The ADAURA Trial
Proof of Benefit is Proof of Principle

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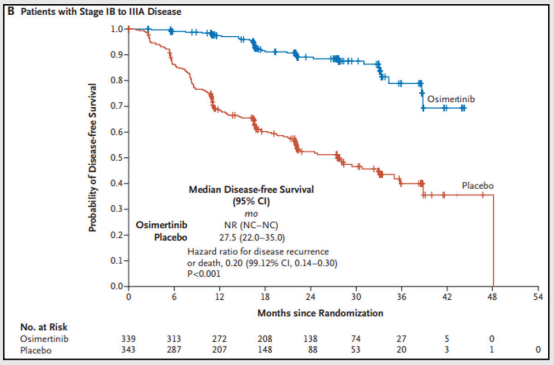
After two years of follow-up, 90% of the lung cancer patients given TAGRISSO® (osimertinib) following surgery were alive without a recurrence of their tumors, doubling the benefit seen with patients offered a placebo. Overall, TAGRISSO reduced the risk of lung cancer relapse by 83% compared to placebo — the strongest result ever reported for a clinical trial of this type.

The profound disease-free survival (DFS) benefit with osimertinib in epidermal growth factor receptor (EGFR) mutated resected lung cancer is the seminal proof of the principle of molecular testing importance and impact in early-stage lung cancer. The argument that this is just a disease-free and not overall survival benefit becomes a digressing academic discussion missing the mark of the patient's perspective. Not having active cancer is a far better quality of life (QOL). Nearly half of patients in the node-positive stages had a recurrence within one year of surgery without osimertinib, even with chemotherapy. Avoiding brain radiation therapy with the marked reduction of central nervous system (CNS) metastasis with osimertinib is also a far better QOL. These proofs of benefit finally open the door to the impact of molecular testing in early-stage lung cancer.



Greatly improved DFS with osimertinib
Nearly half of recurrences occur within one year of surgery with chemotherapy alone
Improved DFS without recurrence of cancer is an improved and enhanced QOL

DFS benefit driven by the osimertinib with or without chemotherapy
Addition of chemotherapy to osimertinib delivers no identifiable additional benefit
Overlapping hazard ratios are 0.16 with adjuvant osimertinib plus chemotherapy and 0.23 with osimertinib alone

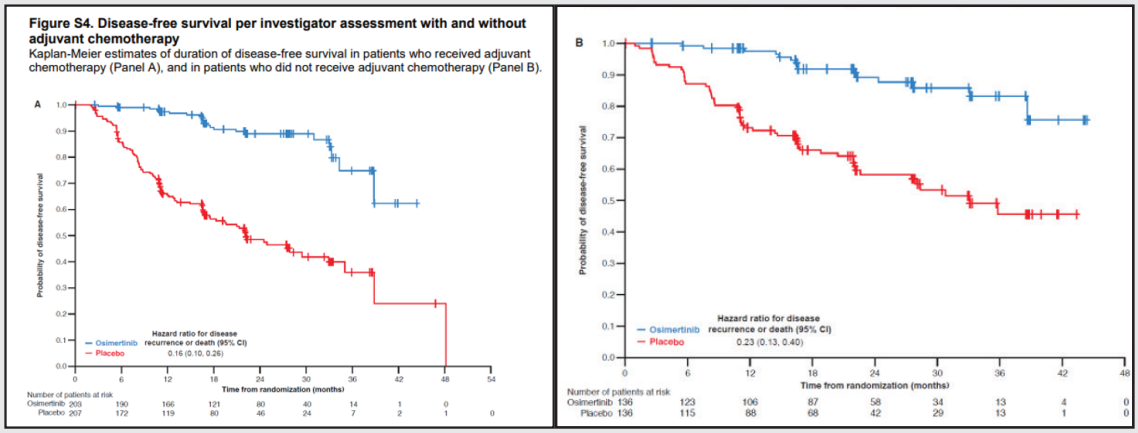


TABLE S3. Sites of disease recurrence in the overall position

Number of patients, n (%)	Osimertinib, n (n=339)	Placebo, n (n=343)
Total disease recurrence or death events*	37 (11)	159 (46)
Disease recurrence	37 (11)	157 (46)
Local/regional only	23 (7)	61 (18)
Distant only	10 (3)	78 (23)
Local/regional and distant	4 (1)	18 (5)
Death	0	2 (1)
Total CNS disease recurrence or death events*	6 (2)	39 (11)
CNS disease recurrence	4 (1)	33 (10)
Death	2 (1)	6 (2)

Greatly reduced distant and CNS metastasis with adjuvant osimertinib compared to chemotherapy

ADAURA Case Study

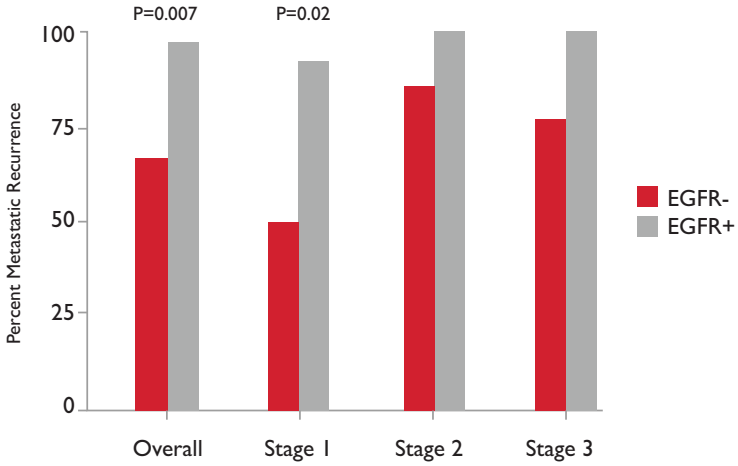
63yo female with a resected single-station N2 stage IIIA EGFR exon19 mutated lung adenocarcinoma

"Adjuvant chemotherapy has been a standard of care for the past two decades since the seminal IALT trial showed a 4.5% group overall survival (OS) benefit. The ADAURA trial from 2020 with an adjuvant targeted therapy and IMpower010 in PD-L1 expressed lung cancers from ASCO 2021 with adjuvant immune therapy have finally stepped beyond the group constraints of previous adjuvant trials.

This patient can benefit from adjuvant treatment. However, is a DFS benefit, without a proven OS benefit as of yet, enough to utilize a targeted therapy? And what about the group standard of care chemotherapy need?

The profound DFS benefit of adjuvant osimertinib is incredibly compelling. A recent study highlights the very high metastatic risk of EGFR mutated lung cancer. 90% of patients, even with stage I anatomical disease, ultimately developed metastatic disease. Delaying, if not preventing, that high of a metastatic risk is a striking benefit. In the stage III subset, half of the recurrences occurred within 12 months from surgery. Living with no cancer is a far better quality of living than knowing that cancer has returned, just when one's life is getting back to a routine of normalcy.

Data from more mature studies support an ultimate overall survival benefit with EGFR TKI targeted therapy. The EVAN trial presented at ASCO 2021 showed a five-year OS of 85% with erlotinib versus 51% with cisplatin-vinorelbine chemotherapy. The benefit of chemotherapy in EGFR mutated lung cancers is far from clear. The placebo arm of chemotherapy alone mirrors the observation arm in the IALT trial right at 40% at the five-year mark. The hazard ratios of adjuvant osimertinib with chemotherapy are 0.16 and without chemotherapy 0.23, nearly identical and completely overlap.



Three years of adjuvant osimertinib achieves a very meaningful benefit and should be recommended, in my opinion. I would be comfortable foregoing cytotoxic cisplatin-based chemotherapy, bearing in mind carboplatin doublets have no proven adjuvant benefit.

Given the ADAURA trial, testing for EGFR mutations in all resected lung cancer is a must. Likewise, given the IMpower010 trial, testing for PD-L1 in resected lung cancer is a must. This need for and patient outcome benefit of molecular testing in early-stage lung cancers is even more evident and impactful as neoadjuvant immunotherapy regimens come to the forefront in resectable lung cancer. In the neoadjuvant setting, knowing EGFR mutations, fusions, and PD-L1, as well as immune resistant mutations such as STK11 and KEAP1, becomes vitally important before stepping forward with immune-based regimens.

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Research Paper

The role of EGFR mutations in predicting recurrence in early and locally advanced lung adenocarcinoma following definitive therapy

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Plasma NGS to assess for ctDNA mutations, RNA fusions, and cfRNA PD-L1 expression can help provide that tumor biology insight to avoid a wrong treatment in a curative setting."

Case Study Prepared by Doctor Paul Walker
Chief Medical Officer, Former Director of Thoracic Oncology at East Carolina University