S2302 Pragmatica-Lung

A Prospective Randomized Study of Ramucirumab (NSC 749128) plus Pembrolizumab (MK-3475; NSC 776864) Versus Standard of Care for Participants Previously Treated with Immunotherapy for Stage IV or Recurrent NSCLC

Chair: Karen Reckamp, MD; Co-chair: Konstantin Dragnev, MD (Alliance)
Statistical Chair: Mary Redman, PhD
Co-statisticians: Jieling Miao, MS, James Moon, MS Study Champion(s): Wade Iams, MD (ECOG)
Lung community engagement subcommittee representative: Daniel Carrizosa, MD, MS

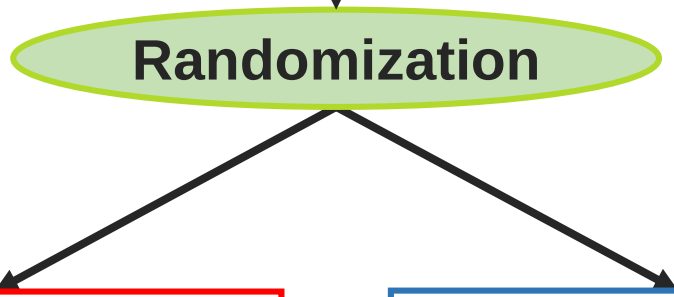
This is an FDA Registration Trial.

Schema

Previously treated Stage IV or recurrent non-small cell lung cancer

Primary endpoint: Overall Survival

Accrual Goal: 700 participants



ARM A
Standard of Care (SoC)*

ARM B
Ramucirumab
+
Pembrolizumab

* SoC treatment is to be determined by the treating investigator and participant. It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a "systemic therapy for advanced or metastatic disease-subsequent."

Background/Overview

- Effective therapy following frontline ICI for NSCLC is needed with limited FDA-approved options.
- S1800A was a Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for NSCLC patients previously treated with immunotherapy performed within the Lung-MAP platform.
  - Overall survival was significantly improved with a hazard ratio 0.69, median OS of 14.5 and 11.6 months, for pembrolizumab and ramucirumab vs. standard of care, respectively.
  - The aim of S2302 is to validate the improvement in overall survival in S1800A.
- S2302 is a clinical trial designed to reduce the burden of clinical trial participation and to promote the inclusion of all participants with the disease.

Pragmatic Design

Specifically, the goals of S2302 include:

- Empowerment of investigators to treat patients as would be done in real world practice.
- To decrease barriers to enrollment.
- To minimize the data collection burden.

- Such trials are in the ***Pragmatic Design*** class of studies***.***

- A **pragmatic** trial is designed to inform decision-makers on effectiveness, the comparative balance of benefits, burdens, and risks of a health intervention in clinical practice. In contrast to an “explanatory” trial that tests efficacy under ideal conditions, a **pragmatic** trial asks,

  “Does this intervention work under usual conditions?”

The **pragmatic** design approach for registrational intent trials is novel and potentially paradigm-changing.

Study Objectives

- **Primary study objective:** To compare **overall survival (OS)** between participants previously treated with platinum-based chemotherapy and immunotherapy for Stage IV or recurrent NSCLC randomized to pembrolizumab and ramucirumab versus SOC.

- **Secondary study objective:** To summarize reports of serious and unexpected high-grade (≥ Grade 3) treatment-related **adverse events** determined by the treating physician within each treatment arm.

** There are no other objectives

Stratification Factors

- Treatment assignment will be determined by block randomization with equal probability within block. Randomization will be stratified by the following two factors:
  - Most recent line of therapy for NSCLC included anti-PD-1 or anti-PD-L1 therapy (yes versus no).
  - Performance status (0 or 1 versus 2).

Eligibility

The eligibility criteria are notable for items that have been removed from historical eligibility lists to increase inclusion and generalizability.

- At least 18 yrs old with Stage IV or recurrent non-small cell lung cancer.
- Received at least one line of anti-PD-1 or anti-PD-L1 therapy for any stage of NSCLC, alone or combination therapy.
- No more than one line of anti-PD-1 or anti-PD-L1 for Stage IV or recurrent disease.
- Disease progression (in the opinion of the treating physician) > 84 days following initiation (C1/D1) of their most recent anti-PD-1 or PD-L1 therapy.
- Best response on anti-PD-1 or anti-PD-L1 therapy of stable, partial response or complete response for stage IV/recurrent NSCLC (in the opinion of the treating physician).
- Disease progression </= 365 days from initiation (C1/D1) of anti-PD-1 or PD-L1 therapy as neoadjuvant, adjuvant, and/or consolidation if only line of anti-PD-1 or anti-PD-L1 therapy.
- Received platinum-based chemotherapy and experienced disease progression (in the opinion of the treating physician) during or after this regimen.
- Known sensitizing mutation, for which an FDA-approved targeted therapy for NSCLC exists (e.g., EGFR, ALK, ROS1, BRAF, RET, NTRK, KRAS, HER2 and MET sensitizing mutations), must have previously received at least one of the approved therapy(s). Prior targeted therapy allowed for pts. with targetable alterations if all other criteria met.
- Ability to safely receive the investigational drug combination and the investigator's choice of SoC regimens per the current FDA-approved package insert(s), treating investigator's discretion, and institutional guidelines.
- Zubrod Performance Status of **0-2.**

** With consent, there are no other eligibility criteria.

Eligibility

The eligibility criteria are notable for items that have been removed from historical eligibility lists to increase inclusion and generalizability.

- At least 18 yrs old with Stage IV or recurrent non-small cell lung cancer.
- Received at least one line of anti-PD-1 or anti-PD-L1 therapy for any stage of NSCLC, alone or combination therapy.
- No more than one line of anti-PD-1 or anti-PD-L1 for Stage IV or recurrent disease.
- Disease progression (in the opinion of the treating physician) > cent anti-PD-1 or PD-L1 therapy.
- Best response on anti-PD-1 or anti-PD-L1 therapy of stabl tage IV/recurrent NSCLC (in the opinion of the treating physician).
- Disease progression </= 365 days from initiation (C1/D1) of a vant, and/or consolidation if only line of anti-PD-1 or anti-PD-L1 therap
- Received platinum-based chemotherapy and experienced disease progression (in the opinion of the treating physician) during or after this regimen.
- Known sensitizing mutation, for which an FDA-approved targeted therapy for NSCLC exists (e.g., EGFR, ALK, ROS1, BRAF, RET, NTRK, KRAS, HER2 and MET sensitizing mutations), must have previously received at least one of the approved therapy(s). Prior targeted therapy allowed for pts. with targetable alterations if all other criteria met.
- Ability to safely receive the investigational drug combination and the investigator's choice of SoC regimens per the current FDA-approved package insert(s), treating investigator's discretion, and institutional guidelines.
- Zubrod Performance Status of **0-2.**

- **Stage IV or Recurrent**
- **Prior Treatment**
- **Performance Status**
- **Safety**

SWOG CANCER RESEARCH NETWORK

** With consent, there are no other eligibility criteria.

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Treatment Overview
Arm A: Standard of Care Drugs

- Treatment is determined by the treating investigator and participant.
- It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a “systemic therapy for advanced or metastatic disease-subsequent”.
- Dosing administration should be based on participant’s previous therapy and disease.
- Drug(s) should be administered according to the current FDA-approved package insert(s).
- Pre-medication should be based on institutional guidelines or investigator practice.

Treatment Overview
Arm B: Ramucirumab plus Pembrolizumab

AGENT	DOSE	ROUTE	DAY	SCHEDULE
Ramucirumab	10 mg/kg	IV (over 30-60 minutes)	Day 1	Q 21 days
Pembrolizumab	200 mg	IV over 30 minutes	Day 1	Q 21 days up to 35 cycles without disease progression

- Per FDA package insert and institutional standard
- 21-day cycle. Treatment continues until one of the criteria for removal is met. (Protocol Section 7.3)
- Ramucirumab will be administered prior to pembrolizumab (MK-3475), over an approximately 60-minute intravenous infusion. If the first infusion is tolerated, all subsequent ramucirumab infusions may be administered over 30 minutes.

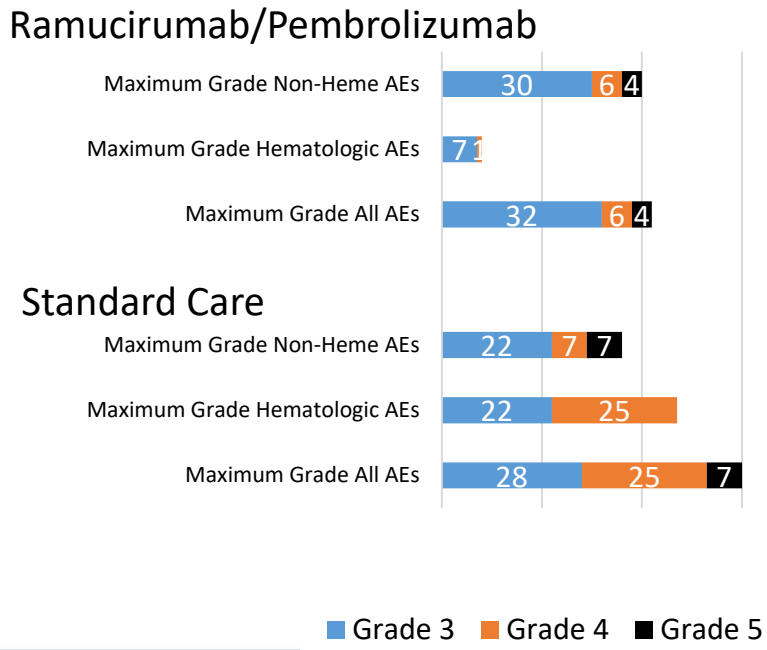
- Participants will receive 35 cycles of pembrolizumab (MK-3475). Maintenance ramucirumab may continue for participants past 35 cycles until reaching a discontinuation criterion.

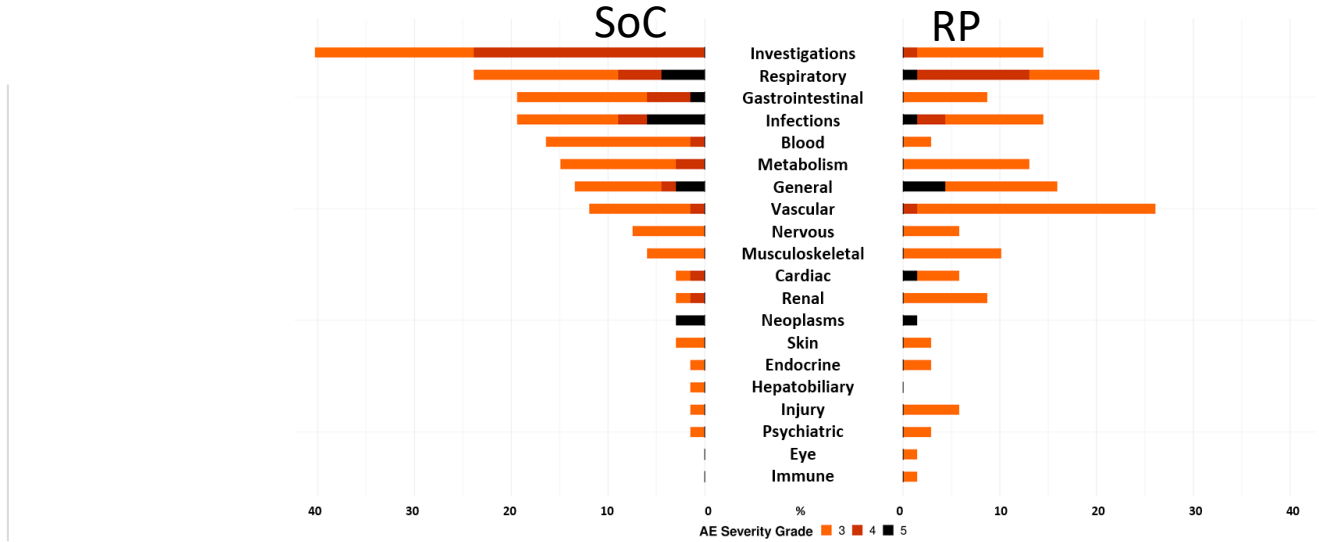
Criteria for Removal from Treatment

- Progression of disease based on investigator assessment.
- Unacceptable toxicity.
- Participants may withdraw from protocol treatment at any time for any reason.

Anticipated Adverse Events

- Per Package Inserts for Ramucirumab/Pembrolizumab and for Standard of Care drugs.
  - S1800A Safety summary—Percentage of patients with Grade 3-5 AEs





- Grade ≥3 TRAEs: 42% on RP; 60% on SOC
- Nine (31%) Grade 3–5 irAEs on RP

Reckamp KL et al ASCO 2022; J Clin Oncol 2022

Serious Adverse Events

- Per Package Inserts for Ramucirumab/Pembrolizumab and for Standard of Care drugs.
- ONLY serious events requiring expedited reporting are to be reported in Medidata Rave. Any AE that does not meet the criteria for expedited reporting does not need to be reported in Rave.
- Adverse Event and Serious Adverse Event reporting requirements that are unique for **S2302 – only grade 5 or reportable and unexpected Grade 3 or 4 treatment-related adverse events**.

Dose Modifications/Interruptions

- Dose modifications for Arm A Standard of Care drugs are per the respective Package Inserts.

- Dose modifications for Arm B:
  - Dose modifications for Ramucirumab are per the Package Inserts.
  - No dose modifications should be made for pembrolizumab.

Ramucirumab dose modifications should be made based on the observed toxicity as per the package insert, which are summarized in the Dose Reductions for Ramucirumab table below.

Dose Reductions for Ramucirumab:

AGENT	DOSE LEVEL	DOSE
Ramucirumab	Full	10 mg/kg
	-1 Level	8 mg/kg
	-2 Level	6 mg/kg
	-3 Level	5 mg/kg
	-4 Level	Discontinue

ARM A (SoC Treatment) Drug Supply

- Arm A Investigator's Choice of Standard of Care:
  - Drug(s) chosen for Arm A will be commercially sourced and will not be supplied by the study.
  - Commercial agents are labeled with an expiration date and that date should be followed.
  - Refer to the current FDA-approved package inserts for commercial agents.
- Important: NCI CTEP Pharmaceutical Management Branch (PMB) supply of pembrolizumab and ramucirumab for Arm B is patient-specific and must NOT be used to treat participants randomized to Arm A.

ARM B (Experimental Treatment) Drug Supply

- Arm B Investigational Treatment:
  - Pembrolizumab and Ramucirumab for Arm B will be supplied free-of-charge throughout the study **as patient-specific clinical supplies.**
    - Pembrolizumab is supplied by Merck. Ramucirumab is supplied by Eli Lilly.
    - Both pembrolizumab and ramucirumab will be distributed by the NCI CTEP PMB.
  - **Starter supplies will NOT be available for this study.**
    - The initial drug supply request will be submitted *automatically* following the completion of participant registration and randomization.
      - Initial supply will be provided in cartons containing a 3-cycle (9-week) supply.
      - Drug will be shipped to the pharmacy shipping address of the registering investigator at the time of randomization and should arrive ~ 5 to 7 days after randomization.

Study Calendar

— Per Institution Standard and FDA-approved package insert(s)

REQUIRED	Cycle Length (+/- 3 days)					At Off Tx	Off Tx FU
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles		
PHYSICAL							
Vital Status Assessment	X	X	X	X	X	X	X
SAE Assessment	X	X	X	X	X	X	X (q 3 mos. until 3 years from date of randomization).
LABORATORY							
Participants must be able to safely receive the investigator's choice of standard of care regimen and ramucirumab plus pembrolizumab described in protocol Section 7.2, per the current FDA-approved package insert(s), treating investigator's discretion, and institutional guidelines.							
TREATMENT							
Arm A: Investigator's Choice of Standard of Care (SoC)							
Chosen SoC drug(s) should be administered according to the current FDA-approved package insert(s). Arm A cycle length may vary.							
Arm B: Ramucirumab plus Pembrolizumab (21-day cycle)							
Ramucirumab	X	X	X	X	X		
Pembrolizumab	X	X	X	X	X (up to 35 cycles)		

Study Calendar

— Per Institution Standard and FDA-approved package insert(s)

REQUIRED	Cycle Length (+/- 3 days)					At Off Tx	Off Tx FU
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles		
PHYSICAL							
Vital Status Assessment	X	X	X				
SAE Assessment	X	X	X				
LABORATORY							
Participants must be able to safely receive the investigato pembrolizumab described in protocol Section 7.2, per the discretion, and institutional guidelines.							
TREATMENT							
Arm A: Investigator's Choice of Standard of Care (So							
Chosen SoC drug(s) should be administered according to the current FDA-approved package insert(s). Arm A cycle length may vary.							
Arm B: Ramucirumab plus Pembrolizumab (21-day cycle)							
Ramucirumab	X	X	X	X	X		
Pembrolizumab	X	X	X	X	X (up to 35 cycles)		

- **No protocol required disease assessment (CT, imaging)**
- **No protocol required lab tests**
- **No specimen collection**
- **Only report all Grade 5 and Unexpected Reportable Gr 3-4 AE**

Simplified Data Reporting Requirements and Forms

- To reduce the burden on sites for participation, the study includes:
  - A reduction in the time points data needs to be submitted,
  - A reduction in the number of forms that need to be submitted, and,
  - A reduction in the number of data elements within a form.

  …relative to a standard clinical trial conducted through the NCTN and definite reduction in the data submission/amount for a registrational intent study.

- The study does not include:
  - Tissue specimen collection,
  - Image submission from disease assessments, or
  - Patient-Reported Outcome instruments.

Data Submission Schedule and Requirements

Baseline (within 15 days after randomization):

- **S2302 Vital Status Form**
- **S2302 Onstudy Forms**
- **S2302 Eligibility Criteria Form**
- **S2302 PD-L1 Results Form**
- **S2302 Genomic Alterations Form**
- **Pathology Report**

No Cycle based Treatment Form
No Disease Assessment Form (BTA, FUTA)

On Treatment (within 30 days after every treatment cycle):

- **S2302 Vital Status Form**
- **S2302 Adverse Event Form**

Off Treatment (within 30 days after discontinuation of treatment):

- **S2302 Vital Status Form**
- **S2302 Treatment Summary Form**

Follow Up (within 60 days after each follow-up visit):

- **S2302 Vital Status Form**
- **Late Adverse Events**

No Detailed Follow Up form, only vital status (alive or not)

Within 30 days after knowledge of death:

- **S2302 Notice of Death**

Simplified Study Forms: Vital Status Reporting

- **Vital Status Form(On Treatment)**

Vital Status *(If dead, complete the Notice of Death.)*	◯ Alive ◯ Dead
Vital Status Date *(If alive, enter last contact date. If dead, enter date of death.)*	☐☐ ☐☐☐ ☐☐☐☐
Is the participant still receiving protocol treatment? *(If no, please complete S2302 Treatment Summary Form).*	◯ Yes ◯ No

- **Vital Status Form(Off Treatment)**

Vital Status *(If dead, complete the Notice of Death.)*	◯ Alive ◯ Dead
Vital Status Date *(If alive, enter last contact date. If dead, enter date of death.)*	☐☐ ☐☐☐ ☐☐☐☐
Has the participant had any reportable* adverse events during this reporting period? *(If yes, complete the Late Adverse Events form.)* **Any Grade 5 or any reportable unexpected Grade 3 or 4 treatment related adverse events, that has not been previously reported.*	◯ Yes ◯ No

Simplified Study Forms: Adverse Events Reporting

- **S2302 Adverse Event Form (cycle based, per CTEP)**

Were adverse events assessed during this time period?	◯ Yes ◯ No
If no, what was the reason adverse events were not assessed?	_____
If yes, what was the date of the most recent adverse event assessment?	☐☐ ☐☐☐ ☐☐☐☐
If yes, did the participant experience any Grade 5 or any reportable unexpected Grade 3 or 4 treatment related adverse events during this reporting period? *(If yes, complete the Adverse Event: Report form.)*	◯ Yes ◯ No

If the participant did not have a Grade 5 or reportable and unexpected Grade 3 or 4 treatment-related Adverse Event, no additional AE reporting is required beyond answering this question.

Participant Initials _____ (L, F M) **Cycle Number** ☐☐

Page: Adverse Events: Assessment

Instructions: Please complete this form after each cycle. Report all Grade 5 and any reportable unexpected Grade 3 or 4 treatment related adverse events (see protocol section 8.5) occurring up until the next cycle of treatment begins. Lower grade (< Grade 3) and Grade 3 or 4 adverse events not related to treatment should NOT be reported. Note that fewer events are required for this study than usual. Follow instructions in Section 8 of the protocol for expedited reporting requirements on this study. Date is in **DD MON YYYY** format.

Simplified Study Forms: Treatment Summary

- **S2302 Treatment Summary Form is submitted once - within 30 days after discontinuation of treatment.**

Page: Treatment Summary

Instructions: Submit this form within 60 days after completion (or discontinuation) of protocol treatment. For multidrug regimens, please list individual drugs separately; end date would be the date each drug was discontinued. Date is in **DD MON YYYY** format.

Did the participant receive any protocol treatment? ◯ Yes ◯ No

If yes, did the participant receive any radiation therapy while receiving protocol treatment? ◯ Yes ◯ No

If yes, fill out the following table.

Treatment Name	Start Date	End Date
Docetaxel	☐☐ ☐☐☐ ☐☐☐☐	☐☐ ☐☐☐ ☐☐☐☐
Gemcitabine	☐☐ ☐☐☐ ☐☐☐☐	☐☐ ☐☐☐ ☐☐☐☐
Pemetrexed	☐☐ ☐☐☐ ☐☐☐☐	☐☐ ☐☐☐ ☐☐☐☐
Ramucirumab	☐☐ ☐☐☐ ☐☐☐☐	☐☐ ☐☐☐ ☐☐☐☐
Pembrolizumab	☐☐ ☐☐☐ ☐☐☐☐	☐☐ ☐☐☐ ☐☐☐☐
Other, specify _____	☐☐ ☐☐☐ ☐☐☐☐	☐☐ ☐☐☐ ☐☐☐☐

What was the off treatment date? *(Date of completion, progression, death or decision to discontinue therapy)* ☐☐ ☐☐☐ ☐☐☐☐

What was the participant's off treatment status?

◯ Adverse Event
◯ Dead
◯ Disease Progression
◯ Physician Decision
◯ Withdrawal by Participant
◯ Other, specify _____

If Withdrawal by Participant, was reason due to adverse event, side effects, or complications? ◯ Yes ◯ No

If yes, specify the reason. _____

If no, specify the other reason not due to adverse event, side effects, or complications. _____

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Simplified Study Forms: Notice of Death

- **Submit within 30 days after knowledge of death.**
  - **If participant was still on treatment at time of death, then also submit:**
    - **Vital Status Form and**
    - **S2302 Treatment Summary Form.**
- **Simplified data collection that is limited to the primary cause of death.**
  - **Contrary to usual data collection, the form does not include contributory causes nor request for the source of the information.**

Page: Notice of Death

Instructions: One Primary cause of death must be reported. Only one cause of death can be chosen as Primary. Date is in **DD MON YYYY** format.

What was the participant's date of death? ☐☐ ☐☐☐ ☐☐☐☐

What phase of the trial was the participant in at the time of death?

(Baseline = prior to initiation of protocol therapy; Follow-up = discontinued protocol therapy and in follow-up)

- ◯ Baseline
- ◯ Protocol Therapy
- ◯ Follow-up

What was the primary cause of death?

- ◯ Study Cancer (including metastatic disease)
- ◯ New Primary
- ◯ Protocol Therapy-Related Adverse Event
- ◯ Other (Non-study cancer, not protocol therapy-related)
- ◯ Unknown

Comments

Pathology, Disease Assessment, and Source Documentation Submission Requirements

- Upload Pathology Report, which confirmed participant's tumor histology.
- Upload PD-L1 and NGS reports performed as SOC at diagnosis.
  - Tissue is not being submitted for central pathology review.

- Imaging for disease assessment should be performed according to institutional standards.
  - Tumor Assessment forms and radiology reports are not collected.
  - Images are not being collected/submitted for central review.

Quality Control

- Although S2302 is considered an FDA Registration Trial and includes the requirement for maintenance of a Trial Master File, due to the pragmatic design, the auditing schedule will follow the standard NCI audit schedule for treatment trials.

Study Monitoring

- The SWOG Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG Cancer Research Network, three SWOG members, three non-voting representatives from the NCI, and the Group Statistician (non-voting).

Informed Consent

- The informed consent document has been simplified and is therefore shorter than the usual NCTN template Informed Consent Document.
- Remote consent is allowed, per procedures indicated in Protocol Section 18.9.

Funding

Funding Source and Study Component		Collect Type	Study Specific Notes	Enter Date in Open?	NCTN Funding per Patient Std/HP LAPS	NCORP Funding per Patient Std/HP
Federal	Base Intervention – Standard / High Performance LAPS & NCORP	Mandatory		No	$3,000/$4,600	$3,000/$4,600
Non-Federal	Additional Per Participant Payment **(PENDING)**	Mandatory		No	$500	$500
Total Potential Funds					**$3,500/$5,100**	**$3,500/$5,100**

- $500 additional per participant payment is pending contract with industry partner
- One credit towards SWOG membership is issued upon participant registration to S2302, if credited to SWOG.

Resources and Materials

- Plans to develop and distribute an enhanced set of resources to aid sites with outreach and patient recruitment.
- **S2302** patient-friendly plain language trial summary and accompanying social media toolkit (tweets and graphics).
  - Available for participating site use on SWOG.org and via the **S2302** protocol abstract page on CTSU.org.
- For **S2302**, CTSU will provide a template to assist with EMR implementation.
  - Institutions that choose to utilize the EMR template are responsible for the verification and modification of the EMR in compliance with local institutional guidelines.

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NCI CTEP
NCTN partners: Alliance; ECOG-ACRIN; NRG Oncology

Foundation for the National Institutes of Health (FNIH)
Friends of Cancer Research (FoCR)

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Data Coordinators: Louise Highleyman
SDMC Project Management: Dani Weatherbee; Study Build: Greg Auger
Protocol Project Manager: Mariah Norman