SWOG CANCER RESEARCH NETWORK

**S2302 | Pragmatica-Lung: A Prospective Randomized Study of Ramucirumab (LY3009806; NSC 749128) plus Pembrolizumab (MK-3475; NSC 776864) versus Standard of Care for Participants Previously Treated with Immunotherapy for Stage IV or Recurrent Non-Small Cell Lung Cancer**

# Pragmatica-Lung FAQ

**for staff use only**

based on protocol version 4/20/2023

## General

1. **Is the Pragmatica-Lung trial (S2302) a sub-study of LUNGMAP?**

   No. There is no functional relationship between **LUNGMAP** and Pragmatica-Lung (**S2302**). The only connection is that the Lung-MAP sub-study **S1800A** is Pragmatica-Lung's Phase II precursor. From a regulatory and operational standpoint, **S2302** is a standalone NCTN trial. Participants do not need to have registered to **LUNGMAP** and sites do not need to have **LUNGMAP** open.

2. **Is co-enrollment on another clinical trial allowed?**

   SWOG does not have any restrictions on co-enrollment with other clinical trials as long as the **S2302** protocol can be followed as written.

## Eligibility

3. **Are patients who have received prior pembrolizumab eligible?**

   Yes. Patients who have received prior anti-PD-(L)1 therapy, including pembrolizumab, are the population of interest for this study.

4. **Are patients who have received prior ramucirumab eligible?**

   Yes. Patients who have received prior ramucirumab are eligible, but the treating investigator must be willing to treat the patient with pembrolizumab + ramucirumab if they are randomized to that arm.

5. **A patient received pembrolizumab, and their cancer progressed during that time. Carboplatin/pemetrexed was added to the treatment with the continuation of pembrolizumab. Will this count as 1 or 2 anti-PD-1/anti-PD-L1 therapies?**

   If a patient is on pembrolizumab and then receives chemotherapy + pembrolizumab it will count as 1 anti-PD-(L)1 therapy, since the patient stayed on the same immunotherapy agent. If they receive 2 different anti-PD-(L)1 drugs, it would count as 2 therapies.

6. **A patient received carboplatin/paclitaxel/pembrolizumab, progressed, then started carboplatin/pemetrexed/pembrolizumab. Will this count as 1 or 2 anti-PD-(L)1 therapies?**

   This will count as 1 anti-PD-(L)1 therapy, since pembrolizumab was continued without interruption.

7. **A patient with stage II NSCLC had tumor resection and then received adjuvant chemotherapy followed by immunotherapy. There was no evidence for recurrence at 3 months, but the patient developed disease progression 6 months after starting adjuvant therapy. Is this patient eligible?**

   Yes. If the patient received neoadjuvant, adjuvant or consolidation immunotherapy for non-metastatic NSCLC and has tumor progression more than 84 days but less than 365 days from the start of immunotherapy, this would count as the required anti-PD-(L)1 agent and chemotherapy.

8. **A patient with stage II NSCLC had tumor resection and then received adjuvant immunotherapy and progressed 6 months after starting adjuvant therapy. Is this patient eligible?**

   No. If the patient received neoadjuvant, adjuvant or consolidation immunotherapy for non-metastatic NSCLC and has tumor progression more than 84 days but less than 365 days from the start of immunotherapy, this would count as the required anti-PD-(L)1 agent, but this patient would also need to receive platinum-based chemotherapy.

9. **A patient with stage III NSCLC received neoadjuvant chemotherapy with immunotherapy followed by resection and then received adjuvant immunotherapy and progressed 6 months after starting adjuvant therapy. Is this patient eligible?**

   Yes. If the patient received neoadjuvant, adjuvant or consolidation immunotherapy for non-metastatic NSCLC and has tumor progression less than 365 days from the start of immunotherapy, this would count as the required anti-PD-(L)1 agent and chemotherapy.

10. **A patient with stage III NSCLC received concurrent chemotherapy with radiation followed by consolidation durvalumab and progressed 6 months after starting consolidation therapy. Is this patient eligible?**

    Yes. If the patient received neoadjuvant, adjuvant or consolidation immunotherapy for non-metastatic NSCLC and has tumor progression less than 365 days from the start of immunotherapy, this would count as the required anti-PD-(L)1 agent and chemotherapy.

11. **A patient received ipilimumab and nivolumab with initial partial response followed by progression after 9 months on therapy. Is this patient eligible?**

    No. If the patient receives chemotherapy without a new anti-PD-(L)1 agent, the patient could be eligible after progression on platinum-based chemotherapy.

12. **A patient received carboplatin/pemetrexed/pembrolizumab, progressed, and next received *[docetaxel, docetaxel + ramucirumab, gemcitabine, etc.].* Is this patient eligible?**

    Yes. There is no limit on the number of lines of prior therapy that do not include an anti-PD-(L)1 agent.

13. **If a patient is not tested for any biomarker in section 5.2.e (EGFR, ALK, ROS1, BRAF, RET, NTRK, KRAS, HER2 and MET sensitizing mutations) are they still eligible?**

    Yes. The protocol does not specifically require testing if results are not available, although comprehensive biomarker testing is recommended as standard of care.

14. **A patient with *[for example: KRAS G12V, BRAF G466A]* mutation has not been treated with a targeted therapy for this mutation. Would this patient be eligible?**

    Yes. If the alteration does not have an approved specific targeted therapy available, the criterion about targeted therapy for a known mutation (5.2.e) does not apply. For details regarding which mutations have approved targeted therapies, view the NCCN guidelines for non-small cell lung cancer as a reference: https://www.nccn.org/

15. **If a patient is scheduled to initiate palliative radiation and/or radiosurgery, could the patient be eligible for the trial after radiation and/or radiosurgery?**

    Yes. **S2302** does not have specific exclusion or washout for radiation. If the treating investigator feels it is safe to start systemic therapy, that is sufficient.

16. **If a patient has current or prior cancer other than NSCLC, is the patient eligible?**

Yes. **S2302** does not have an exclusion for prior or concurrent cancers.

17. **A patient with stage IV NSCLC received prior immunotherapy with response and developed an immune-related adverse event (irAE) with discontinuation of therapy. The patient now has tumor progression one year later and the investigator would like to enroll this patient on trial. Would the prior immune-related adverse event exclude the patient from trial?**

No, not specifically since one of the aims of this protocol is to empower investigators to treat patients as they would in their practice. If the investigator feels that this is the best treatment and either ramucirumab and pembrolizumab or standard of care treatment would be safe, it is acceptable.

18. **A patient has _____ in their medical history, not specifically addressed by protocol section 5. Would this exclude the patient from trial?**

Per Section 5.3.b., participants must be able to safely receive the investigational drug combination and the investigator's choice of standard of care regimens described in Section 7.2, per the current FDA-approved package insert(s), treating investigator's discretion, and institutional guidelines. One of the aims of this protocol is to empower investigators to treat patients as they would in their practice. If the investigator feels this is the best treatment and it would be safe, it is acceptable.

19. **If a patient does not have any measurable target lesions, is the patient eligible?**

Yes. Measurable disease is not required for eligibility.

20. **Does metastatic disease or recurrent disease need to be biopsy-confirmed to meet protocol eligibility?**

No. The diagnosis of NSCLC needs to be pathologically or cytologically confirmed. Metastatic or recurrent disease can be shown on imaging only.

## Treatment

21. **By what ratio are participants randomized and assigned to the study arms?**

Patients are randomized 1:1 on this study.

22. **If a participant is randomized to ARM A - Investigator's Choice of Standard of Care, can we use ramucirumab + pembrolizumab**?

No. Investigators cannot use the investigational combination of ramucirumab + pembrolizumab if the participant is randomized to Arm A (Standard of Care).

**23. If a participant is randomized to ARM A - Investigator's Choice of Standard of Care, can we use ramucirumab?**

Yes, as long as it's not the investigational regimen (ramucirumab + pembrolizumab). Ramucirumab may be used in other combinations (such as docetaxel + ramucirumab), and investigators are encouraged to use NCCN guidelines to choose a SoC regimen.

**24. Can the participant get surgery to address _____ [*issue not related to their cancer*] while receiving protocol therapy? What drug interruptions are recommended?**

There are no specific exclusions or restrictions. The investigator should treat and hold study drug(s) as they would in standard practice.

**25. Can the participant get palliative radiation therapy while continuing on protocol treatment? What drug interruptions are recommended?**

Yes, concurrent palliative radiation is allowed at the treating investigator's discretion. The investigator should hold study drug(s) as they would in standard practice.

**26. A patient randomized to the Standard of Care (SOC) arm of trial initially started with docetaxel 75mg/m$^2$ and then dosage reduced to 65mg/m$^2$ as a result of risk factors. Will a SOC arm dose reduction be acceptable in this trial?**

Yes. The trial is written to empower investigators to treat as they would in standard practice based on institutional guidelines and investigator discretion. The dose reduction is acceptable.

**27. If treatment needs to be held, what is the maximum allowed treatment delay?**

There is no specified maximum delay. The treating investigator can hold and resume treatment as they would standardly and per the FDA-approved package insert(s).

**28. Can you provide the Investigator Brochures (IBs) for pembrolizumab and ramucirumab?**

There are no provided IBs for this study. Sites are to use the FDA-approved package inserts for both drugs. Please see protocol Section 3.

## Study Calendar

29. **Does the study require CT scans, urinalysis, blood draws or other laboratory evaluations?**

    The study does not specifically require any CT scan, urinalysis or other laboratory examinations. These should be done per the FDA label for the drugs, institutional guidelines, and investigator discretion. One of the aims of this protocol is to empower investigators to treat patients as they would in their practice.

30. **Does the study include specimen collection, image submission, or patient-reported outcomes (PROs)?**

    No, it does not include any of these.

## Data Submission

31. **While trying to upload documents on the Baseline: Source Documentation form, I received notification that 'it's too big of a file to save'. How can I upload multiple pages as a single file?**

    We recommend trying to compress the file into a smaller-sized PDF. You can do so using the "Compress File" option in Adobe. In addition, please note that limited source documentation upload is needed for this study. Please refer to protocol section 14.4 for exactly what is requested (**basically, just the Pathology Report**).

32. **Will we be required to enter tumor measurements/RECIST 1.1 reads in the EDC?**

    No. There are no tumor measurement or disease assessment forms for this study. Disease assessment should be done per institutional standards and the investigator's discretion. Disease progression based on investigator assessment is a reason for treatment discontinuation and will be captured on the Treatment Summary Form at that time if appropriate. Otherwise, response and progression are not captured on this study.

**For answer to questions not addressed in this FAQ, please use the contact information below:**

- Eligibility, RAVE, Data Submission: LungQuestion@crab.org
- Regulatory, Protocol, Informed Consent: protocols@swog.org
- Medical Queries (treatment or toxicity related questions): S2302chairs@swog.org