World Health Organization (WHO) performance status < 3

Exclusion Criteria

- Receiving enzyme-inducing anticonvulsants, steroids, or other experimental drugs
- History of migraines
- Clinically significant electrocardiogram (ECG) abnormalities
- White blood cell (WBC) count ≤ 2,000/mm^3

Contacts and Locations

Locations

United States, Maryland

Bethesda, Maryland, United States

More Information

Responsible Party: PRS Results Training
Study ID Numbers: TTTDoseEscalationR
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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
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 4 weeks, with 4 weeks of follow-up after the last dose was administered.

Cohort 1: Dose Level 1 (Weeks 1-8)

	Number of Participants		
	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 (Weeks 9-24)

	Number of Participants		
	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 (Weeks 25-40)

	Number of Participants		
	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

Analysis 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.)

[No text entered.]

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

[A] 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 Terminology Criteria for Adverse Events Version 3.0 (CTCAE 3.0) Grade 3 or 4 adverse events (reported in the subsequent Primary Outcome Measure).
Time Frame	Up to 8 weeks for each dosing cohort
Safety Issue	Yes

Analysis 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.)

[No text entered.]

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 Terminology Criteria for Adverse Events Version 3.0 (CTCAE 3.0) that was possibly Ender-G-related. CTCAE 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 for each dosing cohort
Safety Issue	Yes

Analysis 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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.

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

Analysis 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.)

[No text entered.]

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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.

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] Geometric Mean (Geometric Coefficient of Variation)	0.535 (119%)	1.10 (75%)	1.58 (102%)

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

Analysis 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.)

[No text entered.]

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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.

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

Analysis 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.)

[No text entered.]

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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.

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

Analysis 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.)

[No text entered.]

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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.

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

Adverse Events

	Description
Time Frame	Up to 8 weeks for each dosing cohort
Additional Description	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 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 125 mg/m^2	Cohort 2: Participants were administered 125 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.
Ender-G 150 mg/m^2	Cohort 3: Participants were administered 150 mg/m^2 of Ender-G via IV twice a day for 4 weeks, with 4 weeks of follow-up after the last dose was administered.

Serious Adverse Events

	# Participants Affected/At Risk		
	Ender-G-100 mg/m^2	**Ender-G-125 mg/m^2**	**Ender-G-150 mg/m^2**
Total, serious adverse events	**0/3 (0%)**	**1/6 (16.67%)**	**3/6 (50%)**
Gastrointestinal disorders			
Diarrhea † 1 [A]	0/3 (0%)	0/6 (0%)	1/6 (16.67%)
Vomiting † 1 [B]	0/3 (0%)	1/6 (16.67%)	1/6 (16.67%)
Renal and urinary disorders			
Renal Toxicity † 1 [C]	0/3 (0%)	0/6 (0%)	1/6 (16.67%)

† Indicates events were collected by systematic assessment.
1 Term from vocabulary, CTCAE (3.0)
[A] Grade 4
[B] Grade 4
[C] Grade 3

Other Adverse Events

Frequency Threshold

Threshold above which other adverse events are reported: 0%

	# Participants Affected/At Risk		
	Ender-G-100 mg/m^2	Ender-G-125 mg/m^2	Ender-G-150 mg/m^2
Total, other (not including serious) adverse events	**3/3 (100%)**	**6/6 (100%)**	**6/6 (100%)**
Endocrine disorders			
Chills †1	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Gastrointestinal disorders			
Diarrhea †1	1/3 (33.33%)	3/6 (50%)	2/6 (33.33%)
Nausea †1	3/3 (100%)	3/6 (50%)	3/6 (50%)
Vomiting †1	1/3 (33.33%)	3/6 (50%)	5/6 (83.33%)
General disorders			
Fatigue †1	1/3 (33.33%)	2/6 (33.33%)	6/6 (100%)
Immune system disorders			
Pyrexia †1	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Muscular and connective tissue disorders			
Pain in Extremity †1	2/3 (66.67%)	2/6 (33.33%)	4/6 (66.67%)
Nervous system disorders			
Headache †1	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Psychiatric disorders			
Anorexia †1	3/3 (100%)	1/6 (16.67%)	4/6 (66.67%)
Respiratory, thoracic and mediastinal disorders			
Cough †1	2/3 (66.67%)	2/6 (33.33%)	4/6 (66.67%)
Skin and subcutaneous tissue disorders			
Dry Skin †1	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Pruritus †1	2/3 (66.67%)	1/6 (16.67%)	3/6 (50%)
Rash †1	1/3 (33.33%)	3/6 (50%)	5/6 (83.33%)

† Indicates events were collected by systematic assessment.
1 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.)

[No text entered.]

Results Point of Contact

Name/Official Title: PRS Training Lead
Organization: PRS Results Training
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