Adjuvant Nivolumab in Resected Lung Cancers (ANVIL):
A Randomized Phase III Study of Nivolumab After Surgical Resection and Adjuvant Chemotherapy in Non–Small Cell Lung Cancers

ANVIL—A Part of the ALCHEMIST Trial Platform

- ANVIL is one of the randomized trials under the clinical trial platform, The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST); ALCHEMIST aims to develop adjuvant targeted therapies for genotype-defined lung cancer populations
- ANVIL evaluates adjuvant nivolumab versus observation for patients who do not qualify for treatment in ALCHEMIST-EGFR (A081105) or ALCHEMIST-ALK (E4512) trials because they are not positive for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) aberrations
- To participate in ANVIL, patients must complete the following:
  - Registration to ALCHEMIST-SCREEN (ALLIANCE A151216) and tissue specimens tested centrally for EGFR and ALK (if nonsquamous)
  - Programmed death ligand 1 (PD-L1) status tested centrally prior to randomization

Eligibility

- Patient registered to ALCHEMIST screening trial (A151216)
- No ALK rearrangement or EGFR exon 19 deletion/exon 21 L858R mutation (if nonsquamous)
- No contraindication to nivolumab

Stratification

- Stage IB*/IIA vs IIB/IIIA
- Histology: squamous vs nonsquamous
- Prior adjuvant treatment for lung cancer (none vs chemotherapy vs chemotherapy + radiation)
- PD-L1 status: positive (≥ 1%) vs negative (< 1%/nonevaluable) membranous expression determined centrally

Accrual goal = 903 patients.
Cycle = 4 weeks (28 d).
Patients randomized 1:1 to nivolumab versus observation.
All patients must have undergone complete resection of their lung cancer and completed all planned adjuvant chemotherapy.
*If stage IB, then tumor must be ≥ 4 cm.
†Adenosquamous should be grouped as nonsquamous.
‡Defined as ≥ 1% by immunohistochemistry.
§Duration of therapy will not exceed 1 year.
||Patients will be followed for recurrence and survival for 10 years.

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; PD-L1 = programmed death ligand 1.
Objectives of Biomarker-Driven Substudies

Coprimary Objectives
- Evaluate whether adjuvant therapy with nivolumab improves disease-free survival (DFS) over standard observation in patients with stage IB ≥ 4 cm, II, and IIIA non–small cell lung cancer (NSCLC) following surgical resection and standard adjuvant therapy
- Evaluate whether adjuvant therapy with nivolumab improves DFS over standard observation in patients with stage IB ≥ 4 cm, II and IIIA, NSCLC with high PD-L1 expression (≥ 50% staining) following resection and standard adjuvant therapy
- Evaluate whether adjuvant therapy with nivolumab improves overall survival (OS) over standard observation; OS will be tested hierarchically in either overall or high PD-L1 subset only if the corresponding test of DFS is statistically significant

Secondary Objectives
- Evaluate safety profile
- Evaluate and compare DFS and OS in patients with tumors that express PD-L1 in various patterns associated with nivolumab and standard observation
- Evaluate and compare DFS and OS in patients with tumors that have high mutation load associated with nivolumab and standard observation
- Evaluate OS and DFS by stage
- Evaluate OS and DFS by each stratification factor

How Your Site Can Participate
- All individuals contributing to NCI-sponsored trials must register and renew annually. Registrants must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam)
  - Investigator (IVR), Non-physician Investigator (NPIVR), or Associate Plus (AP) must complete annual registration using CTEP’s Web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr)
- Required documentation for IVR, NPIVR, and AP includes FDA form 1572 (IVR and NPIVR only), Financial Disclosure Form of Principal Investigator (PI) and sub-investigators, NCI Biosketch, HSP/GCP and Protocol Training, Agent Shipment Form (IVR only), IRB Chair Contact Information Form, IRB Approval Letter, IRB Informed Consent Document, and CV of PI and sub-investigators
- IVRs and NPIVRs must list clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on FDA Form 1572 in RCR to allow the following: added to site roster; assigned treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN; acting as site-protocol PI on IRB approval; assigned Clinical Investigator (CI) role on Delegation of Tasks Log (DTL)
- Each site must complete a protocol-specific DTL, which must be reviewed and electronically signed by the CI prior to the site receiving an approved site registration status and enrolling patients
- DTL application is on the CTSU members’ Web site at www.ctsu.org. Any individual at the enrolling site on a participating roster may initiate the site DTL; instructions are embedded in the DTL application
  - For questions, please contact RCR Help Desk via e-mail: RCRHelpDesk@nih.gov
- Site must receive IRB approval, then submit the approval with documentation (CTSU IRB certification, or signed HHS OMB No. 0990-0263 [replaces Form 310]) to the CTSU
  - Site registration forms are available on the EA5142 protocol page on the members’ section of the CTSU Web site https://www.ctsu.org
- Sites participating on the NCI CIRB initiative that are approved by the CIRB need not submit IRB approval documentation to the CTSU Regulatory Office
- For sites using the CIRB, IRB approval information is received from the CIRB and applied to the Regulatory Support System (RSS) in an automated process. Signatory Institutions must submit a Study Specific Worksheet (SSW) for Local Context to the CIRB via IRB Manager to indicate their intent to open the study locally
- Prior to enrollment of the first patient, an investigator from each site must complete a training course providing an overview of the EA5142 trial. Information includes general protocol overview and ECOG-ACRIN recommends that all research staff involved in EA5142 complete training
  - Course is available online at https://coccg813.mindflash.com/PublicCoursePage.aspx?c=1500903044
  - Contact the ECOG-ACRIN Clinical Education Team at EAClinEd@ecog-acrin.org with any training questions
- Verify site registration status by visiting the members’ section of the CTSU Web site, accessed at https://www.ctsu.org
- Once documentation has been submitted and approved,
  - Treatment should start within 14 working days after randomization
  - Patient enrollment is via OPEN, accessed at https://open.ctsu.org. Data collection is through Medidata Rave. Address OPEN and Medidata Rave questions to CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com

For Further Study Information
- For more information about the EA5142 study, please visit the following:
  - Cancer.gov; search EA5142
  - Clinicaltrials.gov; search NCT02595944
- For more information about ECOG-ACRIN, visit ecog-acrin.org

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EA5142 Site Process Summary v.01/23/19