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

Clifford Robinson,[1] Ligang Xing,[2] Hiroshi Tanaka,[3] Sadatomo Tasaka,[4] Shahed N. Badiyan,[1] Haitam Nasrallah,[5] Tithi Biswas,[6] Mikhail Shtivelband,[7] Wolfgang Schuette,[8] Anhui Shi,[9] Adriana Hepner,[10] Karen Barrett,[11] James R. Rigas,[10] Haiyi Jiang,[10] Steven H. Lin[12]

[1]Department of Radiation Oncology, Washington University in St. Louis/Siteman Cancer Center, St. Louis, MO, USA; [2]Department of Radiation Oncology, Shandong Cancer Hospital, Shandong First Medical University, Jinan, Shandong Province, China; [3]Niigata Cancer Center Hospital, Niigata, Japan; [4]Hirosaki University School of Medicine and Hospital, Hirosaki, Japan; [5]Rambam Health Care Campus, Haifa, Israel; [6]Department of Radiation Oncology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, USA; [7]Ironwood Cancer and Research Centers, Chandler, AZ, USA; [8]Städtisches Krankenhaus Martha-Maria Halle-Dölau gGmbH, Halle, Germany; [9]Beijing Cancer Hospital, Beijing, China; [10]AstraZeneca, Gaithersburg, MD, USA; [11]AstraZeneca, Cambridge, UK; [12]Department of Radiation Oncology, Division of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

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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) and is associated with high rates of primary tumour control (i.e. >90% at 5 years).[1–5]
- However, around one-third of patients still experience local or regional/distant failure,[4] with a greater risk of relapse as tumour 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.
- For patients who receive SBRT as primary therapy for stage I/II NSCLC, safety and performance status may preclude receipt of cytotoxic chemotherapy.
- Durvalumab (PD-L1 Ab) is approved as consolidation therapy for patients with unresectable Stage III NSCLC, who have not progressed following chemoradiotherapy.
- Osimertinib (EGFR-TKI) is approved in the adjuvant setting post-surgery for patients with EGFRm NSCLC, but has not been investigated post SBRT.
- Thus, there is an unmet need for effective and more tolerable systemic therapy options to reduce recurrence rates and improve survival among patients with unresected, early-stage NSCLC who receive definitive SBRT.

Immune checkpoint inhibition in early-stage NSCLC: durvalumab

- Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1/CD80.[6]
- Based on the placebo-controlled, Phase 3 PACIFIC trial of patients with unresectable, stage III NSCLC without disease progression after cCRT,[7–9] the PACIFIC regimen (durvalumab after CRT) has been established as the SoC in this setting.[10,11]
  - After ~5 years of follow up in PACIFIC, an estimated 42.9% of patients randomised to durvalumab remained alive and 33.1% remained alive and progression free.[9]
- Based on the findings of the PACIFIC trial, there is a strong rationale for further investigation of durvalumab in early-stage NSCLC.
- A recent single-centre, randomised, open-label, Phase 2 trial compared neoadjuvant durvalumab alone with neoadjuvant durvalumab plus SBRT in patients with early-stage NSCLC.[12] Neoadjuvant durvalumab + SBRT was well tolerated and was associated with a major pathological response rate of 53.3% (versus 6.7% in patients receiving durvalumab alone).
  - These data support further evaluation of durvalumab in combination with SBRT in early-stage NSCLC.

EGFR tyrosine kinase inhibition in early-stage NSCLC: osimertinib

- Osimertinib is a third-generation, irreversible CNS-active EGFR TKI that selectively inhibits NSCLC tumours with EGFRm.[11,13,14]
- In the placebo-controlled Phase 3 ADAURA trial of patients with resected stage IB–IIIA EGFRm NSCLC, osimertinib demonstrated statistically significant and clinically meaningful improvement in DFS (HR 0.20 [99.12% CI, 0.14–0.30], P<0.001).[15]
- The ADAURA trial led to the approval of osimertinib as adjuvant therapy after primary surgery for adults with NSCLC whose tumours have EGFRm (exon 19 deletions or exon 21 L858R mutations).[16]
- The results of the ADAURA study provide strong rationale for the investigation of osimertinib after SBRT in patients with early-stage unresected NSCLC whose tumours have EGFRm.

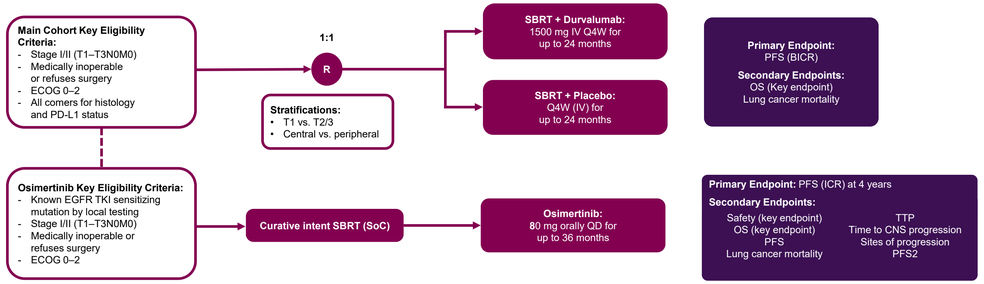
Study objective

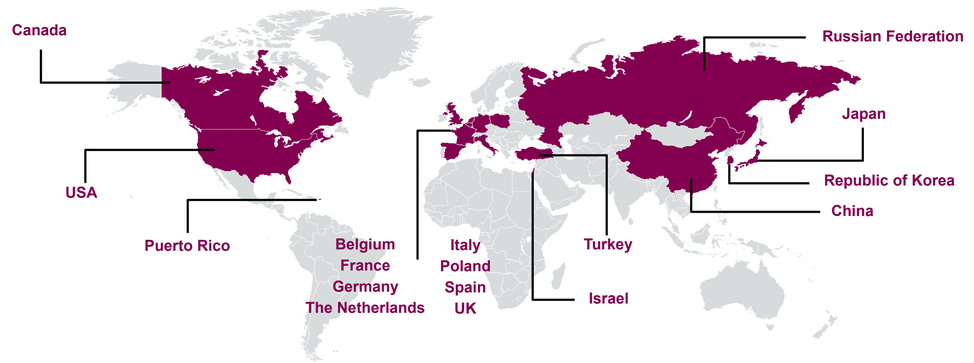
- Based on data for durvalumab and for osimertinib in the early-stage NSCLC setting, PACIFIC-4 (RTOG 3515; NCT03833154) is designed to assess the efficacy and safety of:
  - Durvalumab combined with SBRT (versus placebo with SBRT) in patients with stage I/II unresectable NSCLC.
  - Osimertinib after SBRT in patients with stage I/II, EGFRm unresectable NSCLC.

PACIFIC-4 (NCT03833154) Study design

A Phase 3, randomised, double-blind, placebo-controlled, international, multicentre study

- In PACIFIC-4, a main cohort of ~630 pts will be randomised (1:1) in a double-blind manner, stratified by tumour 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 26 cycles.
- The original protocol was amended (at version 4) to:
  - i. Exclude patients with an identified EGFRm by local testing from the main cohort, and
  - ii. Add a separate cohort of ~60 patients with identified EGFRm (L858R or Ex19del) who will receive oral osimertinib 80 mg QD for up to 36 months, following SoC SBRT.
- This updated protocol is anticipated to open in most countries by end of June 2022.





Key Inclusion Criteria

- Aged ≥18 years and body weight >30 kg.
- Planned SoC SBRT (protocol compliant 3, 4, 5, and 8 fraction regimens) as definitive treatment.
- Histologically or cytologically documented stage I to II (T1–T3, N0, M0; per AJCC v8)[17] unresected NSCLC.
  - Patients with central or peripheral lesions are eligible.
- WHO/ECOG performance status 0–2.
- Patients with a history of metachronous NSCLC are permitted if they have:
  - Stage I/II (T1–T3N0M0) NSCLC treated definitively with surgery only or SBRT only >1 year prior to enrolment.
  - Stage I-III NSCLC treated with curative intent ≥3 years prior to enrolment.
- Patients with synchronous NSCLC tumours are permitted if they have ≤2 intrathoracic lesions.
- Provision of a tumour sample is encouraged (e.g. archived tumour tissue ≤6 months old or recent [≤3 months old] tumour biopsy).
- Mediastinal lymph node sampling by any technique is allowed but not required.
- For the osimertinib cohort: confirmation by a local laboratory that the tumour harbours one of the 2 common EGFR-sensitising mutations (Ex19del or L858R), either alone or in combination with other EGFR mutations, including de novo T790M.

Key Exclusion Criteria

- Mixed small-cell and non-small cell histology.
- Ultra-central tumours.
- Active or prior documented autoimmune or inflammatory disorders.
- 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, with the exception of:
  - 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 lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.
- Patients with a tumour harbouring an EGFRm per local testing will be excluded from the main (durvalumab) 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 Endpoints

1° ***Primary***
- Main cohort: PFS (BICR per RECIST v1.1) [subpopulation]
- Osimertinib cohort: 4-year PFS rate (ICR per RECIST v1.1)

2° ***Secondary***
- OS
- PFS2 (local assessment)
- Lung cancer mortality
- TTP
- Safety and tolerability (per CTCAE v5) for a maximum of 3 years following SoC SBRT

- Main cohort only:
  - PFS (BICR per RECIST v1.1) – All randomised patients
  - 24-month PFS rate and TTDM
  - Health-related quality of life (EORTC QLQ-C30)
  - Pharmacokinetics of durvalumab
  - Immunogenicity of durvalumab (presence of antidrug antibodies)
- Osimertinib cohort only:
  - PFS (ICR per RECIST v1.1)
  - Time to CNS progression
  - Sites of disease progression

References

1. Wegner RE, et al. *Lung Cancer Manag* 2018;7:LMT05.
2. Kumar SS, et al. *Transl Lung Cancer Res* 2019;8(Suppl 2):S213–S221.
3. Ogawa Y, et al. *Radiat Oncol* 2018;13:136.
4. Timmerman R, et al. *JAMA* 2010;303:1070–1076.
5. Timmerman RD, et al. *JAMA Oncol* 2018;4:1287–1288.
6. Stewart R, et al. *Cancer Immunol Res* 2015;3:1052–1062.
7. Antonia SJ, et al. *N Engl J Med* 2017;377:1919–1929.
8. Antonia SJ, et al. *N Engl J Med* 2018;379:2342–2350.
9. Spigel DR, et al. *J Clin Oncol* 2022; JCO2101308. doi: 10.1200/JCO.21.01308 (ePub ahead of print).
10. Daly ME, et al. *J Clin Oncol* 2021; JCO2102528. doi: 10.1200/JCO.21.02528 (ePub ahead of print).
11. Remon J, et al. *Ann Oncol* 2021;32:1637–42.
12. Altorki NK, et al. Lancet Oncol 2021;22:824–35.
13. Cross et al. *Cancer Discov* 2014;4:1–16.
14. Mok et al. *N Engl J Med* 2017;376:629–640.
15. Wu Y-L, et al. *N Engl J Med* 2020;383:1711–1723.
16. Tagrisso (osimertinib) prescribing information. AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA; Revised December 2020. Available at Tagrisso.com [accessed Mar 1, 2022].
17. American Joint Committee on Cancer. Cancer Staging Manual, 8th Edition. AJCC; 2016.

Abbreviations

AE, adverse event; BICR, blinded independent central review; AJCC, American Joint Committee on Cancer; CD80, cluster of differentiation 80; CI, confidence interval; CNS, central nervous system; cCRT, concurrent chemoradiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumour DNA; DFS, disease-free survival; ECG; electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EGFRm, EGFR-sensitizing mutations; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; HR, hazard ratio; ICR, Independent Central Review; IgG1, immunoglobulin G1; IP, investigational product; IV, intravenous; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PFS2, time from randomization to second progression; PRO, patient-reported outcomes; Q4W, every 4 weeks; QD, once daily; QLQ, quality of life questionnaire; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SBRT, stereotactic body radiation therapy; SoC, standard of care; TKI, tyrosine kinase inhibitor; TTDM, time to distant metastasis; TTP, time to progression; WHO, World Health Organization.

Disclosures

C. Robinson reports having participated in advisory boards for Varian, AstraZeneca, EMD Serono, Radialogica and Quantaras; stock ownership in Radialogica and Qantaras; licensing fees with Varian; research grants from Varian and Merck; and having served as a principal investigator for AstraZeneca and Merck. Please refer to the associated abstract for the co-authors' disclosures.

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Contact Email: adriana.hepner@astrazeneca.com

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