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ADAURA Survival Boost For AZ's Tagrisso

More EGFR Testing Needed

by Alex Shimmings

Impressive overall survival data from the Phase III ADAURA trial should boost both EGFR testing in non-small cell lung cancer, and sales of the blockbuster NSCLC therapy.

Any lingering doubts over the benefit of using *AstraZeneca PLC*'s third-generation EGFR inhibitor Tagrisso (osimertinib) in stage IB-IIIA epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer appear to have been laid to rest with overall survival from the ADAURA study showing it reduced the risk of death by 51% at five years after initial surgery. The data are expected to drive increased EFGR testing, reimbursement and prescribing of the product, firmly embedding it into treatment practice in the adjuvant setting.

In the final ADAURA OS analysis, presented to a standing ovation at a plenary session during the American Society Of Clinical Oncology meeting in Chicago on 4 June, 88% of patients with IB–IIIA NSCLC who were given osimertinib for three years following surgical resection were still alive five years after surgery compared with 78% of patients treated with placebo. This translates to a 51% lower risk of death ($p<0.0001$).

For the Stage II-IIIA population (the primary endpoint), the figures were 85% and 73%, respectively, again a 51% lower risk of death (see *table).*

The survival benefit was also apparent across all study subgroups, including in those with stage IB, II, and IIIA NSCLC. Adjuvant chemotherapy had been given to 60% of 682 study participants

before assignment to the study's treatment groups, and the survival benefit of osimertinib was seen regardless of whether prior adjuvant chemotherapy was received.

In a simultaneous publication in the *New England Journal of Medicine,* the investigators noted that the values for five-year overall survival in the placebo group in ADAURA (ranging from 67% among patients with stage IIIA disease to 88% among those with stage IB disease) were toward the higher end of those reported in historical datasets among patients with resectable NSCLC. "This observation may be due to improvements in diagnostic imaging and disease management over time. Even with these encouraging values for five-year overall survival in the placebo group, the benefit of adjuvant osimertinib was significant," they conclude.

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The initial DFS data from ADAURA impressed when they were also presented at ASCO in 2020. (Also see "*ASCO 2020: AZ's Tagrisso Sails Into Early-Stage NSCLC On 'Momentous' ADAURA Trial Data*" - Scrip, 29 May, 2020.)

Prior to ADAURA, the product already enjoyed blockbuster sales in metastatic treatment settings, but the initial data moved it into early-stage settings following expanded approval in the US in December 2020. Before this, standard of care for resected patients with Stage II-IIIA disease and for some Stage Ib patients was cisplatin-based chemotherapy, but recurrence rates remained high.

The lead researcher, Roy Herbst of Yale Cancer Center, said ADAURA was the first trial to show a statistically significant OS benefit with targeted therapy in the adjuvant setting, and reinforced Tagrisso as the standard of care here.

He said they should drive increased EGFR testing: "We've got to find these mutations. We've got to identify these patients."

The data should also increase prescribing of the product. "There are some physicians, many surgeons, even some of my colleagues at Yale [who] do not recommend this, because they're waiting to see does this improve survival?" Herbst told journalists at an ASCO press briefing. Such reluctance may have been due to other trials using older EGFR inhibitors such as Iressa (gefitinib) that also showed improvements in disease-free survival that did not translate into improvements in overall survival.

The study discussant, Benjamin Solomon of Peter MacCallum Cancer Centre in Melbourne, Australia, was similarly effusive. "These unprecedented overall survival results in early-stage NSCLC are practice changing or practice affirming (for those who had already changed practice)

and dispel the notion of equivalence between early treatment with osimertinib and treatment on recurrence," he told the ASCO meeting.

Analysts agree that the OS data reinforce Tagrisso as the standard of care for the adjuvant setting. J.P. Morgan said in a 5 June reaction note: "We believe the very strong OS data significantly further strengthens Tagrisso's profile for adjuvant use, and we expect to see the addition of this OS data to the Tagrisso label accelerating uptake in the adjuvant setting."

They noted that Tagrisso sales growth had not seen as much of an acceleration as they had initially expected upon ADAURA approval in late 2020, which they put down as partly been due to COVID-19 disruption, but this may also have reflected lack of early-stage lung cancer diagnosis and EGFR testing, as well as lack of adjuvant reimbursement in many countries. As such, the OS data should provide a significant boost to Tagrisso adjuvant uptake, they believe, with $1.5bn peak sales potential in an overall Tagrisso forecast of around $8bn in peak sales.

Newer EGFR Inhibitors

Tagrisso is specifically indicated as adjuvant therapy after tumor resection in adult patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

Meanwhile, early data from some newer EGFR inhibitors coming through the pipeline were presented at ASCO. Shanghai-listed *Dizal (Jiangsu) Pharmaceutical Co., Ltd.*, a company formed from *AstraZeneca PLC*'s former drug discovery division in China, is showcasing updated clinical outcomes from its China-only, pivotal Phase II trial WU-KONG6 for sunvozertinib, an EGFR inhibitor targeting the exon20 insertion (exon20ins) with wild-type EGFR selectivity. (Also see "*ASCO Preview: Multiple Chinese Biotechs Showcase NSCLC Assets*" - Scrip, 31 May, 2023.)

US-based *Blueprint Medicines Corporation* is developing some precision therapies to inhibit the broad spectrum of EGFR activating and resistance mutations, including BLU-451, a wildtype-EGFR-sparing, CNS-penetrant oral inhibitor of EGFR exon 20 insertions and atypical mutations, and BLU-945, a potent oral EGFR inhibitor designed to be highly selective over wildtype EGFR, which could be used in combination with other EGFR inhibitors such as osimertinib.