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The path forward in early-stage lung cancer

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Lung cancer is the leading cause of cancer mortality worldwide, with 2.2 million new lung cancer patients (accounting for 11.4% of all cancer cases) and 1.8 million deaths (representing 18% of cancer deaths) in 2020 (1). Early-stage disease non-small cell lung cancer (NSCLC) has better outcomes, but the 5-year survival rates drop from 60% for stage IIA to 36% for stage IIIA disease (2,3). Adjuvant chemotherapy has shown to improve survival by 5.4% but is paired with clinically important toxicity (4).

Neoadjuvant chemotherapy is less extensively studied as adjuvant chemotherapy but has resulted a similar benefit of approximately 5% at 5-year (5).

Two new therapeutic strategies that revolutionized treatment of metastatic disease, have been introduced in the (neo)adjuvant field: targeted therapies and immune checkpoint inhibitors (ICIs). These have now led to a revival of interest for the treatment of non-metastatic lung cancer.

Of the tyrosine kinase inhibitor (TKI)'s, adjuvant osimertinib treatment significantly improved disease-free survival (DFS) after surgery for epidermal growth factor receptor (EGFR) mutated NSCLC (6). Soon after, adjuvant atezolizumab showed to improve outcome, with treatment benefit being most pronounced in patients with a high programmed death-ligand 1 (PD-L1) expression (7). In both trials higher disease stages benefited the most of this

strategy, but all patients were still treated chemotherapy before randomization.

In earlier disease stages however, the improvement was less impressive. Adjuvant pembrolizumab similarly reached the primary endpoint of improved DFS, but no relation with PD-L1 expression was observed, leaving many of us puzzled behind (8).

Adoption of immunotherapy-based strategies were investigated in the neoadjuvant setting, due to several potential advantages over adjuvant therapies: (I) reduction of tumor burden before surgery allowing for less morbid resections; (II) to assess a potential therapeutic response on the resection specimen (pathological response); (III) to induce better immune-surveillance offering protection for disease recurrence. This strategy is in line with preclinical evidence in early disease, probably related to fitness of host immunity and presence of (sufficient) neo-antigens (9-11). Several trials looked at various endpoints such as safety, feasibility, efficacy, and pathological response rate of programmed death-1 (PD-1) inhibitors in monotherapy or combined with other ICIs or chemotherapy (12), all leading to the conclusion that neoadjuvant PD-1 inhibitor-based strategies are promising, safe, feasible and efficacious, leading to larger randomized trials.

In this edition of *Translational Lung Cancer Research*, an expert consensus on perioperative treatment for NSCLC

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is presented. Unique about this consensus meeting is the fact that the invited clinicians are mostly based in the Australasian and European countries, thereby introducing information of studies with new drugs. The paper covers all known studies and gives insight in the way different centers or countries have implemented the scientific data in their daily routine. It is clear that there are still many variations in patient management and questions to be addressed.

Neo-adjuvant therapy

The choice of ICIs to be tested is nowadays immense and primary endpoints do vary. Is major pathological response (mPR) the best endpoint? How toxic will new combinations be and lead to a failure in performing the surgical resection? How many courses of therapy can be given in a safe way? Do we still need chemotherapy as standard of care (SoC)? Can you continue with ICI after surgery when it has shown to be successful?

Recently the results of the CheckMate 816 phase III trial (CM816) were published, showing a benefit of combining chemotherapy plus nivolumab over chemotherapy alone. Both primary endpoints of improved event-free survival (EFS) and pathological response rate were met and did so with excellence (13). Just as in the adjuvant trials this approach appeared to be more advantageous in patients with higher disease stages (such as stage IIIA) and in patients with PD-L1 expression. This trial and other neoadjuvant PD-1 inhibitor-based trials, showed a significant proportion (approximately 15% in the CM816) of patients diagnosed with an operable NSCLC, that did not advance to surgery for various reasons (such as disease progression, toxicity, irresectability, ...) (14).

Adjuvant therapies

Most of the studies have not been able to introduce an arm where no chemotherapy is given. It is well known that not many patients are able to tolerate 3–4 courses of chemotherapy and subsequently can still be randomized to another agent or placebo. One must be careful of a potential selection bias when interpreting the adjuvant data. One clear message is echoed in this consensus meeting: Do preselect your patient for EGFR and anaplastic lymphoma kinase (ALK) mutation. This has major impact on the course of treatment. How long an adjuvant therapy like ICI or targeted agent must be given remains a question.

With the release of data from ongoing studies, we might

be able to solve some of these questions, but time will usually tell.

From our and scientific point of view the path forward is to implement neo-adjuvant therapies, because this will identify those patients who benefit most and will most likely reduce the number of futile and expensive treatments in the adjuvant setting.

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