Immunotherapy or Immuno-Chemotherapy in Non-Small Cell Lung Cancer

Subjects: Surgery

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Surgical resections remain the gold standard for early stages non-small-cell carcinoma (NSCLC) and may be considered for locally advanced tumors. Medical treatment has changed drastically, especially for advanced stages, for which the development of immunotherapy and molecular targeted therapy significantly increased survival and quality of life. The addition of radical surgical resection following immunotherapy or immuno-chemotherapy is feasible and safe with low surgical-related mortality and morbidity in selected patients with initially unresectable NSCLC.

lung cancer immunotherapy thoracic surgery

1. Introduction

Lung cancer is the leading cause of cancer death worldwide. Many new treatment modalities for non-small-cell carcinoma (NSCLC) have been described in the last two decades, introducing thoracic surgery to a multimodality approach [1]. Surgical resections remain the gold standard for early stages (I-II) and are considered in a multidisciplinary approach for stage IIIA. Medical treatment has changed drastically in recent years, especially for advanced stages (IIIB-IV). For unresectable or metastatic diseases, the development of immunotherapy and molecular targeted therapy significantly increased survival and quality of life in lung cancer patients.

Early-stage NSCLC is defined as localized cancer and refers to stages I, II, and IIIA as described by the 8th edition of TNM [2]. Locally advanced tumors include those with direct invasions, such as Pancoast's tumors, chest wall infiltrating neoplasia, and tumors with invasion of the main bronchus, the carina, or the pulmonary artery, which require extended pulmonary resections and complex reconstructions of the chest wall, airways, or vessels [3][4].

However, locally advanced tumors also include those with a mediastinal lymph node involvement defining a very heterogeneous group of patients (stage IIIA-IIIB). For locally advanced tumors, surgery may be considered. However, optimal therapeutic management requires an interdisciplinary approach in order to evaluate the extension of the disease at the diagnosis, the patient's comorbidities and the performance status before the operation, surgical operability, and a systemic induction treatment (also referred to as neo-adjuvant treatment) when indicated for the disease stage, including its potentially toxic effects. In this case, to improve long-term outcomes, the treatment could include platinum-based chemotherapy and, in selected cases, a specific radiotherapy program to reduce tumor size and lymph node involvement before complete resection. Several

studies compared survival and outcomes between definitive chemo-radiotherapy and surgery after induction treatment (chemotherapy or chemo-radiotherapy) [5].

Chemotherapy drugs, especially platinum-based compounds, are associated with side effects [6]. In this view, numerous molecular mutations in cancer biology have been searched and identified in NSCLC patients to develop new therapeutic strategies with lesser adverse reactions and better oncological outcomes in recent years. Specific molecular mutations may classify new therapies as tyrosine kinase inhibitors (target therapy) or immune checkpoint inhibitors (immunotherapy).

Regarding tyrosine kinase inhibitors (TKI), the most commonly identified targets in the adenocarcinoma setting are activating gene K-RAS and EGFR [7], re-arranged genes ALK and ROS-1 [8][9], and many others. Though molecularly targeted therapies in the neo-adjuvant setting are associated with a decrease in the risk of recurrence and an increase in the mediastinal downstaging rate, they are not associated with a complete pathological response [10].

In the last decade, different retrospective studies have shown significant outcome changes in previously unresectable diseases treated with tyrosine kinase inhibitors followed by lung resections for residual disease when feasible [11][12]. Based on these promising results, the latest National Association of Medical Oncology guidelines confirmed that all patients with non-squamous histology or mixed and young non-smoker patients with squamous histology should be tested for ALK and EGFR [13][14].

Erlotinib safety, tolerability, and pathological responses were evaluated in patients with EGFR-mutated NSCLC in a phase II study which showed encouraging results [15]. A reasonable response rate was found on using Lorlatinib and Crizotinib as neoadjuvant therapy in a significant phase III trial in patients with advanced rearranged-ALK NSCLC [16].

Regarding the role of the immune checkpoint inhibitors, Durvalumab has been established in the PACIFIC trial as the standard of care for stage III unresectable NSCLC patients as consolidation therapy after concurrent chemoradiation [17]. This role has been questioned in patients affected by EGFR-mutated NSCLC after definitive chemo-radiotherapy [18].

2. Neoadjuvant Immunotherapy or Immuno-Chemotherapy in Resectable NSCLC

Administering immune checkpoint inhibitors alone or in combination with chemotherapy and followed by surgical resections can benefit patients in terms of OS and DFS. Despite surgical resection being the standard of care for early-stage NSCLC, micrometastases, and isolated tumor cells are very challenging to detect by current technologies. Immune checkpoint inhibitors with or without chemotherapy combined with surgery can lower the probability of recurrence eradicating the micrometastases (**Table 1** and **Table 2**).

Table 1. Clinical Trials: Neoadjuvant immunotherapy in resectable NSCLC.

Neoadjuvant Immunotherapy								
Trial/Study Name	Phase	Patient N	Neoadjuvant Therapy	Patient Population	Outcomes	Safety	MPR	PCR
NEOSTAR [19]	II	88	Nivolumab, Nivolumab ± Ipilimumab	IA-IIIA	Median OS and RFS not reached at 22.2 months	NR	22% vs. 38%	9% vs. 29%
LCMC3 [20]	II	181	Atezolizumab	IB-IIIB (resectable)	NR	NR	20%	7%
Gao et al. [21]	Ib	40	Sintilimab	IA-IIIB	R0 in 37/40	12.5% TRAEs grade 3–5	40.50%	16.20%
NEOMUN [22]	II	15	Pembrolizumab	II-IIIA	NR	33% TRAEs	13%	13%
PRINCEPS [23]	II	30	Atezolizumab	IA-IIIA	R0 in 29/30	3.3% TRAEs	14%	0%
IONESCO [24]	II	50	Durvalumab	IB (≥4 cm)-IIIA	R0 in 45/50	9% of death in 90 days	18.60%	7%
Tong et al. [25]	II	30	Pembrolizumab	IB-IIIA	R0 in 22/25	4% grade 3 TRAEs	28%	0%

Neoadjuvant Immunotherapy								
Trial/Study Name	Phase	Patient N	Neoadjuvant Therapy	Patient Population	Outcomes	Safety	MPR	PCR
Altorki et al. [26]	II	60	Durvalumab ± radiotherapy	IA-IIIA	R0 in 26/30 vs. 26/30	17% vs. 20% grade 3–4 TRAEs	6.7% vs. 26.6%	0% vs. 26.6%

MPR: Major Pathological Response, PCR: Pathological Complete Response. TRAEs: Treatment-Related Adverse Events, OS: Overall Survival, NR: Not Reported.

Table 2. Clinical Trials: Neoadjuvant Immuno-Chemotherapy in resectable NSCLC.

Neoadjuvant Immuno-Chemotherapy								
Trial/Study Name	Phase	Patient N	Neoadjuvant Therapy	Patient Population	Outcomes	Safety	MPR	PCR
NADIM [27]	II	46	Nivolumab + Carboplatin + Paclitaxel	IIIA	PFS 77%, OS 12–18-24 m: 97.8–93.5–89.9%	30% TRAEs grade 3–4	83%	71%
Shu et al. [28]	II	30	Atezolizumab + Carboplatin + nab-paclitaxel	IB-IIIA	R0 in 26/29 pts	50% TRAEs grade 3–4	57%	33%
NADIM II [29]	II	86	Paclitaxel + Carboplatin ± Nivolumab	IIIA-IIIB	Median OS 81.9% at 36 m	25% vs. 10.3% TRAEs grade 3–4	52.6% vs. 13.8%	36.8% vs. 6.9%
CheckMate 816 [30]	III	358	CT ± Nivolumab	IB-IIIA	R0 in 83% vs. 75%	11% vs. 15%	37% vs. 9%	24% vs. 2%

classification. Chest 2017, 151, 193–203.

3. Casiraghi, M.; Maisonneuve, P.; Piperno, G.; Bellini, R.; Brambilla, D.; Petrella, F.; Marinis, F.; Spaggiari, L. Salvage Surgery After Definitive Chemoradiotherapy for Non-small Cell Lung Cancer. Semin. Thorac. Cardiovasc. Surg. 2017, 29, 233–241.

4. Varela, G.; Thomas, P.A. Surgical management of advanced non-small cell lung cancer. J.

Neoadjuvant Immuno-Chemotherapy								
Trial/Study Name	Phase	Patient N	Neoadjuvant Therapy	Patient Population	Outcomes	Safety	MPR	PCR
						TRAEs grade 3–4		
KEYNOTE 671 [31]	III	NR	Pembrolizumab + CT	IIA-IIIA-IIIB (N2)	NR	NR	NR	NR
AEGEAN [32]	III	NR	CT ± Durvalumab	IIA-IIIA-IIIB (N2)	NR	NR	NR	NR
Checkmate 77T [19]	III	NR	CT ± Nivolumab	IIA-IIIB (T3N2)	NR	NR	NR	NR
IMPOWER 030 [33]	III	NR	CT ± Atezolizumab	II-IIIA-IIIB (T3N2)	NR	NR	NR	NR

MPR: Major Pathological Response, PCR: Pathological Complete Response. TRAEs: Treatment-Related Adverse Events, PFS: Progression-Free Survival, OS: Overall Survival, CT: Platinum-doublet chemotherapy, m: months, NR: Not Reported.

3. Adjuvant Immunotherapy

Chemotherapy has been the standard of care for patients with NSCLC in adjuvant therapy, improving the 5-year survival rates by only 4–5%.

Adjuvant therapy plays an essential role in preventing recurrence and eliminating micrometastases. To date, new targeted therapies have been described that showed better DFS than chemotherapy, such as Osimertinib [34], Gefitinib [35], Erlotinib [36].

Wu et al. reported in ADAURA that 90% of patients with stage II to IIIA were alive at 24 months in the Osimertinib group and only 44% in the placebo group.

16. Shaw, A.T.; Bauer, T.M.; de Marinis, F.; Felip, E.; Goto, Y.; Liu, G.; Mazieres, J.; Kim, D.-W.; Mok, T.; Polli, A.; et al. First-line Lorlatinib or Crizotinib in advanced ALK-positive lung cancer. N. Engl. J. Med. 2020, 383, 2018–2029.
17. Gray, J.E.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Antonia, S.J. Three-year overall survival with durvalumab after chemo-radiotherapy in stage III NSCLC-update from PACIFIC. J. Thorac. Oncol. 2020, 15, 288–293.
18. Arrieta, O.; Mamblotsaris, L.; Hellyer, J.A.; Amini, A.; Neal, J.W.; Padda, S.K.; McCoach, C.E.; Riess, J.W.; Cabebe, E.C.; Naidoo, J.; et al. Durvalumab for stage III EGFR-mutated NSCLC after definitive chemoradiotherapy. J. Thorac. Oncol. 2021, 16, 1038–1041.
19. Cascone, T.; Provencio, M.; Sepesi, B.; Lu, S.; Aanur, N.; Li, S.; Spicer, J. Checkmate 77T: A phase III Trial of Neoadjuvant Nivolumab (NIVO) Plus Chemotherapy (Chemo) Followed by Adjuvant Nivo in Resectable Early-Stage NSCLC. J. Clin. Oncol. 2020, 38, TPS9076.
20. Lee, J.; Chaft, J.; Nicholas, A.; Patterson, A.; Waqar, S.; Toloza, E.; Haura, E.; Raz, D.; Reckamp, K.; Merritt, R.; et al. PS01.05 Surgical and Clinical Outcomes with Neoadjuvant Atezolizumab in Resectable Stage IB–IIIB NSCLC: LCMC3 Trial Primary Analysis. J. Thorac. Oncol. 2021, 16, S59–S61.

In recent years, ICIs have become more and more utilized for unresectable locally advanced or metastatic stages with very promising results, as described in the following paragraphs. Based on these results, several new trials are studying the efficacy of ICIs also in early-stage NSCLC patients.

Most of the ongoing clinical trials in this field are evaluating the benefits of ICIs associated with chemotherapy as adjuvant treatment for resectable NSCLC (Stage IB-IIIA and resectable IIIB) (**Table 3**):

- IMpower 010: open-label phase III study with a sample size of 1280 patients from 22 countries. This trial includes EGFR mutations and ALK rearrangements. A total of 1005 patients were randomized to receive adjuvant Atezolizumab (507) or best supportive care (498). In patients with stage II-IIIA NSCLC and an expression of PD-L1 ≥ 1%, the patients who had disease progression were 35% of patients receiving Atezolizumab and 46% of patients receiving best supportive care, reducing the risk of recurrence by 34% (HR = 0.66; 95% CI: 0.50–0.88) [37]. Due to these promising results, the FDA approved Atezolizumab as adjuvant monotherapy in patients with PD-L1 positive in October 2021 [38]. At the 2022 European Lung Cancer Congress (ELCC 2022), Felip et al. presented the updated preliminary results for DFS in patients with PD-L1 ≥ 50% stage II-IIIA NSCLC, with or without EGFR mutations or ALK rearrangements. In patients with EGFR mutations or ALK rearrangements, the 3-year DFS rates were 73.8% in the Atezolizumab group compared to 48.6% in the control group. In patients without EGFR mutations or ALK rearrangements, the 3-year DFS was 75.1% in the Atezolizumab group and 50.4% in the control group [39]. Adjuvant Atezolizumab was associated with a 22% recurrence rate compared to 44%, a median recurrence of 18.1 months vs. 10.1 months, and a lower rate of distant metastasis of 9% vs. 26%. The analyses of OS were presented at the 2022 World Conference on Lung Cancer (WCLC 2022). In the PD-L1 ≥ 1% patients, the Atezolizumab group showed a 5-year OS rate of 76.8% vs. 67.5% in the control group. Furthermore, in the PD-L1 ≥ 50% of patients, the 5-year OS rates were 84.8% in the Atezolizumab group compared to 67.5% in the control group [40].
- KEYNOTE-091: phase III trial with a sample size of 1177 patients with a stage IB-IIIA. In this study, patients after adjuvant chemotherapy are randomized to receive adjuvant Pembrolizumab or placebo for one year [41]. Preliminary results showed an improved DFS of 53.6 months in the Pembrolizumab group compared to 42.0 months in the placebo group. At the ESMO Congress 2022, Peters et al. reported based on the PD-L1 status, the 3-year median DFS which was 65.9% vs. 57.6% in PD-L1 ≥ 50%, 54.6% vs. 44.8% in PD-L1 1–49% and 55.5% vs. 48.8% in PD-L1 < 1% [42].
- BR31/IFCT1401: phase III trial with a sample size of 1415 patients with a stage IB-IIIA NSCLC. After adjuvant chemotherapy, patients are randomized to receive Durvalumab or a placebo for one year. The outcome studied is DFS in patients with PD-L1 ≥ 25%, without EGFR mutations or ALK rearrangements [43].
- ANVIL, ALCHEMIST Chemo-IO, MERMAID-1, MERMAID-2, NADIM-ADJUVANT, and LungMate-008 are ongoing trials studying efficacy: the DFS and the OS of adjuvant ICIs (Nivolumab, Pembrolizumab, Durvalumab, Toripalimab) in patients with resectable NSCLC (see **Table 3** for details) [44][45][46][47][48][49].

21. 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.
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24. 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, S794.
25. Tong, B.C.; Gu, L.; Wang, X.; Wigle, D.A.; Phillips, J.D.; Harpole, D.H.; Klapper, J.A.; Sporn, T.; Ready, N.E.; D'Amico, T.A. Perioperative outcomes of pulmonary resection after neoadjuvant pembrolizumab in patients with non-small cell lung cancer. J. Thorac. Cardiovasc. Surg. 2022, 163, 427–436.
26. Altorki, N.K.; E McGraw, T.; Borczuk, A.C.; Saxena, A.; Port, J.L.; Stiles, B.M.; Lee, B.E.; Sanfilippo, N.J.; Scheff, R.J.; Pua, B.B.; et al. Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: A single-center, randomized phase 2 trial. Lancet Oncol. 2021, 22, 824–835.
27. Provencio, M.; Nadal, E.; Insa, A.; García-Campelo, M.R.; Casal-Rubio, J.; Dómine, M.; Majem, M.; Rodríguez-Abreu, D.; Martínez-Martí, A.; de Castro Carpeño, J.; 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.
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29. Provencio, M.; Serna, R.; Nadal, E.; Larriba, J.L.G.; Martínez-Martí, A.; Bernabé, R.; Bosch-Barrera, J.; Benito, C.G.; Calvo, V.; Insa, A.; et al. Progression free survival and overall survival in NADIM II study. In Proceedings of the 2022 World Conference on Lung Cancer, Vienna, Austria, 6–9 August 2022. Abstract PL03.12.
30. Spicer, J.; Wang, C.; Tanaka, F.; Saylors, G.B.; Chen, K.N.; Liberman, M.; Vokes, E.E.; Girard, N.; Lu, S.; Provencio, M.; et al. Surgical Outcomes from the Phase 3 CheckMate 816 Trial:

As described in the NCCN guidelines, the recommended duration of Atezolizumab as adjuvant therapy is one year [50]. In the previously reported ongoing trials, the adjuvant ICI treatment ranges from 6 months to 2 years. Future results will better define the efficacy and duration of adjuvant therapy, as well as the predictors of response and the combination of multiple therapies.

Table 3. Clinical Trials: Adjuvant Immunotherapy, Immuno-Chemotherapy in resectable NSCLC.

Adjuvant Immunotherapy						
Trial/Study Name	Phase	Patient N	Neoadjuvant Therapy	Patient Population	Outcomes	Safety
IMpower010 [38][39][40]	III	1280	CT ± Atezolizumab	IB-IIIA	PD-L1 ≥ 50%, EGFR+, ALK+: 3-y DFS 73.8% vs. 48.6%. PD-L1 ≥ 50%, EGFR−, ALK−: 3-y DFS 75.1% vs. 50.4%. PD-L1 ≥ 1%: 5-y OS 76.8% vs. 67.5%. PD-L1 ≥ 50%: 5-y OS 84.8% vs. 67.5%.	NR
KEYNOTE-091 [41][42]	III	1177	Pembrolizumab vs. Placebo	IB-IIIA	Median DFS 53.6 months vs. 42.0 months. PD-L1 ≥ 50%: 3-y DFS 65.9% vs. 57.6%. PD-L1 1–49%: 3-y DFS 54.6% vs. 44.8%. PD-L1 < 1%: 3-y DFS 55.5% vs. 48.8%	NR

Nivolumab (NIVO) + Platinum-Doublet Chemotherapy (Chemo) vs Chemo Alone as Neoadjuvant Treatment for Patients with Resectable Non-small Cell Lung Cancer (NSCLC). J. Clin. Oncol. 2021, 39, 8503.

31. Tsuboi, M.; Luft, A.; Ursol, G.; Kato, T.; Levchenko, E.; Eigendorff, E.; Berard, H.; Zurawski, B.; Demedts, I.; Garassino, M.C.; et al. 1235TiP Perioperative Pembrolizumab + Platinum-Based Chemotherapy for Resectable Locally Advanced Non-small Cell Lung Cancer: The Phase III

... 2023. Available online: https://www.fda.gov/drugs/resources-information-approveddrugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer (accessed on 6 February 2023).

39. Felip, E.; Altorki, N.K.; Zhou, C.; Vallieres, E.; Vynnychenko, I.O.; Akopov, A.; Martinez-Marti, A.; Chella, A.; Bondarenko, I.; Ursol, G.; et al. 80O atezolizumab (atezo) vs best supportive care

Adjuvant Immunotherapy						
Trial/Study Name	Phase	Patient N	Neoadjuvant Therapy	Patient Population	Outcomes	Safety
BR31/IFCT1401 [43]	III	1415	Durvalumab vs. Placebo	IB-IIIA	Not yet	Not yet
ANVIL [44]	III	903	Nivolumab vs. Observation	IB-IIIA	Not yet	Not yet
ALCHEMIST Chemio-IO [45]	III	1210	CT ± Nivolumab	IIA-IIIB	Not yet	Not yet
MERMAID-1 [46]	III	332	CT ± Durvalumab	II-III, MRD	Not yet	Not yet
MERMAID-2 [47]	III	284	Durvalumab vs. Placebo	II-III, MRD	Not yet	Not yet
NADIM-ADJUVANT [48]	III	210	Paclitaxel + Carboplatin ± Nivolumab	IB-IIIA	Not yet	Not yet
LungMate-008 [49]	III	341	CT ± Toripalimab	II-IIIB	Not yet	Not yet

could range from local therapies (such as radiotherapy) to systemic therapies (such as standard chemotherapy, target therapy, and immunotherapy), which may be used alone or in association with each other.

4.1. Unresectable Stage III NSCLC

The studies show no benefit for immunotherapy (Durvalumab) in dGA-NSCLC patients, except for NSCLC patients harboring KRAS mutation (**Table 4**).

Table 4. Clinical Trials: Immuno-, Immuno-Chemo-, Immuno-Chemo-Radiotherapy in unresectable NSCLC.

(Suppl. S3), S258–S259.

47. Spigel, D.; Peters, S.; Ahn, M.-J.; Tsuboi, M.; Chaft, J.; Hamole, D.; Barlesi, F.; Abbosh, C.; Mann, H.; May, R.; et al. 93TiP MERMAID-2: Phase III study of durvalumab in patients with resected, stage IB-IIIA NSCLC who become MRD+ after curative-intent therapy. J. Thorac. Oncol. 2021, 16 (Suppl. S4), S745–S746.

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Unresectable Stage III NSCLC								
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety	MPR	PCR
Van Reij et al. [51]	/	319	RT ± CT (Sequential vs. concurrent)	IIIA-IIIB	Seq: Median OS 17.4 m OS 5-y 17%, Con: Median OS 18.6 m OS 5-y 19%	NR	NR	NR
Bradley et al. [52]	III	544	Concurrent CT + High/low dose RT ± Cetuximab	IIIA-IIIB	High-dose RT Median OS 28.7 m, Standard-dose RT Median OS 20.3 m	NR	NR	NR
PACIFIC (Antonia et al.) 2017 [53]	III	713	Durvalumab vs. placebo	IIIA-IIIB	Median PFS 16.8 m vs. 5.6 m, Median time to death or distant metastasis 23.2 m vs. 14.6 m	29.9% vs. 26.1% TRAEs grade 3–4	NR	9% vs. 7%
PACIFIC (Spigel et al.) 2022 [54]	III	713	Durvalumab vs. placebo	IIIA-IIIB	Median OS 47.5 m vs. 29.1 m, Median PFS 16.9 m vs. 5.6 m	NR	NR	NR
PACIFIC-R [55]	III	1399	Durvalumab vs. placebo	IIIA-IIIB	Median PFS 21.7 m, Median OS NR	AESIs 27.7%	NR	NR

cancer. J. Clin. Oncol. 2022, 40, 3383–3393.

59. PACIFIC-9. A Global Study to Assess the Effects of Durvalumab with Oleclumab or Durvalumab with Monalizumab Following Concurrent Chemoradiation in Patients with Stage III Unresectable

Unresectable Stage III NSCLC								
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety	MPR	PCR
PACIFIC-6 [56]	II	117	Durvalumab	IIIA-IIIB	Median PFS 10.9 m, 12 m OS rate 84.1%	4% TRAEs	NR	0.80%
PACIFIC-2 [57]	III	300	Durvalumab	IIIA-IIIB	Not yet	Not yet	Not yet	Not yet
COAST [58]	II	189	Durvalumab ± Oleclumab or Monalizumab	IIIA-IIIB	Median PFS 6.3 with Durvalumab, NR Oleclumab, 15.1 m Monalizumab	TRAEs 39.4% with D, 40.7% with D + O, 27.9% with D + M	NR	3% with D, 1.7% with D + O, 4.8% with D + M
PACIFIC-9 [59]	II	/	Durvalumab ± Oleclumab or Monalizumab	IIIA-IIIB	Not yet	Not yet	Not yet	Not yet
CITYSCAPE [60]	II	135	Tiragolumab + Atezolizumab vs. Placebo	IIIA-IIIB	Median PFS 5.4 m vs. 3.6 m	TRAEs 12% vs. 3% grade 3–4–5	NR	NR
KEYNOTE 799 [61]	II	214	Pembrolizumab + cCRT + Paclitaxel + Carboplatin vs.	IIIA-IIIB	Not yet	TRAEs 64.3% vs. 51%	Not yet	Not yet

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stage III non-resectable NSCLC with driver genomic alterations. Ann. Oncol. 2021, 32, S940–S941.

Unresectable Stage III NSCLC								
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety	MPR	PCR
			Pembrolizumab + cCRT + Pemetrexed + Cisplatin			grade 3–4–5		
NICOLAS [62]	II	79	CRT ± Nivolumab	IIIA-IIIB	Median PFS 12.7 m, Median OS 38.8 m	TRAEs 9% vs. 18% grade 3–4–5	NR	NR
Checkmate 73L [63]	III	/	Nivolumab + cCRT + Nivolumab ± Ipilimumab vs. cCRT + Durvalumab	IIIA-IIIB	Not yet	Not yet	Not yet	Not yet
BTCRC-LUN16-081 [64]	II	105	cCRT + Nivolumab ± Ipilimumab	IIIA-IIIB	Not yet	TRAEs 32% vs. 44% grade 3–4	Not yet	Not yet
DUART [65]	II	150	RT ± Durvalumab	IIIA-IIIB	Not yet	Not yet	Not yet	Not yet
Mazieres et al. [66]	II	551	ICIs	IIIA-IIIB (with dGA)	Median OS 13.3 m, Median PFS 2.8 m	NR	NR	NR

concurrent Chemo-Radiotherapy, D: Durvalumab, O: Oleclumab, M: Monalizumab, m: months, ICIs: Immune-checkpoint Inhibitors, dGA: driver Genic Alteration, NR: Not Reported.

78. Cummings, A.L.; Santoso, K.M.; Goldman, J.W. KEYNOTE- 021 cohorts D and H suggest modest benefit in combining Ipilimumab with pembrolizumab in second-line or later advanced non-small

Unresectable Stage III NSCLC								
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety	MPR	PCR
Guisier et al. [67]	II	107	ICIs	IIIA-IIIB (BRAF-, HER2-,	Median OS 4.7 m,	TRAEs 10% grade	Not yet	Not yet

Metastatic NSCLC without Driver Mutations						
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety
CheckMate 017 [69]	III	272	Nivolumab vs. Docetaxel	IIIB-IV squamous NSCLC	Median PFS: 3.5 m vs. 2.8 m. Median OS 9.2 m vs. 6.0 m	Any AE: 58% vs. 86%
CheckMate 057 [70]	III	582	Nivolumab vs. Docetaxel	IIIB-IV non-squamous NSCLC	Median PFS: 2.3 m vs. 4.2 m. Median OS 12.2 m vs. 9.4 m	Any AE: 69% vs. 88%
KEYNOTE-001 [71]	I	550	Pembrolizumab every 2 or 3 weeks	Locally advanced/metastatic NSCLC	Median OS 22.3 m, 10.5 m	TRAEs 12% vs. 6% grade 3–5

Therapy. Clinical Trial Information: NCT02864251. Available online: https://clinicaltrials.gov/ct2/show/NCT02864251 (accessed on 14 January 2023).

Metastatic NSCLC without Driver Mutations						
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety
KEYNOTE-024 [72]	III	305	Pembrolizumab vs. CT	Advanced NSCLC	Median PFS 10.3 m vs. 6 m, Median OS 30 m vs. 14.2 m	Any AE: 73% vs. 90%
KEYNOTE-042 [73]	III	1274	Pembrolizumab vs. CT	Locally advanced/metastatic NSCLC (PD-L1 ≥ 50%, ≥20%, 1%)	Median PFS 7.1 m, 6.2 m, 5.4 m vs. 6.4 m, 6.6 m, 6.5 m. Median OS 20 m, 17.7 m, 16.7 m vs. 12.2 m, 13.0 m, 12.1 m	NR
Govindan R et al. [74]	III	956	Carboplatin + Paclitaxel ± Ipilimumab	IV or recurrent squamous NSCLC	Median PFS 5.6 m, 5.6 m. Median OS 13.4 m, 12.4 m	TRAEs 51% vs. 35% grade 3–4
NEPTUNE [75]	III	/	Durvalumab + Tremelimumab vs. CT	Metastatic	Not Yet	Not Yet

Metastatic NSCLC without Driver Mutations						
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety
MYSTIC [76]	III	1118	Durvalumab ± Tremelimumab vs. CT	Metastatic	Median PFS 4.3 m, 3.9 m, 5.4 m; Median OS 16.3 m, 11.9 m, 12.9 m	Any AE: 54% vs. 60% vs. 83%
POSEIDON [77]	III	/	Durvalumab + CT ± Tremelimumab followed by Durvalumab ± Tremelimumab; vs. CT	Metastatic	Not Yet	Not Yet
KEYNOTE-021 [78]	I/II	44	Pembrolizumab ± Ipilimumab	Advanced NSCLC	Median PFS 4.1 m, Median OS 10.9 m	TRAEs 29% grade 3–5
KEYNOTE-598 [79]	III	568	Pembrolizumab ± Ipilimumab	Metastatic	Median PFS 8.2 m, 8.4 m. Median OS 21.4 m, 21.9 m	TRAEs 62.4% vs. 50.2% grade 3–5
EMPOWER-lung 4 [80]	II	28	Cemiplimab (3 weeks) ± Ipilimumab or	Advanced NSCLC	PD-L1 1–50%: ORR	TRAEs 18.2%,

Metastatic NSCLC without Driver Mutations						
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety
			Cemiplimab (108 weeks)		45.5% PD-L1 <1%: ORR 36%	18.2%
Checkmate 012 [81]	I	78	Nivolumab + Ipilimumab (every 12 or 6 weeks)	Recurrent IIIB or IV	Median PFS 8.1 m, 3.9 m. Median OS NR	Any AE: 82%, 72%
Checkmate 227 [82]	III	1739	PD-L1 pos or neg: Nivolumab ± Ipilimumab vs. platinum-based CT	IV or recurrent	Median PFS: PD-L1 ≥1%: 5.1 m, 4.2 m, 5.6 m, PD-L1 <1%: 5.1 m, 5.6 m, 4.7 m; Median OS: PD-L1 ≥1%: 17.1 m, 15.7 m, 14.9 m,	Any AE: 77%, 65.5, 84%, 76%, 92%, 78%

Metastatic NSCLC without Driver Mutations						
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety
					PD-L1 <1%: 17.2 m, 15.2 m, 12.2 m.	
Checkmate 9LA [83]	III	719	Platinum-based CT ± Nivolumab + Ipilimumab	IV or recurrent	Median PFS 6.8 m, 5 m. Median OS 15.6 m, 10.9 m	Any AE: 91%, 87%
NCT02239900 [84]	I/II	35	Ipilimumab + SBRT	Advanced NSCLC	Median PFS 3.2 m, Median OS 10.2 m	TRAEs 34% grade 3
NCT03223155 [85]	I	78	Nivolumab/ipilimumab + sequential or concurrent SBRT	Metastatic	Not Yet	Not Yet

TRAEs: Treatment-Related Adverse Events, PFS: Progression-Free Survival, OS: Overall Survival, CT: Platinum-based chemotherapy, m: months, ORR: Overall Response Rate, AE: Adverse Effects, NR: Not Reported.

4.3. Metastatic NSCLC with Driver Mutations

The three clinical trials are ongoing, and the results are pending (**Table 6**).

Table 6. Clinical Trials: Immuno-, Immuno-Chemo-, Immuno-Chemo-radiotherapy in metastatic NSCLC with driver mutations.

Metastatic NSCLC with Driver Mutations						
Trial/Study Name	Phase	Patient N	Treatment Regimen	Patient Population	Outcomes	Safety
Mazieres et al. [69]	II	551	ICIs	Metastatic NSCLC EGFR+ and ALK+	Median PFS 2.1 m, 2.5 m	NR
Chalmers AW et al. [86]	Ib	14	Ipilimumab + Erlotinib/Crizotinib	Advanced NSCLC EGFR+ and ALK+	Median PFS 17.9 m, 21.4 m; Median OS > 42 m, >47 m	TRAEs 78% vs. 33% grade 3
CheckMate 722 [87]	III	367	Nivolumab + Pemetrexed/CT or Nivolumab + Ipilimumab vs. Pemetrexed + CT	Metastatic or Recurrent NSCLC	Not Yet	Not Yet
Mok et al. [88]	III	294	Nivolumab + Platinum + Pemetrexed vs. CT alone	EGFR-mutated NSCLC	Median PFS 5.6 m, 5.4 m; Median OS 19.4 m, 15.9 m	NR
NCT03256136 [89]	II	9	Nivolumab + Carboplatin + Pemetrexed or Nivolumab + Ipilimumab	EGFR+ or ALK+	Not Yet	Not Yet
NCT03091491 [90]	II	31	Nivolumab ± Ipilimumab	EGFR+	Not Yet	Not Yet

TRAEs: Treatment-Related Adverse Events, PFS: Progression-Free Survival, OS: Overall Survival, CT: Platinum-based chemotherapy, m: months, ICIs: Immune Checkpoint Inhibitors, NR: Not Reported.