Adjuvant immunotherapy and targeted therapy in early and locally advanced resectable lung cancer: expanding treatment tentacles?

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Targeted therapies and immunotherapy complement platinum-based chemotherapy in the adjuvant setting of early and locally advanced completely resected lung cancer improving clinical outcomes https://bit.ly/3xKbaTo

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Abstract

Adjuvant platinum-based chemotherapy has been the main treatment following surgical resection with curative intent in early and locally advanced nonsmall cell lung cancer (NSCLC) albeit with a 5% improvement in 5-year survival rates. Recent advances in biomarkers pave the way for targeted treatments and immunotherapy in a broader spectrum of patients with subsequently improved clinical outcomes. Targeted treatments and immunotherapy have established their place in the adjuvant setting of resected NSCLC.

Commentary on:

- Felip E, *et al.* Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet* 2021; 398: 1344–1357.
- O'Brien M, *et al*. Pembrolizumab *versus* placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 2022; 23: 1274–1286.
- Wu Y-L, *et al.* Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2020; 383: 1711–1723.

Updated and complemented by:

- Tsuboi M, *et al*. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med* 2023; 389: 137–147.

Context

Surgical resection with curative intent is the mainstay of treatment in early and locally advanced nonsmall cell lung cancer (NSCLC). Despite the curative intent, lung cancer (LC) recurrence remains relatively high with a 5-year recurrence of 45% in stage IB and 76% in stage III disease.

Adjuvant platinum-based treatment options in selected patients with surgically resected stage II–IIIA NSCLC have been offered to reduce disease recurrence; however, they have only shown a maximum 16% risk reduction in disease recurrence or death [1–4]. The addition of adjuvant treatment to these patients' treatment pathway seems to improve their 5-year survival by up to 5% [5]. Stage IB patients with complete surgical resection may also benefit from adjuvant treatment if their resected tumour measures 4 cm or it presents with poor differentiation and/or visceral pleura involvement [1–4, 6].

To improve this, targeted therapy and immunotherapy have been studied in addition to chemotherapy to investigate whether these therapies would show a survival benefit. Over the past few years, there have been significant advances in the identification of targetable mutations and biomarkers in LC paving the way for precision medicine applications in daily clinical practice.

The use of targeted treatments and immune checkpoint inhibitors as adjuvant treatment of patients with resected LC tumours that harbour epidermal growth factor receptor (EGFR) mutations or present increased programmed death-ligand 1 (PD-L1) expression seems a reasonable approach. Important studies have addressed this matter and resulted in changing daily clinical practice. This journal club will briefly present three important studies in the field where the initial results have informed clinical practice guidelines and contributed to improved LC treatments and patient care with the administration of targeted treatment and immunotherapy in the adjuvant setting for early and locally advanced completely resected NSCLC: Impower010, PEARLS/KEYNOTE-091 and the ADAURA study [7–9]. Table 1 summarises the study design and main findings of these trials.

IMpower010 TRIAL: methods and results

The IMpower010 trial was a multicentre, open label, randomised, phase 3 study focusing on investigation of the efficacy and safety profile of adjuvant atezolizumab in early and locally advanced NSCLC, following complete surgical resection. The study included 1005 patients with stage IB–IIIA NSCLC, and the patients were randomised in a ratio of 1:1 to either receive a placebo or atezolizumab for 16 cycles or 1 year [7].

The primary end-point of this trial was disease-free survival (DFS), as determined by the investigator, in the stage II–IIIA population with a tumour demonstrating PD-L1 expression on 1% or more of the tumour cells. DFS was considered as a secondary end-point in the entire stage II–IIIA population, and overall survival (OS) was another secondary end-point in the intent-to-treat (ITT) population.

Every 3 weeks patients received either intravenous infusions of atezolizumab or placebo for 16 cycles or until 1 year. The rationale for the choice of treatment duration and/or treatment cycles was not clearly justified in the trial, and to date, remains a matter of discussion in the adjuvant setting as there is no definitive response regarding the optimal number of cycles or treatment duration. Safety assessment of localised reactions and adverse events related to the investigational medicinal products was performed periodically during the whole study period and 30 days after the last administration of the investigational medicinal products (90 days for serious adverse events and immune-mediated adverse events).

The study was powered at 90% for the primary analysis of DFS in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of the tumour cells, with a hazard ratio (HR) for disease recurrence or death of 0.65. The primary analysis of all-patient DFS in the stage II–IIIA population specified a HR for disease recurrence or death of 0.73 at 91% power. The power of the trial for primary analysis of DFS in the ITT population was 76%, with the HR for disease recurrence or death being 0.78.

TABLE 1 Summary of the trial designs and main findings

Study	Type	Study population	Arms	Main results
Impower010 (2021) [7]	Multicentre, open-label, randomised, phase 3 trial	Adults with completely resected stage IB (⩾4 cm)–IIIA NSCLC	Chemotherapy followed by atezolizumab 1200 mg for 16 cycles *versus* best supportive care	DFS benefit in stages II–IIIA HR 0.66 (95% CI 0.50–0.88; p=0.002)
PEARLS/KEYNOTE-091 (2022) [8]	Multicentre, triple-blind, randomised, phase 3 trial	Adults with completely resected stage IB (⩾4 cm), II or IIIA NSCLC	Chemotherapy followed by pembrolizumab 200 mg for up to 18 cycles *versus* placebo	Median DFS 53.6 *versus* 42 months HR 0.76 (95% CI 0.63–0.91; p=0.0014)
ADAURA (2023) [9, 10]	Multicentre, double-blind, randomised phase 3 trial	Adults with primary nonsquamous stage IB–IIIA NSCLC with central confirmation of an EGFR exon 19 deletion or L858R mutation	Osimertinib *versus* placebo	5-year overall survival 85% *versus* 73% in stage II–IIIA

NSCLC: nonsmall cell lung cancer; DFS: disease-free-survival; HR: hazard ratio; EGFR: epidermal growth factor receptor.

In the interim analysis of the study, a markedly improved DFS with adjuvant atezolizumab compared with placebo was apparent in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of the tumour cells (HR 0.66, 95% CI 0.50–0.88; p=0.002). However, statistical significance for DFS was not achieved in ITT population (including patients with stage IB disease) and the OS data were immature at this interim analysis and hence should be interpreted with caution.

Thus, the IMpower010 trial demonstrated that adjuvant atezolizumab significantly improved DFS in patients with resected NSCLC with tumours expressing PD-L1 on 1% or more of the tumour cells. Overall, the study provides encouraging results for improving outcomes following complete surgical resection of NSCLC and can contribute as proof of concept for the adjuvant use of immunotherapy for other solid tumours in which immunotherapy is being used in later lines of therapy (*e.g.* cervical cancer, head and neck carcinoma, oesophageal cancer).

PEARLS/KEYNOTE-091 trial: methods and results

The PEARLS/KEYNOTE-091 trial was a randomised, triple blind, phase 3, multicentre trial, that was designed to assess the benefit and safety of adding pembrolizumab after standard therapy of completely resected NSCLC of any histology, stage IB to IIIA (American Joint Committee on Cancer (AJCC) seventh edition) [8].

The co-primary end-points of the trial were DFS in the overall population and in patients with a PD-L1 tumour proportional score of 50% or more. Secondary end-points were DFS in the PD-L1 $\geqslant$1% population, OS in the overall population and OS by PD-L1 expression, LC-specific survival and safety. A total of 1178 patients were registered: 590 were assigned to pembrolizumab and 587 to placebo.

Neoadjuvant or adjuvant radiotherapy was not permitted while adjuvant chemotherapy was strongly recommended for stage II to IIIA and to be considered for stage IB.

Patients were randomised (1:1) to pembrolizumab or placebo and stratified according to stage, receipt of adjuvant chemotherapy or not, PD-L1 expression (<1%, 1–49%, >50%) and geographical region.

At a median follow-up time of 35.6 months, 52% of the pembrolizumab group and 66% of the placebo group completed treatment. The remaining population discontinued treatment before receiving 18 administrations and this was mainly due to adverse events in the pembrolizumab arm and progressive disease in the placebo arm.

Median DFS was 53.6 months in the pembrolizumab group while in the placebo group median DFS was 42 months (HR 0.76, 95% CI 0.63–0.91; p=0.0014). Regarding those patients with high PD-L1 expression (>50%, n=333), median DFS was not reached for those in the pembrolizumab group (44.3 months to not reached) or for those of the placebo arm (35.8 months to not reached). Median OS was not reached. 96% of the pembrolizumab arm participants and 91% of those in the placebo arm had adverse events of any cause, while grade 3 or worse events were 34% and 26%, respectively. Four deaths were attributed to pembrolizumab while no deaths were attributed to placebo.

The ADAURA study: methods and results

The ADAURA study was a double-blind, randomised phase 3 trial looking at the efficacy and safety of osimertinib, a third generation EGFR tyrosine kinase inhibitor, as adjuvant treatment in resected LC. The trial aimed to determine if osimertinib could improve DFS [9, 10].

682 patients (post-surgical pathological stage IB–IIIA according to the AJCC/International Union Against Cancer seventh edition, tumour size in stage IB >4 cm) with EGFR-mutated, either exon 19 deletion or exon 21 L858R substitution, NSCLC were included between 2015 and 2019. Patients were randomly assigned 1:1 (stratified by stage, mutational status and race) to receive either osimertinib 80 mg once daily or placebo until disease recurrence was seen or for 3 years. The trial included patients who had (60%) or had not received adjuvant chemotherapy prior to randomisation.

The primary end-point was DFS in the overall stage II–IIIA population. Secondary end-points were analysis of DFS in the stage IB–IIIA group, OS and the safety profile of osimertinib. After a planned interim analysis in 2020 the independent committee recommended to unblind the study at a level of 2 years because of the efficacy benefit shown.

The final results were presented in 2023 [10]. The 5-year OS in the stage II–IIIA group was 85% in the osimertinib group and 73% in the placebo group. The hazard ratio for death was 0.49 (95% CI 0.33–0.73;

p<0.001). Similar results were shown in stage IB–IIIA group (88% in the osimertinib group *versus* 78% for placebo, HR 0.49 (95% CI 0.34–0.70; p<0.001)). Analysis showed that central nervous system (CNS) DFS improved significantly in the osimertinib group at 24 months (HR for CNS disease or recurrence 0.18 (95% CI 0.10–0.33)).

The overall safety analysis showed adverse events in 98% of the osimertinib group *versus* 89% in the placebo group. Investigator deemed causality related adverse events to osimertinib were presented separately to overall side-effects. Grade 3 or higher adverse events were reported in 20% in the osimertinib group and 13% in the placebo group. Interstitial lung disease was reported in 3% in the osimertinib group *versus* 0% in the placebo group. The most common causally related adverse events were diarrhoea, paronychia, dry skin, pruritus and stomatitis. No fatal adverse events were reported.

Commentary

Information on atezolizumab as an effective treatment for patients with early and locally advanced NSCLC who had attained complete surgical resection largely comes from confirmed analyses of several subgroups of clinical trials in patients with more developed disease. The IMpower010 study showed a dramatically improved DFS in patients that had tumours expressing PD-L1 on at least 1% of the tumour cells [7]. Nevertheless, data remained immature for OS, and in the ITT population, which also included patients with stage IB disease, statistical significance for DFS was not met.

Based on these data, research on adjuvant immunotherapy in other solid tumours is prompted. However, longer follow-up is needed to define the effect of adjuvant atezolizumab on OS. The study also points out that accurate and standardised biomarker testing is critical for the selection of patients that are most likely to benefit from immunotherapy [7].

All in all, the IMpower010 study contributes some important evidence over the adjuvant use of atezolizumab in resected NSCLC [7]. The research indicates immunotherapy provides the way forward in enhancing outcomes following complete surgical resection in NSCLC. However, longer trial follow-up is needed to establish the effect of adjuvant atezolizumab on OS and there is a need for further research to identify predictably accurate biomarkers that will signify response to immunotherapy.

Similar results to the IMPower010 trial were extracted from the PEARLS/KEYNOTE-091 study, despite the differences between the two trials, regarding the proportion of participants between stages (stage II: 53.9% *versus* 56%; stage III: 46.1% *versus* 30% in the ITT population), prior use of chemotherapy (93.9% *versus* 86%) and the proportion of nonsmokers (12.3% *versus* 8% in the PD-L1 >50% group). Adjuvant pembrolizumab as monotherapy was found to offer significantly longer DFS for the overall population (regardless of PD-L1 expression) after completion of standard treatment for resectable NSCLC stages IB to IIIA [8].

Although the relative benefit of pembrolizumab monotherapy increases with increasing PD-L1 expression in the setting of locally advanced or metastatic NSCLC, the boundary for significance was not crossed for those with high PD-L1 expression. This paradox is mainly attributed to the fact that the placebo group had a better-than-expected performance and secondly to a possible imbalance of unknown factors, such as molecular alterations, that may have had such an effect. Longer follow-up regarding DFS and OS may answer this question.

Secondary end-points (DFS in the PD-L1 ⩾1% group, OS in the overall population and OS by PD-L1 status) are in follow-up as planned.

The difference in DFS at 24 and 36 months remains consistent over time in the overall population, but due to the small numbers of patients in subgroups, such as those with stage IB disease, smokers, those with EGFR mutations, those with no prior use of adjuvant chemotherapy and patients with squamous histology, no safe conclusion can be drawn.

The safety profile of pembrolizumab is known and consistent with other studies but the curative intent of this regimen should be taken into consideration as four deaths were attributed to pembrolizumab in the trial population.

Appropriate treatment for patients harbouring EGFR mutations has always been considered a challenge in NSCLC. In the metastatic setting, osimertinib had previously been shown to have a higher treatment

potency than gefitinib or erlotinib, mainly due to overcoming the frequently developed T790M resistance mutation [11, 12]. Osimertinib has also shown significant benefit in treating CNS disease even on a background of the T790M resistance mutation [13]. Therefore, researching and finally implementing the use of EGFR inhibitors in resected NSCLC constitutes a rational next step.

The ADAURA trial showed significantly longer OS in patients treated with adjuvant osimertinib. The survival benefit remained consistent across subgroups (by stage) and irrespective of the administration of adjuvant chemotherapy [9, 10]. The hazard ratio for CNS recurrence or death showed an 82% risk reduction for CNS disease in the osimertinib group.

The significant benefit seen in the interim analysis of the ADAURA trial led to the approval of osimertinib as an adjuvant treatment in stage IB–IIIA EGFR-mutated LC [9].

Looking ahead, a subgroup analysis in the primary analysis suggested that DFS improvement with adjuvant osimertinib is independent of adjuvant chemotherapy. Further studies are required to facilitate the abolishment of platinum-based chemotherapy administration in the adjuvant setting for these cancers.

Implications for practice

Taking into account the results of all three studies, we can emphasise adjuvant treatment intensification, which is guaranteed for some of the patients with resected stage II–IIIA NSCLC and potentially for those with stage IB EGFR-mutated tumours. An algorithm that incorporates stage, PD-L1 expression, EGFR and anaplastic lymphoma kinase (ALK) status can be proposed, taking into account the small numbers per subgroup of the trials described in the current literature and the awaited results from ALINA trial [14].

IMpower010 provides data for the use of adjuvant atezolizumab for those patients whose tumours express PD-L1 on 1% or more cells, and especially for those with PD-L1 expression of $\geqslant$50% and non-squamous histology. No definite conclusion can be drawn for patients with no smoking history, stage IB disease, EGFR mutations, ALK alterations or low/no PD-L1 expression as statistical significance was not met for those subgroups [7].

The results of the PEARLS/KEYNOTE-091 trial can prompt towards the adjuvant use of pembrolizumab for patients with smoking history, stage II–IIIA, non-squamous histology, and low/no PD-L1 expression [8].

Immunotherapy cannot be proposed for patients with EGFR mutations, as the results of ADAURA trial provide enough evidence for the adjuvant use of osimertinib in this population [9, 10].

In addition, patients harbouring ALK rearrangements were underrepresented in both IMpower010 and PEARLS/KEYNOTE-091 trials and therefore, no safe conclusions can be made for immunotherapy use in this population. Results of the ALINA trial could shed light on the treatment options for this special subgroup [14].

Similarly to the adjuvant setting [8–11], the concept of perioperative immunotherapy has evolved to the neoadjuvant pathway. Neoadjuvant treatment intensification has emerged with several trials [15–18] published after the ones discussed in this journal club [7–10]. Checkmate 81, Keynote 671, Aegean and Checkmate 77t [15–18] have all reported that the neoadjuvant use of immunotherapy followed by resection results in improved pathological complete response and longer event-free survival than chemotherapy alone.

Adjuvant targeted treatment (osimertinib) in resected stage IB disease is proposed in EGFR positive patients, while adjuvant chemotherapy is required when the resected tumour is 4 cm or it invades the visceral pleura. There is no evidence on the use of adjuvant immunotherapy in stage I disease. Stage II and IIIA of resected NSCLC seems to benefit from immunotherapy regardless of PD-L1 status. The adjuvant use of immunotherapy and targeted therapy in resected NSCLC is promising in improving clinical outcomes. Its integration in clinical pathways and daily clinical practice relies on national guidelines, assessments of drug implementation efficiency and reimbursement policies. Patients' access to these adjuvant treatments may be restricted by existing financial constraints therefore limiting treatment availability.

Conflict of interest: The authors have nothing to disclose.

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