Surgically Resectable NSCLC

Subjects: Medicine, General & Internal

Contributor: Ping-Chih Hsu

Early-stage NSCLC (stages I and II, and some IIIA diseases) accounts for approximately 30% of non-small cell lung cancer (NSCLC) cases, with surgery being its main treatment modality. The risk of disease recurrence and cancer-related death, however, remains high among NSCLC patients after complete surgical resection. In previous studies on the long-term follow-up of post-operative NSCLC, the results showed that the five-year survival rate was about 65% for stage IB and about 35% for stage IIIA diseases. Platinum-based chemotherapy with or without radiation therapy has been used as a neoadjuvant therapy or post-operative adjuvant therapy in NSCLC, but the improvement of survival is limited. Immune checkpoint inhibitors (ICIs) have effectively improved the 5-year survival of advanced NSCLC patients. Cancer vaccination has also been explored and used in the prevention of cancer or reducing disease recurrence in resected NSCLC.

Keywords: immunotherapy ; programmed death-ligand 1 (PD-L1) ; cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) ; immune checkpoint inhibitor ; non-small cell lung cancer (NSCLC) ; cancer vaccination ; early stage ; surgery

1. Introduction

The global incidence of lung cancer has prominently increased among the various cancers in the last three decades. Lung cancer has become the leading cause of cancer-related deaths in both males and females [1][2]. It is histologically classified as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); NSCLC accounts for 85% of cases [3][4]. Surgery remains the main treatment for early-stage NSCLC (stages I and II, and some IIIA diseases), and approximately 30% of NSCLC patients present with the surgically resectable disease at initial diagnosis [5]; however, the risk of disease recurrence and cancer-related mortality are high, even for those NSCLC patients receiving complete resection [5][6]. Previous studies focusing on the long-term follow-up of post-operative NSCLC have shown that the five-year survival rate is lower than 70% for IB and about 35% for IIIA diseases [6][7]. Platinum-based chemotherapy has been recommended as a post-operative adjuvant therapy for stages II to IIIA patients in the past 20 years [6][7]. Post-operative adjuvant chemotherapy decreases the disease recurrence rate by about 15% and the mortality rate at five years by about 5% [6][7]. Platinum-based chemotherapy, with or without radiation therapy, has been used as induction neoadjuvant therapy before surgery; however, the improvement of survival in resectable NSCLC patients is still limited [6][7]. A recent pivotal clinical study (ADAURA) showed that the third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) osimertinib significantly reduced the disease recurrence rate in stage IB to IIIA resected EGFR-mutated NSCLC patients [8]; however, the advances in neoadjuvant and post-operative adjuvant therapies for surgically resectable NSCLC have been very limited over the last three decades.

Immunotherapies are a new therapeutic modality, which has been studied and used for the treatment of advanced NSCLC in the past 10 years [9][10]; for example, anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) have been developed and widely studied in clinical trials, and have been used to treat advanced NSCLC. The clinical trials showed that immunotherapies targeting the PD-1/PD-L1 axis have a promising response (~45%) and can significantly prolong the survival of metastatic NSCLC patients [9][10]. Therefore, the application of immunotherapy in early-stage NSCLC has been explored in recent studies [11].

2. Neoadjuvant and Adjuvant Immunotherapy in Surgically Resectable NSCLC

2.1. Immune Checkpoints Inhibitors (ICIs) in Neoadjuvant Therapy

Uncompleted resection by surgery is always considered in NSCLC with locally advanced disease or mediastinal lymph node metastasis (stage II and III disease), where neoadjuvant therapies, e.g., chemotherapy, radiation therapy, or concurrent chemoradiotherapy, are suggested before surgery [12][13]. Recently, ICIs have been applied and investigated for neoadjuvant therapy in NSCLC. In a previous preclinical study, Cascone et al. established a mouse model by

inoculating NSCLC 344SQ-OVA+ cells into the flank of syngeneic mice, where the mice were divided into four groups to compare the efficacy of different neoadjuvant immunotherapies. The mice were treated with 3 doses of the neoadjuvant anti-PD-1 antibody, anti-CTLA-4 antibody, or anti-PD-1 plus anti-CTLA-4 antibodies, or observation, followed by surgical resection of primary tumors in all mice. The observational mice received post-surgery adjuvant therapies with anti-PD-1 antibody, anti-CTLA-4 antibody, or anti-PD-1 plus anti-CTLA-4 antibodies. The results of this study showed that either single-agent or combination neoadjuvant therapies contributed to significantly longer survival than all adjuvant therapies in the mouse model. In a subgroup analysis of mice receiving neoadjuvant therapies, the combination was significantly superior to a single agent in prolonging survival. In addition, the neoadjuvant combination therapy significantly reduced lung metastasis, when compared with a single agent and all treatment modalities, in the adjuvant setting (single and combination) [14]. Based on the promising results of this pre-clinical study, several clinical trials investigating neoadjuvant immunotherapy have been initiated [14][15]. A previous study has shown that neoadjuvant therapy with single nivolumab before surgery had a 45% major pathological response (MPR), acceptable toxicity, and no delay of surgery [16]. A previous report found that nivolumab plus ipilimumab therapy had the trend of more effective in current or former smokers than never smokers based on the results of the CheckMate 227 trial [17]. Another clinical study showed that neoadjuvant nivolumab plus ipilimumab in resectable NSCLC is feasible, and all the patients enrolled in the study were active and former smokers [18]. A previous meta-analysis review showed that neoadjuvant immunotherapy was more effective than neoadjuvant chemotherapy regarding the MPR and pathological complete response (PCR) in resectable NSCLC. In the same analysis, the surgical resection rate was also similar between neoadjuvant immunotherapy and neoadjuvant chemotherapy (88.7% vs. 70–90%) [19].

In a recent phase 2 clinical trial (NEOSTAR), stages I to IIIA NSCLC patients were randomized to receive neoadjuvant therapies with nivolumab alone or nivolumab plus ipilimumab, followed by surgery. In the analysis of 37 patients with surgical resection, the MPR was 24% for nivolumab alone, and 50% for nivolumab combined with ipilimumab. The NEOSTAR trial indicated that neoadjuvant therapy, with either nivolumab alone or the combination of nivolumab and ipilimumab, achieved pathological response in surgery. The results of the same trial showed that the neoadjuvant combination of nivolumab and ipilimumab produced significantly higher pathologic responses, immune infiltrations, and immunologic memory in the resected tumor than nivolumab alone [20]. Cytotoxic chemotherapy augments the immunogenicity of cancer cells by inducing antigenicity and adjuvanticity [21]. Immunogenic cell death (ICD) is associated with adaptive stress response which promotes the maturation of dendritic cells (DCs). In a lung cancer mouse model, chemotherapy promotes the ICD pathway to enhance the anti-tumor ability of anti-PD-1 and anti-CTLA4 antibodies [21][22]. In addition, chemotherapy might have off-target effects on suppressing myeloid-derived suppressor cells (MDSCs) or regulatory T (Treg) cells to stimulate anti-tumor immunity [23]. Together, these indicated that chemotherapy in combination with ICIs successfully improved the survival of metastatic NSCLC patients [24][25][26][27][28][29]. The addition of ICIs to conventional chemotherapy in neoadjuvant therapy for resectable NSCLC has been tested in two previous clinical trials. Nivolumab in combination with conventional chemotherapy as neoadjuvant therapy for resectable stage IIIA NSCLC was explored in phase 2 clinical study (NADIM), where the results of this trial showed 77.1% 24-month PFS in patients receiving tumor resection after neoadjuvant therapy [30]. Another phase 2 clinical trial investigated the efficacy of neoadjuvant atezolizumab plus chemotherapy in stage II-IIIA NSCLC. A total of thirty patients were enrolled in this phase 2 clinical trial, of which 29 finally received surgery and 17 (57%) had MPR, which was achieved with the neoadjuvant atezolizumab in combination with chemotherapy [31]. Single atezolizumab and pembrolizumab monotherapy as neoadjuvant therapy has been also tested in two previous clinical studies. Both clinical trials recruited potentially resectable stage I to III NSCLC [15][32]. Neoadjuvant single atezolizumab achieved 18% MPR in the LCMC3 clinical trial [15][32]. Ready et al. showed that neoadjuvant single pembrolizumab had 28% MPR in the other phase 2 clinical trial [20].

There are remaining some early-stage NSCLC patients who do not receive surgery because of reasons including poor cardiopulmonary reserve, extremely old age, poor performance status, and personal refusal. Therefore, radiotherapy such as stereotactic ablative radiotherapy (SABR) can be an alternative treatment for early-stage NSCLC patients who are unable to receive surgery [33][34]. Previous studies had shown that local radiation therapy can stimulate the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs). The TAAs and DAMPs promote immune cell priming and destruct immunosuppressive tumor-supporting stroma and these result in the enhancement of the anti-cancer effect of ICIs in NSCLC [22][35]. The efficacy of ICIs enhanced by radiotherapy is also called the abscopal effect [22][35], and compatible with the promising results shown in the PACIFIC trial. Using the combination of local radiation therapy and ICIs to improve local control and survival in early-stage NSCLC is warranted in future clinical trials. The results of trials using immunotherapy, with or without chemotherapy, as neoadjuvant therapy in surgically resectable NSCLC patients are summarized in **Table 1**.

Table 1. Results of clinical trials using immunotherapy with or without chemotherapy as neoadjuvant therapy for resectable NSCLC patients.

Trial [Reference]	Stage	Number of Patients Recruited	Drugs Used in Neoadjuvant Therapy	Primary Endpoint	MPR (%)
Forde et al. (NCT02259621) [16]	Stages I-IIIA	21	Nivolumab (monotherapy)	Safety and feasibility	45
NEOSTAR (NCT03158129) [20]	Stages IA-IIIA	44	Nivolumab or nivolumab + ipilimumab	MPR	24 in nivolumab group 50 in nivolumab + ipilimumab group
NADIM (NCT03081689) [30]	Stages IIIA	46	Nivolumab + carboplatin + paclitaxel	24-month PFS (77.1%)	83
Shu et al. (NCT02716038) [31]	Stages II-IIIA	30	Atezolizumab + carboplatin + nab-paclitaxel	MPR	57
LCMC3 (NCT02927301) [15][32]	Stages IB-IIIB	82	Atezolizumab (monotherapy)	MPR	18
Ready et al. (NCT02818920) [32]	Stages IB-IIIB	25	Pembrolizumab (monotherapy)	MPR	28
PRINCEPS (NCT02994576) [36]	Stages IA (>2 cm)-IIIA	30	Atezolizumab (monotherapy)	Toxicity	Not available
Gao et al. (ChiCTR-OIC-17013726) [37]	Stages IA-IIIB	40	Sintilimab (monotherapy)	MPR	40.5

Abbreviations: MPR, major pathological response; PFS, progression-free survival.

At present, several ongoing clinical trials are investigating the use of ICIs with or without chemotherapy as neoadjuvant therapy in resectable NSCLC (**Table 2**.). Several previous early-phase (phases I & II) had shown that ICIs with or without chemotherapy were feasible and effective as a neoadjuvant therapy before surgery [15][16][17][18][19][20][21][22][23][30][31][32][33][34][35][36][37][38][39][40]. Therefore, four main phase III clinical trials (KEYNOTE 617, CheckMate 816, IMpower 030, AEGEAN) are conducted and ongoing now. All four trials enrolled control groups, and explore the consolidation ICIs therapy after surgery. These four clinical trials are expected to be completed in 2024 [15][41][42][43].

Table 2. Ongoing clinical trials using immunotherapy with or without chemotherapy as neoadjuvant therapy for resectable NSCLC patients.

Trial [Reference]	Phase	Stage	Number of Patients Recruited or Target Number	Drugs Used in the Trial	Primary Endpoint
NEOMUN (NCT03197467) [38]	II	Stages II-IIIA	30	Pembrolizumab (monotherapy)	Safety and feasibility
IFCT-1601 IONESCO (NCT03030131) [39]	II	Stages IB (>4 cm)-IIIA	50	Durvalumab (monotherapy)	Complete surgical resection (R0)
ACTS-30 (NCT03694236) [40]	Ib	Resectable Stage IIIA	14	Durvalumab + chemoradiotherapy	Safety and feasibility
KEYNOTE 617 (NCT03425643) [15]	III	Stages II-IIIB	786	Chemotherapy + pembrolizumab/placebo × 4 cycles → surgery → pembrolizumab/placebo × 13 cycles	Event-free survival (EFS) and OS

Trial [Reference]	Phase	Stage	Number of Patients Recruited or Target Number	Drugs Used in the Trial	Primary Endpoint
CheckMate 816 (NCT02998528) [41]	III	Stages IB-IIIA	350	Chemotherapy + nivolumab × 3 cycles vs. chemotherapy alone × 3 cycles → surgery	EFS and pathological complete response (pCR)
IMpower 030 (NCT03456063) [42]	III	Stages II-IIIB	374	Chemotherapy + atezolizumab/placebo × 4 cycles → surgery → pembrolizumab/placebo × 16 cycles	MPR, EFS
AEGEAN (NCT03800134) [43]	III	Stages IIA-IIIB	300	Chemotherapy + durvalumab/placebo × 3 cycles → surgery → durvalumab/placebo × 12 cycles	MPR

Abbreviations: EFS, even-free survival; pCR, pathological complete response; MPR, major pathological response.

2.2. Immune Checkpoint Inhibitors (ICIs) in Post-Operation Adjuvant Therapy

Some early-stage NSCLC patients receive surgical resection without neoadjuvant therapy, and post-operation adjuvant chemotherapy is generally recommended for those with high risks of recurrence [21]. The risks of post-operation recurrence in NSCLC include lymph node metastases, the main tumor size being larger than 4 cm, and extensive local invasion [44]. The use of anti-PD-1/PD-L1 ICIs with or without chemotherapy as post-surgery adjuvant therapy in NSCLC is under investigation, and no mature study result is available to date [15][45]. There are four ongoing phase 3 clinical trials considering anti-PD-1/PD-L1 ICIs for early-stage NSCLC patients after receiving complete tumor resection (ANVIL, PEARLS, IMpower010, and BR31) [15][45][46][47]. The details of these four clinical trials are summarized in **Table 3**. The four phase 3 clinical trials are planning to recruit about 4600 NSCLC patients receiving surgery, and are expected to be completed between 2024 and 2027. Disease-free survival (DFS) is the main primary endpoint of all four trials [15][45][46][47]. The results of these phase 3 clinical trials may bring a substantial impact on the clinical practice of NSCLC patients receiving complete resection in the future. Though the design of the four ongoing trials is similar, there is little difference among the 4 ongoing trials. First, post-operative platinum-based chemotherapy before randomized to atezolizumab or best supportive care group is a required treatment for participants of the IMpower010 trial whether post-operative chemotherapy is optional for the participants of the other 3 ongoing trials. Second, the patients in the control group of IMpower010 and ANVIL trials receive the best supportive care or observation, and the patients in the control group of the other 2 ongoing trials (PEARLS and BR31) receive placebo [15][45][46][47]. Patients in the BR31 trial would have the tests EGFR mutation and ALK rearrangement for further subgroup analysis. Patients with EGFR mutation or ALK rearrangement would be excluded from the ANVIL trial. The tests of EGFR mutation and ALK rearrangement are not mandatory in PEARLS and IMpower010 trials. All the trials have the test of tumor tissue PD-L1 expressions for further subgroup analysis in the future [15][45][46][47]. The results of the four ongoing trials will provide information on ICIs with or without chemotherapy as post-operative adjuvant therapy for clinical practice.

Table 3. Ongoing clinical trials using ICIs as adjuvant therapy for post-surgery NSCLC patients.

Trial	Stage	Estimated Enrollment	Treatment Procedure	Primary Endpoint
ANVIL (NCT02595944)	Stages IB-IIIA	903	Surgery +/− chemotherapy → nivolumab vs. observation	DFS, OS
PEARLS (NCT02504372)	Stages IB-IIIA	1177	Surgery +/− chemotherapy → pembrolizumab vs. placebo	DFS
IMpower010 (NCT02486718)	Stages IB-IIIA	1280	Surgery +/− chemotherapy → atezolizumab vs. best supportive care	DFS
BR31 (NCT02273375)	Stages IB-IIIA	1360	Surgery +/− chemotherapy → durvalumab vs. placebo	DFS

Abbreviations: ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; DFS, disease-free survival; OS, overall survival.

2.3. Immune Checkpoint Inhibitors (ICIs) in Neoadjuvant Therapy or Adjuvant Therapy

According to the results of a pre-clinical study by Cascone et al., the neoadjuvant ICIs seem to contribute better survival benefits than the adjuvant setting has in the mouse model [14]. The complete clinical trials showed that ICIs with or without chemotherapy as neoadjuvant therapy achieved pathological response and contribute to complete surgical resection. However, there were remaining some NSCLC patients receiving neoadjuvant therapy who did not receive surgical resection finally because of complication or disease progression in neoadjuvant therapy [15][16][20][30][31][32][36][37]. In the main four ongoing trials investigating ICIs as adjuvant therapy for post-surgery NSCLC patients, the enrolled patients were required to have complete surgical resection (R0) [15][45][46][47]. However, some NSCLC patients have incomplete surgical resection in real-world clinical practice [48]. Post-operative adjuvant therapy such as chemotherapy and radiotherapy are suggested for incomplete resection NSCLC patients. However, the survival benefit of post-operative conventional chemotherapy and radiotherapy is limited for incomplete resection NSCLC patients, and the prognosis of these patients are not well [49]. ICIs in addition to chemotherapy or radiotherapy may provide survival benefits for incomplete resection NSCLC patients, but the 4 ongoing trials of adjuvant ICIs cannot answer this clinical query [15][45][46][47].

In currently ongoing four main phase III clinical trials (KEYNOTE 617, CheckMate 816, IMpower 030, AE-GEAN) with neoadjuvant chemotherapy plus ICIs or placebo, post-operative consolidation ICIs therapy is administrated in the treatment group patients [15][41][42][43]. These four clinical trials will provide clear evidence on the efficacy of ICIs administrated before and after surgery in early-stage and resectable NSCLC.

References

1. McIntyre, A.; Ganti, A.K. Lung cancer-A global perspective. J. Surg. Oncol. 2017, 115, 550–554.
2. Cao, M.; Chen, W. Epidemiology of lung cancer in China. Thorac. Cancer 2018, 10, 3–7.
3. Gridelli, C.; Rossi, A.; Carbone, D.P.; Guarize, J.; Karachaliou, N.; Mok, T.; Petrella, F.; Spaggiari, L.; Rosell, R. Non-small-cell lung cancer. Nat. Rev. Dis. Prim. 2015, 1, 15009.
4. Chen, Z.; Fillmore, C.M.; Hammerman, P.S.; Kim, C.F.; Wong, K.-K. Non-small-cell lung cancers: A heterogeneous set of diseases. Nat. Rev. Cancer 2014, 14, 535–546.
5. Donington, J.S.; Kim, Y.T.; Tong, B.; Moreira, A.L.; Bessich, J.; Weiss, K.D.; Colson, Y.L.; Wigle, D.; Osarogiagbon, R.U.; Zweig, J.; et al. Progress in the Management of Early-Stage Non–Small Cell Lung Cancer in 2017. J. Thorac. Oncol. 2018, 13, 767–778.
6. Kris, M.G.; Gaspar, L.E.; Chaft, J.E.; Kennedy, E.B.; Azzoli, C.G.; Ellis, P.M.; Lin, S.H.; Pass, H.; Seth, R.; Shepherd, F.A.; et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non–Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. J. Clin. Oncol. 2017, 35, 2960–2974.
7. Goldstraw, P.; Chansky, K.; Crowley, J.; Rami-Porta, R.; Asamura, H.; Eberhardt, W.E.; Nicholson, A.G.; Groome, P.; Mitchell, A.; Bolejack, V.; et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J. Thorac. Oncol. 2016, 11, 39–51.
8. Wu, Y.-L.; Tsuboi, M.; He, J.; John, T.; Grohe, C.; Majem, M.; Goldman, J.W.; Laktionov, K.; Kim, S.-W.; Kato, T.; et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. N. Engl. J. Med. 2020, 383, 1711–1723.
9. Hsu, P.-C.; Jablons, D.M.; Yang, C.-T.; You, L. Epidermal Growth Factor Receptor (EGFR) Pathway, Yes-Associated Protein (YAP) and the Regulation of Programmed Death-Ligand 1 (PD-L1) in Non-Small Cell Lung Cancer (NSCLC). Int. J. Mol. Sci. 2019, 20, 3821.
10. Vaddepally, R.K.; Kharel, P.; Pandey, R.; Garje, R.; Chandra, A.B. Review of Indications of FDA-Approved Immune Check-point Inhibitors per NCCN Guidelines with the Level of Evidence. Cancers 2020, 12, 738.
11. Broderick, S.R. Adjuvant and Neoadjuvant Immunotherapy in Non-small Cell Lung Cancer. Thorac. Surg. Clin. 2020, 30, 215–220.
12. Suh, J.W.; Park, S.Y.; Lee, C.Y.; Lee, J.G.; Kim, D.J.; Paik, H.C.; Chung, K.Y. Feasibility and surgical outcomes of video-assisted thoracoscopic pulmonary resection in patients with advanced-stage lung cancer after neoadjuvant chemoradiotherapy. Thorac. Cancer 2019, 10, 1241–1247.
13. Hsu, P.C.; Chang, J.W.; Wang, C.C.; Wu, C.T.; Lin, Y.C.; Wang, C.L.; Lin, T.Y.; Li, S.H.; Wu, Y.C.; Kuo, S.C.; et al. Oral vi-norelbine plus cisplatin with concomitant radiotherapy as induction therapy for stage III non-small cell lung cancer: Results of a single-arm prospective cohort study. Thorac Cancer. 2019, 10, 1683–1691.

14. Cascone, T.; Hamdi, H.; Zhang, F.; Poteete, A.; Li, L.; Hudgens, C.W.; Williams, L.J.; Wu, Q.; Gudikote, J.; Peng, W.; et al. Abstract 1719: Superior efficacy of neoadjuvant compared to adjuvant immune checkpoint blockade in non-small cell lung cancer. Immunology 2018, 78, 1719.
15. Uprety, D.; Mandrekar, S.J.; Wigle, D.; Roden, A.C.; Adjei, A.A. Neoadjuvant Immunotherapy for NSCLC: Current Concepts and Future Approaches. J. Thorac. Oncol. 2020, 15, 1281–1297.
16. Forde, P.M.; Chaft, J.E.; Smith, K.N.; Anagnostou, V.; Cottrell, T.R.; Hellmann, M.D.; Zahurak, M.; Yang, S.C.; Jones, D.R.; Bro derick, S.; et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N. Engl. J. Med. 2018, 378, 1976–1986.
17. Bersanelli, M.; Tiseo, M.; Banna, G.L. Nivolumab plus Ipilimumab in Non-Small-Cell Lung Cancer. N. Engl. J. Med. 2020, 382, 874–875.
18. Reuss, E.J.; Anagnostou, V.; Cottrell, T.R.; Smith, K.N.; Verde, F.; Zahurak, M.; Lanis, M.; Murray, J.C.; Chan, H.Y.; McCarthy, C.; et al. Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer. J. Immunother. Cancer 2020, 8, e001282.
19. Jia, X.-H.; Xu, H.; Geng, L.-Y.; Jiao, M.; Wang, W.-J.; Jiang, L.-L.; Guo, H. Efficacy and safety of neoadjuvant immunotherapy in resectable nonsmall cell lung cancer: A meta-analysis. Lung Cancer 2020, 147, 143–153.
20. Cascone, T.; William, W.N., Jr.; Weissferdt, A.; Leung, C.H.; Lin, H.Y.; Pataer, A.; Godoy, M.C.B.; Carter, B.W.; Federico, L.; Reuben, A.; et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: The phase 2 randomized NEOSTAR trial. Nat. Med. 2021, 27, 504–514.
21. Beatty, G.L.; Gladney, W.L. Immune Escape Mechanisms as a Guide for Cancer Immunotherapy. Clin. Cancer Res. 2015, 21, 687–692.
22. Gotwals, P.; Cameron, S.; Cipolletta, D.; Cremasco, V.; Crystal, A.; Hewes, B.; Mueller, B.; Quaratino, S.; Sabatos-Peyton, C.; Petruzzelli, S.C.A.C.B.H.S.Q.L.; et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat. Rev. Cancer 2017, 17, 286–301.
23. Galon, J.; Bruni, D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat. Rev. Drug Discov. 2019, 18, 197–218.
24. Gandhi, L.; Rodríguez-Abreu, D.; Gadgeel, S.; Esteban, E.; Felip, E.; De Angelis, F.; Domine, M.; Clingan, P.; Hochmair, M.J.; Powell, S.F.; et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N. Engl. J. Med. 2018, 378, 2078–2092.
25. Paz-Ares, L.; Luft, A.; Vicente, D.; Tafreshi, A.; Gümü¸s, M.; Mazières, J.; Hermes, B.; Çay ¸Senler, F.; Cs˝oszi, T.; Fülöp, A.; et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N. Engl. J. Med. 2018, 379, 2040–2051.
26. Paz-Ares, L.; Ciuleanu, T.-E.; Cobo, M.; Schenker, M.; Zurawski, B.; Menezes, J.; Richardet, E.; Bennouna, J.; Felip, E.; Juan-Vidal, O.; et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. Lancet Oncol. 2021, 22, 198–211.
27. Socinski, M.A.; Jotte, R.M.; Cappuzzo, F.; Orlandi, F.; Stroyakovskiy, D.; Nogami, N.; Rodríguez-Abreu, D.; Moro-Sibilot, D.; Thomas, C.A.; Barlesi, F. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N. Engl. J. Med. 2018, 378, 2288–2301.
28. Reck, M.; Mok, T.; Nishio, M.; Jotte, R.M.; Cappuzzo, F.; Orlandi, F.; Stroyakovskiy, D.; Nogami, N.; Rodríguez-Abreu, D.; Moro-Sibilot, D.; et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): Key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir. Med. 2019, 7, 387–401.
29. West, H.; McCleod, M.; Hussein, M.; Morabito, A.; Rittmeyer, A.; Conter, H.J.; Kopp, H.-G.; Daniel, D.; McCune, S.; Mekhail, T.; et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019, 20, 924–937.
30. Provencio, M.; Nadal, E.; Insa, A.; García-Campelo, M.R.; Casal-Rubio, J.; Dómine, M.; Majem, M.; Rodríguez-Abreu, D.; Martínez-Martí, A.; Carpeño, J.D.C.; et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): An open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020, 21, 1413–1422.
31. Shu, A.C.; Gainor, J.F.; Awad, M.M.; Chiuzan, C.; Grigg, C.M.; Pabani, A.; Garofano, R.F.; Stoopler, M.B.; Cheng, S.K.; White, A.; et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: An open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020, 21, 786–795.

32. Kris, M.G.; Faivre-Finn, C.; Kordbacheh, T.; Chaft, J.; Luo, J.; Tsao, A.; Swisher, S. Making Checkpoint Inhibitors Part of Treat ment of Patients with Locally Advanced Lung Cancers: The Time Is Now. Am. Soc. Clin. Oncol. Educ. Book 2020, 40, 1–12.
33. Hopstaken, J.S.; de Ruiter, J.C.; Damhuis, R.A.M.; de Langen, A.J.; van Diessen, J.N.A.; Klomp, H.M.; Klompenhouwer, E.G.; Hartemink, K.J. Stage I non-small cell lung cancer: Treatment modalities, Dutch daily practice and future perspectives. Cancer Treat. Res. Commun. 2021, 28, 100404.
34. Belluomini, L.; Fiorica, F.; Frassoldati, A. Immune Checkpoint Inhibitors and Radiotherapy in NSCLC Patients: Not Just a Fluke. Oncol. Ther. 2019, 7, 83–91.
35. Ngwa, W.; Irabor, O.C.; Schoenfeld, J.D.; Hesser, J.; Demaria, S.; Formenti, S.C. Using immunotherapy to boost the ab-scopal effect. Nat. Rev. Cancer 2018, 18, 313–322.
36. Besse, B.; Adam, J.; Cozic, N.; Chaput-Gras, N.; Planchard, D.; Mezquita, L.; Masip, J.R.; Lavaud, P.; Naltet, C.; Gazzah, A.; et al. 1215O—SC Neoadjuvant atezolizumab (A) for resectable non-small cell lung cancer (NSCLC): Results from the phase II PRINCEPS trial. Ann. Oncol. 2020, 31, 794–795.
37. Gao, S.; Li, N.; Gao, S.; Xue, Q.; Ying, J.; Wang, S.; Tao, X.; Zhao, J.; Mao, Y.; Wang, B.; et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J. Thorac. Oncol. 2020, 15, 816–826.
38. Eichhorn, F.; Klotz, L.V.; Bischoff, H.; Thomas, M.; Lasitschka, F.; Winter, H.; Hoffmann, H.; Eichhorn, M.E. Neoadjuvant anti-programmed Death-1 immunotherapy by Pembrolizumab in resectable nodal positive stage II/IIIa non-small-cell lung cancer (NSCLC): The NEOMUN trial. BMC Cancer 2019, 19, 413.
39. Wislez, M.; Mazieres, J.; Lavole, A.; Zalcman, G.; Carre, O.; Egenod, T.; Caliandro, R.; Gervais, R.; Jeannin, G.; Molinier, O.; et al. 1214O Neoadjuvant durvalumab in resectable non-small cell lung cancer (NSCLC): Preliminary results from a multicenter study (IFCT-1601 IONESCO). Ann. Oncol. 2020, 31, 794.
40. Hong, M.; Ahn, B.; Kim, H.; Lim, S.; Lee, S.; Park, S.; Lee, C.; Lee, J.; Kim, D.; Yoon, H.; et al. FP03.02 Interim Analysis of Neoadjuvant Chemoradiotherapy and Durvalumab for Potentially Resectable Stage III Non-Small Cell Lung Cancer (NSCLC). J. Thorac. Oncol. 2021, 16, 194–195.
41. Felip, E.; Brahmer, J.; Broderick, S.S.; Swanson, S.; Awad, M.; Mitsudomi, T.; Girard, N.; Kerr, K.; Spicer, J.; Cai, J.; et al. P2.16-03 CheckMate 816: A Phase 3 Trial of Neoadjuvant Nivolumab Plus Ipilimumab or Chemotherapy vs Chemotherapy in Early-Stage NSCLC. J. Thorac. Oncol. 2018, 13, 831–832, ISSN 1556-0864.
42. Peters, S.; Kim, A.; Solomon, B.; Gandara, D.; Dziadziuszko, R.; Brunelli, A.; Garassino, M.; Reck, M.; Wang, L.; To, I.; et al. IMpower030: Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy. Ann. Oncol. 2019, 30, 30.
43. Heymach, J.; Taube, J.; Mitsudomi, T.; Harpole, D.; Aperghis, M.; Trani, L.; Powell, M.; Dennis, P.; Reck, M. P1.18-02 The AEGEAN Phase 3 Trial of Neoadjuvant/Adjuvant Durvalumab in Patients with Resectable Stage II/III NSCLC. J. Thorac. Oncol. 2019, 14, 625–626.
44. Salazar, M.C.; Rosen, J.E.; Wang, Z.; Arnold, B.N.; Thomas, D.C.; Herbst, R.S.; Kim, A.W.; Detterbeck, F.C.; Blasberg, J.D.; Boffa, D.J. Association of Delayed Adjuvant Chemotherapy with Survival After Lung Cancer Surgery. JAMA Oncol. 2017, 3, 610–619.
45. Bai, R.; Li, L.; Chen, X.; Chen, N.; Song, W.; Cui, J. Neoadjuvant and Adjuvant Immunotherapy: Opening New Horizons for Patients with Early-Stage Non-small Cell Lung Cancer. Front. Oncol. 2020, 10, 575472.
46. Battiloro, C.; Della Gravara, L.; Rocco, D.; Gridelli, C. What pharmacotherapeutics should one use for early stage non-small cell lung cancer? Expert Opin. Pharmacother. 2018, 19, 1403–1406.
47. Pirker, R.; Filipits, M. Adjuvant Therapy in Patients with Completely Resected Non–small-cell Lung Cancer: Current Status and Perspectives. Clin. Lung Cancer 2019, 20, 1–6.
48. Gagliasso, M.; Migliaretti, G.; Ardissone, F. Assessing the prognostic impact of the International Association for the Study of Lung Cancer proposed definitions of complete, uncertain, and incomplete resection in non-small cell lung cancer surgery. Lung Cancer 2017, 111, 124–130.
49. Califano, R.; Karamouzis, M.; Banerjee, S.; de Azambuja, E.; Guarneri, V.; Hutka, M.; Jordan, K.; Kamposioras, K.; Martinelli, E.; Corral, J.; et al. Use of adjuvant chemotherapy (CT) and radiotherapy (RT) in incompletely resected (R1) early stage Non-Small Cell Lung Cancer (NSCLC): A European survey conducted by the European Society for Medical Oncology (ESMO) Young Oncologists Committee. Lung Cancer 2014, 85, 74–80.