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REVIEW ARTICLE

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# Advancements in non-small cell lung cancer treatment: from early to advanced stages

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## ABSTRACT

Over the past years, tremendous progress has been made in the treatment available for non-small cell lung cancer patients (NSCLC), both in the early and advanced stages of the disease. In early-stage NSCLC, perioperative immunotherapy is emerging as a promising approach. Several studies in preoperative chemoimmunotherapy showed a significant increase in the rate of complete pathologic response and prolonged event-free survival in resectable NSCLC patients. Similarly, atezolizumab and osimertinib are the standard of care in some patients after complete resection in *EGFR*-mutated or programmed cell death ligand 1 (PD-L1) high-expressing tumors. In locally advanced disease, durvalumab consolidation therapy following chemoradiotherapy improved progression-free survival (PFS) and overall survival (OS) in unresectable NSCLC while other immunotherapies in combination with chemotherapy showed promising results. In advanced NSCLC, novel immunotherapies or immunoconjugates such as trastuzumab deruxtecan are also demonstrating efficacy. Furthermore, molecularly targeted therapy targeting *KRAS*, *EGFR*, and other genetic aberrations, guided by next-generation sequencing, offers new treatment options. However, challenges remain, including patient selection, sequencing, and reimbursement. This article reviews the latest treatments for patients with NSCLC in the early and advanced stages of the disease.

**Keywords**: non-small cell lung cancer, treatment, immunotherapy, targeted therapy, immunoconjugates

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## Early-stage non-small cell lung cancer

### Perioperative immunotherapy

Currently, perioperative treatment is used for patients with stage II and III non-small cell lung cancer patients (NSCLC) after complete lung resection and consists of four cycles of postoperative chemotherapy. Chemotherapy before surgical treatment is not standard, and the complete pathologic response (pCR) rate achieved after initial systemic treatment does not exceed 10%.

In the CheckMate 816 study, whose results were published in 2022, the use of three cycles of nivolumab immunotherapy in combination with platinum-based two-drug chemotherapy in patients with stage IB to IIIA resectable NSCLC enabled an increase in the pCR rate to 24% *versus* 2% with standard chemotherapy. At the same time, event-free survival (EFS) defined as prolongation of the median time without progression or death before the next line of treatment increased to 32 months in the group of patients who received preoperative chemoimmunotherapy (from 21 months in the control group) [1]. The greatest benefit was seen in patients who had a minimum of 1% programmed cell death ligand 1 (PD-L1) expression in tumor cells from a biopsy specimen before surgery. It should be noted that 12–17% of patients originally qualified for surgery were dropped from the surgical treatment group after preoperative chemoimmunotherapy. The reasons for omission of patients from surgery are not known in most cases.

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The use of preoperative chemoimmunotherapy requires the expression of PD-L1 status at the initial diagnosis before planned surgical treatment. Given the limited burden of the disease, difficulty in collecting samples, and turnover time for biomarker evaluation, this can be a challenge in some centers. Observations from other studies that compare the use of preoperative chemoimmunotherapy with chemotherapy are similar. Currently, only the combination of nivolumab with three cycles of preoperative chemotherapy has European registration (as of April 2024) and is limited to populations with PD-L1 expression greater than 1% [2]. For postoperative treatment in stage II/III patients, the standard adjuvant treatment is four cycles of cisplatin plus vinorelbine.

The pathology report after lung tumor resection should include determination of PD-L1 expression status and, in NSCLC patients, also some tumor biomarkers (e.g. EGFR, ALK). In a group of patients with stage IB–IIIA NSCLC after complete resection followed by postoperative chemotherapy, the efficacy of atezolizumab administered for one year compared to standard observation was evaluated.

The superiority of atezolizumab over placebo in terms of disease-free survival (DFS) was confirmed in all endpoints of the IMpower 010 trial tested hierarchically. The greatest benefit of atezolizumab was observed in patients with stage II and IIIA, high PD-L1 expression (PD-L1 $\geq$ 50%) and patients with lymph node metastases. A significant reduction in the relative risk of recurrence [hazard ratio (HR) = 0.43; confidence interval (CI) 0.27–0.68] and overall risk of death (HR = 0.42; CI 0.23–0.78) was observed. To date, the median time to overall survival (OS) has not been reached. In the group of patients who received atezolizumab, almost 20% did not complete the 16 planned cycles of treatment due to adverse events [3, 4].

There are promising results from studies using immunotherapy in a perioperative setting. Study designs include administration of 3–4 preoperative cycles of chemoimmunotherapy followed by adjuvant immunotherapy for 12 months after definitive surgery. One of the first studies for this indication was the KEYNOTE 671 trial using pembrolizumab [5]. In a group of patients with resectable NSCLC, the use of neoadjuvant pembrolizumab with chemotherapy followed by surgery and postoperative immunotherapy, compared to preoperative chemotherapy and standard follow-up after surgery, improved event-free survival (EFS at two years 51% *vs.* 35%) and increased the rate of pCR (18% *vs.* 4%). Despite the lack of maturity, a significant trend toward an improved overall survival time was observed (OS after two years, 78% *vs.* 81%). It should be noted that the patients in this study did not receive postoperative chemotherapy.

Perioperative use of immunotherapy raises several questions about the optimal sequence of treatment and the need to update indications for preoperative and postoperative chemotherapy and immunotherapy. There is an unknown benefit in terms of survival after preoperative chemoimmunotherapy *versus* standalone postoperative immunotherapy administered after or instead of postoperative chemotherapy.

## Molecularly targeted therapy

In the double-blind phase III ADAURA study, 682 patients in stage IB–IIIA with epidermal growth factor receptor (EGFR) exon 19 or L858R substitution after complete resection and possible adjuvant chemotherapy were randomized to receive osimertinib or placebo for three years. The osimertinib treatment improved disease-free survival (DFS) in the stage II–IIIA population [medians — not reached (NR) *vs.* 19.6 months with placebo; HR = 0.17; 99.06% CI 0.11–0.26; p < 0.00] and the intent to treat population (medians — NR *vs*. 27.5 months with placebo; HR = 0.20; 99.12% CI 0.14–0.30; p < 0.001) [6, 7]. The benefit of osimertinib was independent of prior adjuvant chemotherapy and the stage of the disease. In the experimental arm, a lower rate of central nervous system (CNS) recurrence was observed (HR = 0.18; 95% CI 0.10–0.33) [8].

A recent OS analysis showed a sustained benefit in overall survival in stage II-IIIA, with 5-year survival rates of 85% compared to 73% in the placebo group (HR = 0.49; 95.03% CI 0.33–0.73; p < 0.001) [7]. The results of the subgroup analysis indicate that OS benefit was greater in patients with stage IIIA than in those with stage IB or II [7, 9]. The ADAURA trial is the first phase III study that showed improved OS after molecularly targeted therapy in the adjuvant setting after NSCLC resection. Other studies with osimertinib in pre- and postoperative settings are ongoing (ADAURA2, NeoADAURA trials) [10, 11].

Analyses of other third-generation tyrosine kinase inhibitors (TKIs) for adjuvant therapy are currently ongoing. The APEX trial that compares the efficacy and safety of almonertinib with adjuvant chemotherapy after surgical resection in patients with EGFR mutation is ongoing (NCT04762459) [12], as is the FORWARD trial in stage II–IIIA NSCLC resected using furmonertinib as postoperative treatment (NCT04853342) [13].

The open-label phase III ALINA trial evaluated the use of alectinib as adjuvant therapy in patients with stage IB (4 cm)–IIIA with confirmed ALK rearrangement. Alectinib was used for up to 24 months and was compared to four cycles of platinum-based postoperative chemotherapy [14]. More than three years of follow-up showed an improvement in investigator-assessed DFS

in the alectinib arm in the stage II-IIIA (median NR *vs*. 44.4 months with chemotherapy; HR = 0.24; 95% CI 0.13–0.45; p < 0.0001). A benefit was also observed in terms of a prolonged time to CNS metastasis (HR = 0.22; 95% CI 0.08–0.58) [14].

Data on adjuvant treatment directed at other molecular targets are limited. The rarity of these mutations and the need for advanced molecular testing is a challenge for large phase III clinical trials. For example, the ongoing LIBRETTO-432 trial evaluates the efficacy of selpercatinib in patients with *RET* gene fusion in stage IB–IIIA NSCLC after curative radiotherapy or radical surgery [15].

## Locally advanced disease

Currently, the standard of care for patients diagnosed with locally advanced unresectable NSCLC is chemoradiotherapy concurrent with consolidative durvalumab treatment according to the PACIFIC trial protocol [16]. Recent data from a 5-year follow-up showed median PFS of 16.9 and 5.6 months in the durvalumab and placebo groups, respectively (HR = 0.55; 95% CI 0.45–0.68). The observed 5-year PFS rates were 33.1% and 19.0% in the durvalumab group and the placebo group, respectively. Durvalumab, compared to placebo, significantly improved median OS from 29.1 to 47.5 months and the 5-year survival rate from 33.4% to 42.9% (HR = 0.72; 95% CI 0.59–0.89) [17].

In the KEYNOTE-799 trial, pembrolizumab in combination with chemotherapy was administered for one cycle and then continued in combination with concurrent chemoradiotherapy and after its completion as consolidation therapy [18]. The objective response rate (ORR) in cohort A patients diagnosed with squamous cell carcinoma was 71.4% and in cohort B patients diagnosed with non-squamous cell carcinoma 75.5%. Median PFS in cohort A was 30.6 months and the 2-year PFS rate was 55.3%, while in cohort B median PFS was not reached and the 2-year PFS rate was 60.6%. In terms of safety, the KEYNOTE-799 study showed the incidence of grade 3 or more severe pulmonary toxicity in 8.0% and 6.9% of patients in cohorts A and B, respectively [18, 19]. In contrast, in the PACIFIC study, the incidence of grade 3 and 4 pneumonia in the immunotherapy consolidation group was 4.4% and 3.8%, respectively [16].

The Gemstone-301 trial is a phase III study conducted in China. It compared sugemalimab therapy with placebo after concurrent or sequential chemoradiotherapy in stage III NSCLC patients [20]. Consolidation therapy with sugemalimab resulted in prolonged median PFS (9.0 *vs*. 5.8 months) and a 36% reduction in the risk of recurrence compared to placebo. Based on these results, sugemalimab was accepted only in China for stage III inoperable lung cancer patients after concurrent or sequential chemoradiotherapy. Recent results of the Gemstone-301 trial in patients after chemoradiotherapy showed longer median PFS after sugemalimab compared to placebo (medians 10.5 and 6.2 months; HR = 0.65, respectively). The benefit was greater in concurrent chemoradiotherapy at 15.7 and 8.3 months (HR = 0.71) than in sequential setting at 8.1 and 4.1 months (HR = 0.57) [21]. At more than two years of follow-up, median OS in the experimental groups was NR *versus* 25.9 months in the placebo arm.

The use of consolidation immunotherapy in patients with locally advanced NSCLC with molecular abnormalities is not standardized. The subgroup analysis of patients with EGFR-activating mutations in the PACIFIC trial did not show significant differences in PFS or OS in the durvalumab arm *versus* placebo (PFS — HR = 0.91; 95% CI 0.39–2.13; OS — HR = 1.02; 95% CI 0.39–2.63) [22]. In a retrospective study evaluating the role of durvalumab in patients with *EGFR* or *HER2* mutations, patients with confirmed molecular abnormalities treated with consolidation therapy had shorter PFS compared to those with wild-type genes (7.5 months *vs.* NR; p = 0.04) [23]. These findings suggest that in locally advanced NSCLC, patients with *EGFR* or *HER2* mutations are unlikely to benefit from immunotherapy. Studies evaluating the optimal management strategy in this group of patients are ongoing. The LAURA trial is a phase III study that compares osimertinib with placebo after chemoradiotherapy for *EGFR*-mutated NSCLC [24], and the NCT05170204 trial is a multicenter study that evaluates the efficacy and safety of ALK and ROS1 TKIs used in patients according to their molecular status [25].

## Advanced stage

### Immunotherapy

The following section summarizes the latest and most promising research findings, new drug combinations, and new drugs evaluated in patients with advanced NSCLC.

In the EMPOWER-Lung 1 study, which included patients with PD-L1 expression ≥ 50%, first-line therapy with cemiplimab improved median PFS (8.1 *vs.* 5.3 months; HR = 0.51; 95% CI 0.42–0.62; p < 0.0001) and OS (26.1 *vs.* 13.3 months; HR = 0.57; 95% CI 0.46–0.71; p < 0.0001) [26, 27].

In another phase III study, EMPOWER-Lung 3 recruiting patients with advanced NSCLC regardless of PD-L1 expression, cemiplimab in combination with chemotherapy was associated with significant improvements in both PFS and OS compared to chemotherapy

alone [28, 29]. The median OS rate was 21.1 months for the combination of cemiplimab and chemotherapy, compared to 12.9 months for chemotherapy alone, while the median PFS rate was 8.2 months *versus* 5.5 months [29].

POSEIDON was a phase III trial that evaluated tremelimumab (T) combined with durvalumab (D) and chemotherapy (CTH) (T + D + CTH) in the first line. A significant improvement in PFS (6.2 *vs.* 4.8 months; p = 0.0003) and OS (14 *vs.* 11.7 months; p = 0.003) compared to chemotherapy alone was observed [30, 31]. The benefit was most prominent in patients with non-squamous cell carcinoma and positive PD-L1 expression ≥ 1% [30, 31]. Updated analyses after a median follow-up of more than 5 years revealed sustained OS benefits for T + D + CTH *versus* CTH, with a hazard ratio of 0.76 and 5-year OS rates more than double (15.7% *vs.* 6.8%). The benefit of OS in the T + D + CTH subgroup compared to CTH was even more pronounced in patients with nonsquamous cell histology. Consistent with previous analyses, the addition of tremelimumab to durvalumab and chemotherapy provided OS benefits regardless of PD-L1 expression, including in patients with PD-L1 < 1% [32]. In immunotherapy treatment, the potential role of coexisting mutations (*KEAP1*/*STK11*/*KRAS*) is broadly explored.

## Immunoconjugates

Trastuzumab emtansine (T-DM1) is an example of an immunoconjugate used in NSCLC. It is a conjugate consisting of trastuzumab and the microtubule inhibitor emtansine (DM1). Trastuzumab emtansine was the first immunoconjugate assessed in advanced NSCLC with alterations in the *HER2* gene. In a phase II clinical trial involving 18 patients, 8 achieved a partial response (PR), with a median PFS rate of 5 months [33]. In another phase II trial, comparable results were achieved, with an objective response of 51% and a median PFS rate of 5 months in 49 patients with HER2 overexpression or mutation [34].

Trastuzumab deruxtecan (T-DXd) is another immunoconjugate that targets HER2. It was evaluated in the phase II DESTINY-Lung01 clinical trial, where T-DXd was used in patients with metastatic NSCLC with *HER2* mutations, who had failed previous standard treatment [35]. In NSCLC 91 patients with *HER2* mutations, the ORR was 55%, disease control rate (DCR) was 92%, median PFS was 8.2 months, and median OS was 17.8 months [35]. Drug-related adverse events of grade 3 or greater occurred in 46% of the patients; the most common was neutropenia (19%). Drug-related interstitial lung disease occurred in 26% of the patients, with 2 fatalities [35].

Patritumab deruxtecan (U3-1402) is an immunoconjugate that targets HER3. In a phase I study involving 57 patients with advanced NSCLC, who progressed after EGFR-TKI therapy (without the *T790M* mutation) and with HER3 expression, U3-1402 achieved an ORR of 39% with median PFS of 8.2 months [36]. Further studies are ongoing, including the phase II HERTHENA-Lung01 trial, evaluating patritumab deruxtecan in advanced NSCLC with *EGFR* mutations after at least two lines of therapy, including an EGFR-TKI and a platinum-based chemotherapy regimen. The ongoing phase III trial (HERTHENA-Lung02) compares patritumab deruxtecan with platinum-based chemotherapy in second-line treatment after EGFR-TKI failure [37].

Sacituzumab govitecan (IMMU-132) is a combination of the topoisomerase I inhibitor SN-38 with a human antibody against Trop-2 [38]. In a phase II trial involving NSCLC patients, sacituzumab govitecan achieved an ORR of 19%, median PFS of 4.4 months, and median OS of 7.3 months [39]. Grade 3 adverse events included neutropenia, nausea, diarrhea, fatigue, and anemia [39, 40]. The ongoing trials include the phase III EVOKE-01 trial, which evaluates sacituzumab govitecan in second-line treatment compared to docetaxel in advanced NSCLC, and the phase II EVOKE-02 trial, which evaluates sacituzumab govitecan in first-line therapy in combination with pembrolizumab or platinum-based chemotherapy [37].

Datopotamab deruxtecan (Dato-DXd) was evaluated in the phase Ib TROPION-Lung02 trial for safety and efficacy in combination with pembrolizumab, with optional platinum-based chemotherapy in advanced or metastatic NSCLC in the first or subsequent lines of treatment [41]. The preliminary results showed promising activity for this combination in first-line therapy, with an ORR of 62% in the experimental group and 50% in the control group. In the second-line groups, the ORR was 24% and 29%, respectively. This drug combination was generally well tolerated [41]. There are other ongoing studies evaluating datopotamab deruxtekan, such as TROPION-Lung01, a phase III trial that compares Dato-DXd with docetaxel in previously treated patients with or without identified genetic alterations. Another study, TROPION-Lung05, is a phase II trial that evaluates datopotamab deruxtekan for the same indication but is limited to patients with NSCLC who have confirmed alterations and have undergone targeted therapy and platinum-based chemotherapy [37].

Telisotuzumab vedotin (Teliso-V) is an antibody-drug conjugate targeting MET, bound to a cytotoxic payload that inhibits microtubule polymerization. Phase I studies demonstrated satisfactory efficacy for Teliso-V, both in monotherapy and in combination with erlotinib, in patients with advanced MET-positive NSCLC [42]. However, a phase II trial evaluating Teliso-V in advanced squamous NSCLC with positive MET expression

was terminated early due to severe adverse events [43]. A phase III trial comparing Teliso-V with docetaxel in previously treated advanced NSCLC with c-MET overexpression is ongoing [37].

These results suggest the role of immunoconjugates in the treatment of NSCLC, offering new options, especially for patients with resistance to immunotherapy or molecularly targeted drugs. The use of immunoconjugates in everyday clinical practice will require identifying the optimal patient population with potential biomarkers of response, who are likely to benefit from therapy.

### Molecularly targeted therapy

Advances in molecular diagnostics and the identification of new targets for molecularly targeted therapy have allowed the introduction of TKIs into routine clinical practice. Anti-EGFR and anti-ALK treatments have been the standard of care for patients with molecularly driven NSCLC for many years. Nowadays, many TKIs targeting multiple molecular pathways are approved around the world.

The first molecular alteration identified in patients with NSCLC was a mutation in the *KRAS* gene. However, it has recently become possible to use a TKI targeting KRAS-related pathways, such as sotorasib. This drug is registered for patients with the G12C point mutation in the *KRAS* gene for second-line treatment after failure of previous chemotherapy and/or immunotherapy. The use of sotorasib reduces the relative risk of disease progression compared to docetaxel without a significant improvement in overall survival [44]. The second drug approved for this indication is adagrasib [45]. Adagrasib approval was based on a phase I/II study without a control group, resulting in PFS of 6.5 months and OS of 12 months.

Patients with insertions in exon 20 of *EGFR* do not respond to first-, second-, or third-generation EGFR TKIs. Until recently, the only treatment option for these patients was chemotherapy. In the PAPILLON trial, the addition of amivantamab — a bispecific antibody targeting EGFR and MET — to chemotherapy significantly improved PFS from 6.7 to 11.4 months [46]. Overall survival data are not yet mature. In the group that received amivantamab with chemotherapy, treatment-related adverse events were significantly more frequent. Before administration of amivantamab, the appropriate premedication is necessary to prevent hypersensitivity reactions.

Next-generation sequencing (NGS) is crucial for modern lung cancer treatment and should be available for all patients with advanced nonsquamous NSCLC. Next-generation sequencing enables detection of dozens of molecular alterations for which molecularly targeted therapy is available, especially for low-frequency alterations. An example of such a molecular aberration is the fusion of the *NTRK1/2/3* gene, which occurs in fewer than 1% of NSCLC patients. For patients with this molecular alteration, regardless of histopathological diagnosis, treatment with larotrectinib or entrectinib is possible. Both drugs provide an objective response rate of more than 60% and a PFS rate of more than 12 months [47–49]. Other molecularly targeted pathways recommended for molecularly targeted therapy according to the European Society for Medical Oncology (ESMO) guidelines include *ROS1, HER2*, *MET, RET*, and *BRAF* gene aberrations [50]. Unfortunately, drugs registered for *HER2, MET, RET*, and *BRAF* are not reimbursed in Poland.

## Summary

Novel immunotherapies and molecularly driven therapies led to significant advances in the treatment of patients with NSCLC at different stages of the disease. Perioperative immunotherapy demonstrated an improvement in the complete pathologic response rate and event-free survival in patients with resectable NSCLC. However, challenges remain in determining the expression status of PD-L1 before surgery. Studies evaluating targeted therapies such as EGFR and ALK demonstrated significant DFS benefits in adjuvant settings, other molecularly driven studies are ongoing. In locally advanced diseases, concurrent chemoradiotherapy with consolidative immunotherapy is the standard of care. In the advanced setting, immunoconjugates such as trastuzumab deruxtecan and sacituzumab govitecan have promising outcomes in patients with specific molecular alterations. In the near future, all efforts should be made to emphasize the importance of routine next-generation molecular testing for personalized treatment selection.

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### Author contributions

A.Płużański: conception, draft manuscript preparation, correction, final manuscript approval; A.Piórek: draft manuscript preparation, correction, final manuscript approval.

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Authors declare no conflict of interest

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