**Phase 3 study of durvalumab with SBRT for unresected stage I/II, lymph-node negative NSCLC (PACIFIC-4/RTOG 3515)**

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**Key inclusion criteria**

- Aged ≥18 years and body weight ≥50 kg.
- Planned SBRT (protocol compliant 3, 4, 5, and 6 fraction regimens) as definitive treatment.
- Histologically or cytologically documented stage I to II (T1–T3, N0, M0) per AJCC v8 of unresected NSCLC.
  - Patients with central or peripheral lesions are eligible.
- WHO/EORTC performance status 0–2.
- Patients with a history of metastatic NSCLC are permitted if they have:
  - Stage III–I NSCLC treated definitively with surgery or SBRT only >1 year prior to enrolment.
  - Patients with synchronous NSCLC tumors are permitted if they have ≤2 intractable lesions.
- Provision of a tumor sample is encouraged (e.g., archived tumor tissue ≤6 months old or recent [≤3 months old] tumor biopsy).
- Mediastinal lymph node sampling by any technique is allowed but not required.
- For the osimertinib cohort: confirmation by a local laboratory that the tumor harbors one of the 2 common EGFR-sensitizing mutations (Exon 19 deletion or L858R), either alone or in combination with other EGFR mutations, including de novo T790M.

**Posters**

- TPS8607

**Background**

The current SoC for patients with unresectable, stage I/II, lymph-node negative NSCLC is SBRT,1 which is well tolerated (typically with AEs of grade 2 or 3) and is associated with high rates of primary tumor control (i.e., >90% at 5 years).2,3 However, around one-third of patients still experience local or regional/distant failure,4 with a greater risk of relapse as tumor size increases; for example, Timmerman et al. reported disseminated recurrence for patients with T1 of 18.2% vs T2 of 45.5%.5 Despite the risk of relapse in these patients and high recurrence rates, there is no current SoC adjuvant therapy.6

**Why are we performing this research?**

- When surgery is not an option, a type of radiotherapy called stereotactic body radiation therapy (SBRT) is the standard of care for patients with Stage I/II non-small-cell lung cancer (NSCLC) that has not spread to nearby lymph nodes. SBRT is a drug that blocks the activity of a protein called PD-L1, making cancer cells more susceptible to being killed by the body’s immune system. Based on the PACIFIC study, SBRT is approved for patients with Stage II NSCLC for whom surgery is not an option, provided they have completed chemotherapy and radiotherapy without the cancer growing or spreading.
- Osimertinib is a drug that blocks the activity of a protein called EGFR on cancer cells, reducing their growth and spread. Based on the ADJUVANT study, osimertinib is approved for use following surgery in patients with early-stage NSCLC and certain mutations in the EGFR gene.

**How are we performing this research and who will participate?**

Patients diagnosed with Stage III NSCLC who are not eligible for surgery, or who refuse to undergo surgery, will be enrolled into one of two separate cohorts:

- Main cohort: approximately 630 patients will be randomly assigned to receive either durvalumab or placebo alongside SBRT.
- Osimertinib cohort: approximately 480 patients with known mutations in certain EGFR genes will be assigned to receive SBRT alone followed by osimertinib.

The primary efficacy measure is progression-free survival, measured as the length of time that participants remain alive without cancer growing or spreading.

**Where can I access more information?**

PACIFIC-4 is ongoing, and no final results are available. The study is expected to complete in March 2026. More information about PACIFIC-4 can be found at: https://clinicaltrials.gov/ct2/show/NCT03833374?term=IPACIFIC&recid=700058&amp;cond=&amp;rank=1

You may also speak to your doctor about clinical studies.


**Key exclusion criteria**

- Mixed small-cell and NSCLC histology.
- Ultra-central tumors.
- Active or prior documented autoimmune or inflammatory disorders (main cohort only).
- Prior exposure to immune-mediated therapy (main cohort only) or any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment.
- History of another primary malignancy, except for:
  - Malignancies treated with curative intent and no known active disease/active treatment required in the past 3 years.
  - Adequately treated non-melanoma skin cancer or laryngeal malignancy without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease.
- Patients with a tumor harboring an EGFR mutation per local testing will be excluded from the (durbanumab) cohort and may be eligible for the osimertinib cohort.

For the osimertinib cohort: QTc >470 msec, clinically important abnormalities in resting ECG, factors increasing risk of QT prolongation or arrhythmias.

**Study objective**

- Based on data for durvalumab and for osimertinib in the early-stage NSCLC setting, PACIFIC-4 (RTOG 3515; NCT03833374) is designed to assess the efficacy and safety of:
  - Durvalumab combined with SBRT (versus placebo in SBRT) in patients with stage I/II NSCLC.
  - Osimertinib after SBRT in patients with stage III, EGFR-mutated NSCLC.

**Study endpoints**

1. **Primary**
   - Main cohort: PFS (BCR per RECIST v1.1) 
   - Osimertinib cohort: 4-year PFS rate (ICR per RECIST v1.1)

2. **Secondary**
   - OS
   - PFS (local assessment)
   - Lung cancer mortality

**PACIFIC-4 (NCT03833374): A phase 3, randomized, double-blind, placebo-controlled, international, multicenter study**

- In PACIFIC-4, a main cohort of 630 patients will be randomized (1:1) in a double-blind manner, stratified by tumor size (T1 vs T2/3) and location (central vs. peripheral), to receive concurrent SoC SBRT with either durvalumab (1500 mg iv) or placebo Q4W for up to 24 cycles.
- The original protocol was amended (at version 4) to:
  i. Exclude patients with an identified EGFR mutation by local testing from the main cohort, and
  ii. Add a separate cohort of ≥60 patients with identified EGFR mutations (L858R or exon 19del) who will receive oral osimertinib 80 mg QD for up to 36 months, following SoC SBRT.
- This updated protocol is approved in all countries except France and the UK, where the osimertinib cohort is not available.

**Abbreviations**

- AEs: adverse events
- AJCC: American Joint Committee on Cancer
- BCR: bidimensional internal review
- CNET: central nervous system
- CTCAC: Common Terminology Criteria for Adverse Events
- ECOG: Eastern Cooperative Oncology Group
- EMA: European Medicines Agency
- EORTC: European Organisation for Research and Treatment of Cancer
- IP: investigational product
- ICR: independent central review
- ICRR: independent central review reaction
- mAb: monoclonal antibody
- MPR: major pathological response
- NRTD: national radiation therapy development center
- PFS: progression-free survival
- RECIST: Response Evaluation Criteria in Solid Tumors
- RTOG: Radiation Therapy Oncology Group
- SoC: standard of care
- SBRT: stereotactic body radiation therapy
- TTP: time to progression
- TTDM: time to disease manifestation
- TTOS: time to OS progression
- TCR: time to clinical response
- TQ: time to QOL improvement
- TS: time to SOR progression
- TSG: time to SOR progression
- TTP: time to progression
- TTPD: time to progression death
- TWSS: time to WSS progression
- TwSS: time to WSS progression
- V: volume
- V2: volume 2
- V3: volume 3
- V4: volume 4

**Study status**

- Patient recruitment ongoing

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**References**