European Journal of Respiratory Medicine

2022; 4(2): 306- 312. doi: 10.31488/EJRM.131

Research article

Neo-Adjuvant Therapies in Lung Cancer – Past Present and Future Directions

Jonah M. Cooper[#1],Waleed Kian[#2], J, Laila C. Roisman[*1], Bilal Krayim[1], Walid Shalata[3], Dekel Shlomi[4], Areen A. Remilah[1], Dina Levitas[1], Ranin Marei[1], Alexander Yakobson[3], Dina Levitas[1], Nader Abdel Rahman[5], Nir Peled[#1]

1. The Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel

2. Medical School for International Health, Israel

3. Ben-Gurion University of the Negev, Beer Sheva, Israel

4. The Legacy Heritage Oncology Center & Dr. Larry Norton Institute, Israel

5. Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel

6. Adelson School of Medicine, Ariel University, Ariel, Israel & Clalit Health Services, Dan- Petah-Tiqwa District, Israel

7. Interventional Pulmonology and Bronchoscopy, Shaare Zedek Medical Center, Jerusalem, Israel

[*]Corresponding author: Prof. Nir Peled, The Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel

#These authors contributed equally to this work

Received: March 01, 2022; Accepted: March 28, 2022; Published: March 29, 2022

Abstract

Lung cancer is the leading cause of neoplasm mortality worldwide, with most cases being non-small cell lung cancer (NSCLC). Over the last 20 years, the treatment of lung cancer has changed significantly and includes the neo-adjuvant and adjuvant setting. Initially, adjuvant chemotherapy presented curative benefit in stages beyond Ib. Recently, targeted therapy and immunotherapy has been implemented in that setting. The neo-adjuvant setting has been investigated mainly with concomitant radiation, while systemic therapy has not shown a breakthrough yet. This review summarizes adjuvant therapy, present neoadjuvant immunotherapy, and explores future neoadjuvant targeted therapy treatments of NSCLC. In addition, we will mention the use of induction-targeted therapy prior to radiotherapy for unresectable NSCLC. This includes both completed and ongoing clinical trials.

Keywords: Lung cancer, Neoadjuvant therapy, NSCLC, EGFR, Targeted therapy

Introduction

Lung cancer is the leading cause of neoplasm incidence and mortality worldwide [1]. Non-small cell lung cancer (NSCLC) can account for 85% of lung cancer cases [2]. The treatment has changed significantly over the last approximate 20 years to improve patient survival and response rates. The main advances were at the systemic approach to advance disease, while there was little advancement in the adjuvant and neo-adjuvant setting [3]. This review does not encompass advances for advanced disease but focuses on the current and future direction of adjuvant and neo-adjuvant approaches.

Adjuvant therapies

Adjuvant chemotherapy after surgical resection has become standard of care in stages II- IIIC while in stage IB it is still controversial. This recommendation is based on patients' overall survival, disease-free survival, and 3-year survival benefits [5,6]. For several years, trials continued to demonstrate the beneficial impact of adjuvant chemotherapy compared to observation alone for Stage IB-III NSCLC patients [6–8]. Recently, immunotherapy has been shown significant impact in DFS and atezolizumab has approved in this setting. Likewise, osimertinib has been shown DFS benefit with HR of 0.50, 0.17, and 0.12 for stage IB, II, and IIIA, respectively [8]. This recent study was the first to demonstrate the impact of a precision approach in the adjuvant setting.

Neoadjuvant studies

A neo-adjuvant approach is limited in the NCCN guidelines to early-stage NSCLC with the aim to improve the surgical outcomes, and specifically to downstage T and/or N status.

However, little has been understood regarding the usage of

adjuvant, compared to neoadjuvant, chemotherapy regimens. The first of many trials that compared these two therapies, the NATCH trial, determined that there was no statistically significant difference between these therapies [11]. Following the NATCH trial, several of the patients participated in a secondary trial assessing the major pathological response (MPR) after neoadjuvant chemotherapy [12]. From this, 22.8% of patients achieved an MPR. Furthermore, the overall survival in patients that had achieved MPR was 84.6%, significantly greater than the 58.5% in those who did not achieve MPR. Moreover, when subdivided based on histological findings, the 5-year OS in the squamous NSCLC patients that achieved MPR was significantly longer at 100%, compared to 48% in those that did not achieve an MPR. Several trials have since identified a remarkable progress of neoadjuvant immunotherapy in early-stage NSCLC patients [13-16].

Immunotherapy as neo-adjuvant therapy

Several different neoadjuvant therapies were explored that utilized monoclonal antibody therapy regimens against different stages of NSCLC. This included nivolumab, sintilimab, atezolizumab, and ipilimumab (Table 1). Major pathologic response (MPR) of these therapies throughout trials ranged from 20-83%, varying with the number of cycles and the respective therapies used [11–13,15–18].

Targeted therapy as neo-adjuvant therapy

It was determined that many treatment-resistant patients possessed cases of NSCLC that had mutations in their molecular pathways, preventing the utilization of these regimens. Particularly, mutations in the Epidermal Growth Factor Receptor (EGFR) pathway were present. As a result, the development of EGFR Tyrosine Kinase Inhibitors (TKIs) has significantly improved the treatment of NSCLC cases with EGFR mutations [21]. Neoadjuvant EGFR-TKIs are often taken daily, and clinical trial regimens have ranged from 4-12 weeks [22–24]. Most trials assessing the use of TKIs are implemented as a secondary or tertiary treatment of severe NSCLC cases that have demonstrated resistance to prior treatment regimens. Despite the previously demonstrated resistance to treatments, patients have continued to respond favourably with objective response rates greater than 47.5% following these targeted therapies [25]. From these promising findings, the use of TKIs as a primary treatment for NSCLC cases with EGFR mutations has begun to be explored [26]. This article will also portray completed and ongoing trials with ALK inhibitors and ROS inhibitors. A summary of these findings can be found in table 2 and will be explored below.

The NeoADAURA trial (NCT04351555), a phase III randomized clinical trial, is set-out to identify the safety and efficacy of osimertinib (third generation TKI) with and without chemotherapy, compared to chemotherapy and a placebo as a neoadjuvant treatment in resectable Stage II-III NSCLC patients with an EGFR-mutation and no previous treatment [26].

Here, we present a review of past and current treatments of resectable Stage IA-III NSCLC patients. We also explore the future of NSCLC treatments and suggest a consideration of TKIs for the treatment of NSCLC with rarer mutations.

Materials and Method

Multiple searches were conducted in Pubmed for completed adjuvant therapy clinical trials. Similar searches were conducted for completed and in-progress neoadjuvant therapy clinical trials.

Neoadjuvant measures

Throughout this review, several measures have been used to measure the use and efficacy of neoadjuvant therapies. These include pathological complete response (pCR), major pathological

Table 1. Results of Trials Using Neoadjuvant Immunotherapy with or without chemotherapy with resectable NSCLC

Study	Stage	Sample Size	Neoadjuvant Therapy	No. of Cycles	Failure to undergo Surgery After Neoadjuvant, %	Primary End Point	MPR after surgery, %
Forde et al., 2018 [11]	I – IIIA	22	Nivolumab	2	9.0	Safety and feasibility	45
Li et al, 2019 [12]	IB – IIIA	22	Sintilimab	2	0	Safety and efficacy	45.5
Provencio et al., 2020 [13]	IIIA	46	Nivolumab + carboplatin + paclitaxel	3	12.2	PFS at 24 months	83
Shu et al., 2020 [15]	IB – IIIA	30	Atezolizumab + carboplatin + nab-paclitaxel	4	13.3	MPR	57[b]
Lee et al, 2021 [16]	IB – IIIB	181	Atezolizumab	2	16	MPR	20
Cascone et al., 2021 [17]	I – IIIA	44	Nivolumab + Ipilimumab vs. Nivolumab	3[a]	16	MPR	38% vs. 22% (ITT) 50% vs. 24% (resected)
Forde et al., 2021 [18]	IB – IIIA	358	Nivolumab	3	17 vs 25	pCR	24%

[a]Three cycles of nivolumab with or without one dose of ipilimumab
[b]Intention-to-treat analysis
MPR: major pathologic response; PFS: progression-free survival; ITT: Intention-To-Treat; pCR: pathologic complete response

Table 2. Results of Trials Using Targeted therapy with NSCLC

Study	Stage	Sample Size	Targeted Therapy	Duration of Treatment (weeks)	Primary End Point	Result, %
Xiong et al., 2019 [29]	IIIA (N2)	19	Erlotinib	8	Radical resection rate	68.4%
Zhang et al, 2019 [33]	IIIA/B	11	Crizotinib	4-17	Not indicated.	N/A
Fu et al., 2020 [21]	IIIA/B	28	Gefitinib	Not mentioned	Objective response rate	75
Lv et al., 2020 [20]	I-IIIA	134	Afatinib/ Erlotinib/ Gefitinib / Icotinib/ Osimertinib	4-12	Efficacy of neoadjuvant TKIs compared to chemotherapy	55.8
Bao et al, 2021 [23]	IB-IIIC	42	Afatinib/ Erlotinib / Gefitinib / Icotinib	6	Objective response rate	47.6
Hotta et al., 2021 [30]	IIIA/B	20	Gefitinib	8	2-yr Overall Survival Rate	90
Kian et. al., 2021 [31]	IIIA/B	13	Osimertinib	12	Objective response rate	100
Zhang et al., 2021 [32]	II-IIIA	33	Gefitinib	6	Objective response rate	54.5
Leonetti et al., 2021 [34]	IIIA/B	33	Alectinib	8	Major pathological response	Not reported to date.
[1]Zhou et al., 2022 [36]	IIIA	1	Pralsetinib	4	Major pathological response	74%
[1]Zhao et al., 2021 [37]	IIIB	1	Crizotinib	43	Major pathological response	60%

[1]Case report;

response (MPR), objective response rate (ORR), resection (R0) rate, disease-free survival (DFS), and overall survival (OS). pCR is defined as the absence of residual viable tumor after resection. MPR is defined as less than or equal to 10% of residual viable tumor after surgical resection. ORR is defined as an assessment of tumor burden after receiving treatment in solid tumors. R0 is defined as complete resection with negative surgical margins. DFS is defined as the period after successful treatment without any signs or symptoms of the cancer. OS is defined as the length of time from the date of diagnosis to the most recent measurement that the patient is still alive.

Past: Neoadjuvant/adjuvant chemotherapy

For many years, adjuvant chemotherapy was known as the pharmacological treatment for Non-Small Cell Lung Cancer (NSCLC) in addition to surgical resection. Initially, the beneficial effects of chemotherapy were questioned by the Adjuvant Lung Cancer Project Italy identifying no statistically significant improvement for patients compared to surgery alone for Stage I-IIIA NSCLC [4,27]. However, patient compliance in this trial with chemotherapy was low. A year later, the International Adjuvant Lung Trial determined a statistically significant advantage for patients with Stage IA-III NSCLC using adjuvant cisplatin-based chemotherapy [28].

After this, the effectiveness of chemotherapy in each stage of NSCLC was trialled. For example, the Cancer and Leukemia Group (CALGB) protocol 9633 (2004), a randomized clinical trial for Stage IB NSCLC, initially determined adjuvant chemotherapy to improve overall survival by 12%, compared to surgery alone [7]. An updated preliminary analysis (2006) of CALGB revealed that there was no longer an overall survival advantage for adjuvant chemotherapy of Stage IB [5]. Though the overall survival was no longer statistically significant, potentially due to the power of the study, there was support for improved disease-free survival and 3-year survival for patients with continued use of chemotherapy (paclitaxel and carboplatin) [5]. Similarly, the ANITA trial (2006) demonstrated extended 5-year and 7-year survival in patients with adjuvant chemotherapy (vinorelbine and cisplatin) compared to surgical resection alone [6].

The role of adjuvant chemotherapy in Stage IB NSCLC (T2N0M0) was reassessed using a larger data set of patients than the previous CALGB protocol [28]. This was a retrospective study that included patients from 2004-2011, excluding those who died within a month of the operation. Patients with adjuvant chemotherapy experienced a longer median and 5-year overall survival rate compared to those who had undergone strictly surgical resection [28]. This finding was particularly significant in patients with T2 tumors that were smaller than 4cm [28].

As a result of the several trials supporting adjuvant chemotherapy for NSCLC, the European Society of Medical Oncology (ESMO) supported its use for Stage II-III and Stage IB tumors greater than 4 cm. However, the advantage of providing adjuvant chemotherapy was uncertain compared to neoadjuvant treatment. In 2014, the NATCH trial demonstrated that there was no statistically significant difference [11].

In summary, at this point, it was believed that for stages IB, II, and III NSCLC, adjuvant chemotherapy provided the best outcomes for patients. However, there were several trials being

conducted that aimed to compare adjuvant to neoadjuvant chemotherapies.

Present: Neoadjuvant immunotherapy

As a result of the various ongoing and completed studies regarding delivery of immunotherapy, it is evident that neoadjuvant immunotherapy demonstrates a significant role in treating early-stage cancer. Forde et al. [11] composed a trial of Stage I-IIIA NSCLC patients treated with neoadjuvant nivolumab every 2 weeks. 22 patients were enrolled in the trial, with 20 patients preceding to surgery after therapy. The primary endpoint of the trial was to assess the safety and feasibility. With the neoadjuvant use of nivolumab, there were no previously unreported toxic effects of patients experiencing any adverse effects. The MPR was 45% in patients that received neoadjuvant nivolumab. Furthermore, there was a significant expansion of CD8+ T cells in the resected tumor and patient's blood after surgery that correlated with a patient's response to therapy and supported previous literature [29].

In 2019, Li et al. [12] composed a trial to assess the use of neoadjuvant sintilimab, an anti-PD-1 antibody, used for resectable sqNSCLC patients in China. 22 patients were enrolled in the study as of January 28, 2019, with all patients proceeding to surgery after two cycles of sintilimab therapy. The primary endpoint of the trial was to assess the safety and efficacy of similimab. A MPR was achieved by 45.5% (10/22) of patients. The pCR was 18.2% (4/22) in patients that received neoadjuvant sintilimab prior to surgical resection.

In 2020, Provencio et al. [13] composed an ongoing open-label, phase 2 (NADIM) trial that assessed Stage IIIA NSCLC patients being treated with neoadjuvant nivolumab, carboplatin, and paclitaxel. 46 patients were enrolled in the study, with 41 patients proceeding to surgery after three cycles of therapy. The primary endpoint was progression-free survival at 24 months which was assessed in a modified intention-to-treat population. At 24 months, the progression-free survival was 77.1%. An MPR was achieved by 83% (34/41; 95% CI 68-93%) with 63% (26/41; 95% CI 62-91%) patients demonstrating a pCR.

In 2020, Shu et al. [15] composed an open-label, phase 2 trial that assessed Stage IB-IIIA NSCLC patients being treated with neoadjuvant atezolizumab, carboplatin, and nab-paclitaxel. 30 patients were enrolled in the study, with 26 patients that proceeded with surgery after four cycles of therapy. The primary endpoint of the trial was an MPR. The MPR, reported as an intention-to-treat-analysis of all 30 patients, was 57% (17/30; 95% CI 37-75%).

In 2021, Lee et al. [16] composed the phase 2 Lung Cancer Mutation Consortium 3 study that assessed Stage IB-IIIB NSCLC patients being treated with neoadjuvant atezolizumab. 181 patients were enrolled in the study, with 152 patients that proceeded with surgery after two cycles of atezolizumab therapy. The primary endpoint of the trial was an MPR. The MPR, reported in patients without EGFR/ALK mutations that proceeded with surgery, was 20% (30/147, 95% CI: 14%-28%). A pCR was reported in 7% (10/147; 95% CI: 3-12%) of patients that received neoadjuvant atezolizumab prior to surgical resection.

In 2021, Cascone et al. [17] composed the phase 2 randomized NEOSTAR trial that assessed Stage I-IIIA NSCLC patients being treated with neoadjuvant nivolumab and ipilimumab or nivolumab alone. 44 patients were enrolled in the study, with 37 patients that proceeded with surgery after three cycles of therapy. The primary endpoint of the trial was an MPR. The MPR was achieved by 50% in the nivolumab and ipilimumab arm versus 24% in the nivolumab-alone arm. There was also a larger pCR of 38% in the nivolumab and ipilimumab arm versus 10% in the nivolumab arm.

In 2021, Forde et al. [18] composed the phase 3 CheckMate 816 trial which assessed Stage IB-IIIA NSCLC patients being treated with nivolumab and chemotherapy or chemotherapy alone. To be included, patients had to have no known history of EGFR or ALK alterations. Overall, there were 358 patients enrolled in this trial with a total of 284 patients (149 in nivolumab and chemotherapy vs. 135 in chemotherapy alone) proceeding to surgery after three cycles of therapy. The primary endpoint of the trial was a pCR. The pCR was measured in the nivolumab and chemotherapy arm as 24%, compared to 2.2% in the chemotherapy alone arm (Odds ratio 13.94 [99% CI 3.49-55.75]; $P < 0.0001$). The combination of nivolumab-and chemotherapy also improved MPR rates compared to chemotherapy in the ITT (36.9% vs 8.9%, respectively) [18]. From these findings, it was concluded that nivolumab and chemotherapy led to more significant pCR than chemotherapy alone.

Future: Neoadjuvant targeted therapy

With the well-established data surrounding treatments of NSCLC, the potential for a better treatment was unknown. However, several of these cancers were determined to create specific gene mutations that allowed for the development of resistance to treatments, increased disease severity, and other complications. From this, the investigation of targeted immunotherapy for specific gene mutations began. The pivotal role of the tyrosine kinase pathway has been well-established for NSCLC. As a result, several tyrosine kinase inhibitors (TKIs) were and are being created to combat specific mutations in the tyrosine kinase pathway.

Xiong et al. [29] explored the safety and efficacy of erlotinib as a neoadjuvant treatment in Stage IIIA-N2 NSCLC with an activating EGFR mutation. 19 patients were recruited for the 8-week study, with daily intake of erlotinib. The primary endpoint of the study was the radical resection rate which was 68.4%.

Using gefitinib (250mg), Fu et al. [21] explored its neoadjuvant usage with radiotherapy in Stage IIIA NSCLC patients that were unable to undergo surgery or chemoradiotherapy. This was a phase II open-label clinical trial. 29 patients were recruited for the study, with 28 patients included in the analysis, that took gefitinib daily. The primary endpoint was the objective response rate (ORR). The ORR was 75%.

In support of the targeted therapies, Lv et al. [20] explored the usage of neoadjuvant targeted therapies (using TKIs) compared to using chemotherapy prior to surgery retrospectively in Stage I-IIIA NSCLC patients. The TKIs included were afatinib, erlotinib, gefitinib, icotinib, and osimertinib. Among patients harboring an EGFR mutation, the objective response rate was greater in the patients receiving TKIs (55.8%) compared to chemotherapy alone (32.6%). Similarly, Bao et al. [23] assessed the use

of afatinib, erlotinib, gefitinib, and icotinib in EGFR-mutated patients receiving neoadjuvant EGFR-TKI treatment for Stage IB-IIIC NSCLC prior to surgery. The primary endpoint of ORR was 47.6%.

The use of gefitinib (250mg) was further explored by Hotta et al. [30] in a phase II study of unresectable, EGFR-mutant, stage III (A and B) NSCLC. 20 patients were enrolled in the study, receiving gefitinib for eight weeks, followed by standard chemoradiotherapy. The primary endpoint of the 2-year overall survival rate was hypothesized to be a minimum of 60% and determined to be 90% (90% CI: 71.4%-96.8%). This was the first study to demonstrate the safety and efficacy of an EGFR-targeted TKI followed by standard chemoradiotherapy in an EGFR-mutant, stage III NSCLC. Further studies were conducted in Stage III NSCLC patients using TKIs to confirm these unique findings.

Kian et al. [31] is assessing the use of daily osimertinib (80mg) in a phase II open-label study of EGFR-mutant Stage IIIA/B NSCLC over 12 weeks. 13 people are being assessed in this study, with preliminary analyses of 9 patients already performed. From the preliminary analysis of these 9 patients, the primary endpoint of the objective response rate was assessed and determined to be 100% with two patients experiencing a complete response and seven experiencing a partial response to therapy. Osimertinib's usage led to a significant reduction of the radiation field, preserving lung tissue toxicity from radiation.

In another phase II study, Zhang et al. [32] assessed the use of daily gefitinib (250mg) in Stage II-IIIA NSCLC patients. 33 patients were included in the trial and received treatment for 6 weeks. The primary endpoint of determining the ORR was determined to be 54.5%. The median disease-free survival was 33.5 months among patients, with no reported grade 3 or grade 4 adverse events.

With the beneficial impact of TKIs throughout these clinical trials for treatment-resistant NSCLC, the neoADAURA trial is set to explore the usage of osimertinib as a first-line treatment in EGFR-mutated NSCLC patients.

With the success of TKIs, especially if demonstrated to be advantageous as a primary treatment for NSCLC EGFR-mutated patients, its use will have been shown as an adjuvant or neoadjuvant treatment, whether the patient has a metastatic or non-metastatic disease. Based on these findings, several other trials are currently studying more rare mutations, such as ALK rearrangements using the same TKIs, such as crizotinib and alectinib. Other rare mutations that are being explored with mutation-specific TKIs include RET and ROS mutations.

Zhang et al. [33] assessed the use of crizotinib in Stage III (A and B) ALK-positive NSCLC patients. 11 patients were included in the trial, receiving crizotinib for 4-17 weeks. As a result of the trial, 91.0% of participants achieved R0 (complete resection) and 18.2% achieved a pCR. Apart from one participant, tumor shrinkage after therapy was reported to range from 31.4-100%. Based on the successful treatment of a patient with Stage III ALK-positive NSCLC, Leonetti et al. [34] composed the ongoing ALNEO trial.

The ALNEO trial (NCT05015010) [35] is an open-label, phase 2 trial that assesses patients with Stage III NSCLC being treated with alectinib. 33 patients have been enrolled in the trial that is composed of two chemotherapy cycles, totalling 8 weeks prior to surgery. After surgery, patients will receive 96 weeks of adjuvant alectinib therapy. The primary endpoint of the trial is an MPR.

Another mutation that is being explored is a RET mutation in NSCLC patients that have been treated with pralsetinib. Zhou et al. [36] reported a patient with resectable Stage IIIA NSCLC with a RET mutation (KIF5B-RET fusion). The patient was treated with neoadjuvant pralsetinib for 4 weeks, showing a 74% response rate post-operatively.

In exploring the rare ROS mutation, Zhao et al. [37] reported a patient with resectable Stage IIIB NSCLC containing a ROS1 mutation (CCDC6-ROS1 rearrangement. The patient was treated with crizotinib for 43 weeks, showing a 60% pathological response and tumor shrinkage.

Due to the rarity of these mutations (ALK, RET, ROS), it is difficult to attain enough trial participants for evidence-based conclusions to be drawn. We suggest the usage of EGFR-TKIs for these patients, regardless of the specific rare mutation, as EGFR-TKIs has demonstrated efficacy in metastatic diseases that possess several levels of mutations in even the most severe metastatic diseases.

Conclusion

From the initial use of adjuvant chemotherapy with surgical resection, the use of drug therapies has significantly evolved. With the current use of neoadjuvant therapies for treating NSCLC, the need for more targeted mutation-specific therapies has become evidently necessary. With the use of these targeted therapies, patients with neoadjuvant treatment-resistant NSCLC have demonstrated remarkable improvements in objective responses rates and overall survival. More studies are needed to assess the necessity of TKIs for rarer NSCLC mutations, rather than EGFR-TKIs as a potential empiric treatment.

References

1. C Fitzmaurice, D Abate, N Abbasi, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-Adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncology. 2019; 5: 1749–1768. https://doi.org/10.1001/jamaoncol.2019.2996.

2. RL Siegel, KD Miller, A Jemal. Cancer Statistics. 2018; (n.d.). https://doi.org/10.3322/caac.21442.

3. DS Ettinger, DE Wood, DL Aisner, et al. NCCN Guidelines Insights: Non–Small Cell Lung Cancer, Version 2.2021: Featured Updates to the NCCN Guidelines. J National Comprehensive Cancer Network. 2021; 19: 254–266. https://doi.org/10.6004/JNCCN.2021.0013.

4. GM Strauss, JEH II, MA Maddaus, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol. 2006; 9633, 7007–7007.

5. JY Douillard, R Rosell, M de Lena, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected

stage IB–IIIA non-small- cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA])- a randomised controlled trial. Lancet Oncol. 2006; 7: 719–727. https://doi.org/10.1016/S1470- 2045(06)70804-X.

6. GM Strauss, J Herndon, MA Maddaus, et al. Randomized Clinical Trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in Stage IB Non-Small Cell Lung Cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol. 2004; 9633:7019–7019. https://doi.org/10.1200/JCO.2004.22.90140.7019.

7. D Morgensztern, L Du, SN Waqar, et al. Adjuvant Chemotherapy for Patients with T2N0M0 NSCLC. J Thoracic Oncol. 2016; 11:1729–1735. https://doi.org/10.1016/J.JTHO.2016.05.022.

8. YL Wu, M Tsuboi, J He. Osimertinib in Resected EGFR -Mutated Non–Small-Cell Lung Cancer. New England J Med. 2020; 383:1711–1723.

9. E Felip, R Rosell, JA Maestre, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol : Official J American Society of Clin Oncol. 2010; 28:3138–3145. https://doi.org/10.1200/JCO.2009.27.6204.

10. J Remon, A Martinez-Marti, EC Costa. Major pathological response after preoperative chemotherapy as a surrogate marker of survival in early-stage non-small cell lung cancer: cohort of NATCH phase III trial. Annals of Oncol. 2017; 28: v454. https://doi.org/10.1093/ANNONC/MDX381.004.

11. PM Forde, JE Chaft, KN Smith. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer, New England J Med. 2018; 378: 1976–1986. https://doi.org/10.1056/nejmoa1716078.

12. N Li, J Ying, X Tao. Efficacy and safety of neoadjuvant PD-1 blockade with sintilimab in resectable squamous non-small cell lung cancer (sqNSCLC). Https://Doi.Org/10.1200/JCO.2019.37.15_suppl.8531. 37 (2019) 8531–8531.

13. M Provencio, E Nadal, A Insa, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. The Lancet Oncol. 2020; 21: 1413–1422. https://doi.org/10.1016/S1470-2045(20)30453-8.

14. J Spicer, C Wang, F Tanaka, et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). Https://Doi.Org/10.1200/JCO.2021.39.15_suppl.8503.

15. CA Shu, JF Gainor, MM Awad, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. The Lancet Oncol. 2020; 21:786–795. https://doi.org/10.1016/S1470-2045(20)30140-6.

16. J Lee, J Chaft, A Nicholas, et al. PS01.05 Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB–IIIB NSCLC: LCMC3 Trial Primary Analysis. J Thoracic Oncol. 2021; 16:S59–S61. https://doi.org/10.1016/J.JTHO.2021.01.320.

17. T Cascone, WN William, A Weissferdt, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. Nature Med. 2021; 27:3.

18. PM Forde, J Spicer, S Lu, et al. Abstract CT003: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo as neoadjuvant treatment (tx) for resectable (IB-IIIA) non-small cell lung cancer (NSCLC) in the phase 3 CheckMate 816 trial, Cancer Research. 2021; 81: CT003–CT003. https://doi.org/10.1158/1538-7445.AM2021-CT003.

19. AJ Piper-Vallillo, Lv Sequist, Z Piotrowska. Emerging treatment paradigms for EGFR-mutant lung cancers progressing on osimertinib: A review. J Clin Oncol. 2020; 38: 2926–2936. https://doi.org/10.1200/JCO.19.03123.

20. C Lv, Y Ma, Q Feng, et al. Does neoadjuvant targeted therapy provide an opportunity for resectable EGFR-mutant lung cancer: A real-world retrospective study. 2020; J Thoracic Dis. 12:5324–5335. https://doi.org/10.21037/jtd-20-1265.

21. Z Fu, X Yang, W Wang, et al. Radiotherapy combined with gefitinib for patients with locally advanced non-small cell lung cancer who are unfit for surgery or concurrent chemoradiotherapy: A phase II clinical trial, Radiation Oncol. 2020; 15. https://doi.org/10.1186/s13014-020-01596-2.

22. L Sun, YJ Guo, J Song, et al. Neoadjuvant EGFR-TKI Therapy for EGFR-Mutant NSCLC: A Systematic Review and Pooled Analysis of Five Prospective Clinical Trials. Frontiers in Oncol. 2021;10 (2021): 3021.

23. Y Bao, C Gu, H Xie, et al. Comprehensive study of neoadjuvant targeted therapy for resectable non-small cell lung cancer. Annals of Translational Med. 2021; 9: 493–493. https://doi.org/10.21037/atm-21-1134.

24. M Tsuboi, W Weder, C Escriu, et al. P03.02 Neoadjuvant Osimertinib with/without Chemotherapy vs Chemotherapy for EGFR Mutated Resectable NSCLC: NeoADAURA. J Thoracic Oncol. 2021; 16: S258. https://doi.org/10.1016/J.JTHO.2021.01.375.

25. Gv Scagliotti, R Fossati, V Torri, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer, Journal of the National Cancer Institute. 2003; 95: 1453–1461. https://doi.org/10.1093/jnci/djg059.

26. JP Pignon, H Tribodet, G v Scagliotti, et al. Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE collaborative group. J Clin Oncol. 2008; 26: 3552–3559. https://doi.org/10.1200/JCO.2007.13.9030.

27. R Arriagada, I de Radiomedic-Ina, C Santiago, et al. Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non-Small-Cell Lung Cancer The writing committee for the International Adjuvant Lung Cancer Trial (IALT). 2004. www.nejm.org.

28. J Liu, SJ Blake, MCR Yong, et al. Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease. Cancer Discovery. 2016; 1382–1399. https://doi.org/10.1158/2159-8290.CD-16-0577.

29. L Xiong, R Li, J Sun, et al. Erlotinib as Neoadjuvant Therapy in Stage IIIA (N2) EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Prospective, Single-Arm, Phase II Study. The Oncol-

ogist. 2019; 24:157. https://doi.org/10.1634/THEONCOLOGIST.2018-0120.

30. K Hotta, S Saeki, M Yamaguchi, et al. Gefitinib induction followed by chemoradiotherapy in EGFR-mutant, locally advanced non-small-cell lung cancer: LOGIK0902/OLCSG0905 phase II study. ESMO Open. 2021; 6. https://doi.org/10.1016/j.esmoop.2021.100191.
31. W Kian, LC Roisman, J Dudnik, et al. 1173P Induction osimertinib in EGFR-mutant stage IIIA/B.
32. Y Zhang, F Fu, H Hu, et al. Gefitinib as neoadjuvant therapy for resectable stage II-IIIA non–small cell lung cancer: A phase II study. J Thoracic and Cardiovasc Surg. 2021; 161: 434-442.e2. https://doi.org/10.1016/j.jtcvs.2020.02.131.
33. C Zhang, S lei Li, Q Nie, et al. Neoadjuvant Crizotinib in Resectable Locally Advanced Non-Small Cell Lung Cancer with ALK Rearrangement. J Thoracic Oncol : Official Publication of the International Association for the Study of Lung Cancer. 2019; 14: 726–731. https://doi.org/10.1016/J.JTHO.2018.10.161.
34. A Leonetti, R Minari, L Boni, et al. Phase II, Open-label, Single-arm, Multicenter Study to Assess the Activity and Safety of Alectinib as Neoadjuvant Treatment in Surgically Resectable Stage III ALK-positive NSCLC: ALNEO Trial, Clinical Lung Cancer. 2021; 22: 473–477. https://doi.org/10.1016/J.CLLC.2021.02.014.
35. Alectinib in Neo-adjuvant Treatment of Stage III NSCLC (ALNEO), (n.d.).
36. N Zhou, T Li, M Liang, et al. Use of Pralsetinib as Neoadjuvant Therapy for Non-Small Cell Lung Cancer Patient With RET Rearrangement. Frontiers in Oncol. 2022; 349. https://doi.org/10.3389/FONC.2022.848779.
37. S Zhao, S Zhu, X Lei, et al. Use of crizotinib as neoadjuvant therapy for non-small cell lung cancers patient with ROS1 rearrangement: A case report. Thoracic Cancer. 2021; 12: 2815–2818. https://doi.org/10.1111/1759-7714.14112.

To cite this article: Cooper JM, Kian W, Roisman LC, et al. Neo-Adjuvant Therapies in Lung Cancer – Past Present and Future Directions. European Journal of Respiratory Medicine. 2022; 4(2): 306-312. doi: 10.31488/EJRM.131.