

Immunotherapy through Non-Small Cell Lung Cancer

Subjects: [Immunology](#)

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The landscape of non-small cell lung cancer has changed dramatically. This is largely due to the introduction of immunotherapy, and in particular, immune checkpoint blockade inhibitors. Anti-PD-1 immunotherapy is now standard treatment for patients with non-small cell lung cancer. However, not all patients respond to immunotherapy, and few patients achieve long-term survival. Moreover, some patients experience adverse effects from the treatment.

non-small cell lung cancer

clinical trials

immune checkpoint inhibitors

immune-related adverse events

biomarkers

1. Immunotherapy for Advanced Stage Non-Small Cell Lung Cancer

In 2012, a phase I study was conducted to determine the safety and efficacy of nivolumab in patients with certain types of cancers. Surprisingly, this trial showed a response rate of 18% among patients with non-small cell lung cancer (NSCLC) and led to further clinical development and other anti-PD(L)1 agents in NSCLC [\[1\]](#). Checkmate-017 was a landmark phase III trial that examined the safety and efficiency of nivolumab versus docetaxel. The trial showed significantly improved overall survival (OS), overall response rate (ORR), and progression-free survival (PFS) with nivolumab over docetaxel in patients who had received one prior line of therapy [\[2\]](#). In March 2015, Checkmate-017 together with Checkmate-057, which had the same study design but was conducted in patients with non-squamous NSCLC [\[3\]](#), led to the approval by the FDA of nivolumab as the first ICI for the treatment of patients with advanced NSCLC after platinum-based chemotherapy. The five year outcomes of pooled data from both these trials revealed that at five years, nivolumab continued to demonstrate a survival benefit compared with docetaxel, with an OS of 13.4% versus 2.6%, and a PFS of 8.0% versus 0% [\[4\]](#). This is a significant and life-changing advance for patients with NSCLC.

The approval of nivolumab was quickly followed by the approval of subsequent ICIs (**Table 1**). In October 2016, results from the KEYNOTE-010 [\[5\]](#) and KEYNOTE-024 [\[6\]](#) trials led to the approval of the PD-1 inhibitor, pembrolizumab, for the treatment of patients with metastatic NSCLC. In KEYNOTE-024, pembrolizumab was compared with cytotoxic chemotherapy as a first-line treatment for patients with advanced NSCLC and a PD-L1 tumour percentage score of 50% or greater. Pembrolizumab was shown to have significantly longer PS and OS

and fewer adverse effects compared with platinum-based chemotherapy and so became a new standard of care for the first-line treatment of patients with 'PD-L1 high' NSCLC [6]. Following positive results from the POPLAR and OAK trials, another ICI inhibitor, atezolizumab, was approved for second-line treatment for patients with locally advanced or metastatic NSCLC [7][8]. While anti-PD-(L)1 monotherapy had demonstrated benefit in a subset of patients with pre-treated NSCLC, it was also postulated that combination immunotherapy may be a useful strategy in NSCLC.

Table 1. Immune checkpoint inhibitors approved for the treatment of NSCLC.

Name	Approval	Type of MA	Action	Usage	Reference
Nivolumab	March 2015	IgG4	PD-1	Stage III OR IV metastatic NSCLC.	[2]
Pembrolizumab	October 2016	Humanized IgG4-K isotope antibody.	PD-1	Stage IV metastatic NSCLC.	[5][6]
Atezolizumab	October 2016	IgG1	PD-L1	Stage III or IV metastatic NSCLC.	[7][8]
Durvalumab	February 2018	IgG1 k	PD-L1	Stage III NSCLC	[9]
Ipilimumab	May 2020 (in combination with nivolumab)	IgG1	CTLA-4	NSCLC	[10]
Cemiplimab	November 2022 (in combination with platinum-based chemotherapy)	IgG4	PD-L1	Stage III OR IV metastatic NSCLC	[11]
Tremelimumab	November 2022 (in combination with durvalumab and platinum-based chemotherapy)	IgG2	PD-L1	Stage III OR IV metastatic NSCLC	[12]

Ipilimumab and tremelimumab are CTLA-4 inhibitors previously used in metastatic melanoma. In a phase II trial conducted more than 10 years ago, single agent ipilimumab combined with chemotherapy demonstrated modest benefit compared with ipilimumab monotherapy in NSCLC [13]. However, the combination of ipilimumab and nivolumab had demonstrated deep and durable responses in patients with melanoma [14], and it was hoped this could be recapitulated in NSCLC. In early phase studies of this combination, it was clear that the doses used for melanoma resulted in unacceptable toxicity in patients with NSCLC. After modification of this dose to ipilimumab every 6 weeks, the Checkmate-227 explored this combination in a complex eight-arm clinical trial. Broadly, this research demonstrated a significant benefit in PFS and OS as well as durable responses in patients with both PD-L1 > 1% and PD-L1 < 1% NSCLCs, and is approved as a 'chemotherapy-free' option in the first-line treatment for patients with advanced PD-L1 > 1% NSCLC [10]. In addition, a novel regimen from the Checkmate 9LA trial incorporating two doses of platinum-doublet chemotherapy in addition to ipilimumab and nivolumab also resulted in

both PFS and OS benefits for this combination compared with chemotherapy alone, and is also an approved treatment option for first-line advanced NSCLC in all-comers for PD-L1 status [15]. This regimen is thought to potentially provide the ‘neoantigen release’ of cytotoxic chemotherapy alongside the long-term durable outcomes seen with ipilimumab and nivolumab.

While the use of ICIs has undoubtedly changed the landscape of patient care for NSCLC, there remains an urgent need to transform more patients from immunotherapy non-responders to responders. Hence, current research strategies are focused on improving the response rate of ICIs, and these efforts are mainly centred around creating effective combination regimens with chemotherapy, radiotherapy, and other anti-cancer drugs (Table 2). In 2018, the FDA approved the use of pembrolizumab in combination with chemotherapy for first-line treatment of metastatic non-squamous NSCLC, independent of PD-L1 tumour expression status. This approval was based on the results of the KEYNOTE-189 trial which demonstrated a longer OS and PFS in patients receiving pembrolizumab in addition to standard chemotherapy of pemetrexed and a platinum-based drug compared with patients receiving chemotherapy alone [16]. This combination regimen was also approved for first-line treatment in metastatic squamous NSCLC following the results of the KEYNOTE-407 trial, again independent of PD-L1 tumour expression status [17]. The positive results from the Impower150 trial led to the approval of atezolizumab with chemotherapy and bevacizumab for first-line treatment of metastatic non-squamous NSCLC [18]. Interestingly, it has been demonstrated that the combination of chemotherapy with bevacizumab induces proliferation of peripheral CD8 T cells, particularly memory and effector subsets [19], perhaps offering the rationale for combining chemotherapy and bevacizumab with ICIs. This is also now an approved option for first-line treatment of advanced NSCLC independent of PD-L1 status, based on the phase III IMPower150 trial [18].

Table 2. Selected clinical trials investigating combination strategies with approved ICIs in advanced NSCLC.

Ipilimumab						
Additional Treatment	Drug Type	NCT/EU Identifier	Trial Name	Phase	Status	Reference
Chemotherapy	Paclitaxel, Carboplatin	NCT01285609		Phase III	Completed	[20]
Other	Radiotherapy	NCT02221739		Phase I/II	Completed	[21]
	Erlotinib or Crizotinib	NCT01998126		Phase I	Completed	[22]
Cemiplimab						
Additional Treatment	Drug Type	NCT/EU Identifier	Trial Name	Phase	Status	Reference
Chemotherapy	Platinum-doublet	NCT03409614	EMPOWER-	Phase	Active, not	[11]

	chemotherapy		Lung 3	III	recruiting	
Other	Isatuximab	NCT03367819		Phase I/II	Terminated	[23]
Nivolumab						
Additional Treatment	Drug Type	NCT/EU Identifier	Trial Name	Phase	Status	Reference
Chemotherapy	Platinum-doublet chemotherapy	NCT01454102	CheckMate 012	Phase I	Completed	[24]
	Ipilimumab plus chemotherapy	NCT03215706	CheckMate 9LA	Phase III	Active, not recruiting	[25]
	Platinum-doublet chemotherapy	NCT02477826	CheckMate 227	Phase II	Active, not recruiting	[10]
	Veliparib, and platinum-doublet chemotherapy	NCT02944396		Phase I	Completed	[26]
Immune Checkpoint Inhibitors	Ipilimumab	NCT01454102	CheckMate 012	Phase I	Completed	[27]
		NCT02659059	CheckMate 568	Phase II	Completed	[28]
		NCT02785952	Lung-MAP S1400I	Phase III	Active, not recruiting	[29]
		NCT02477826	Checkmate 227	Phase III	Active, not recruiting	[10]
Vaccines	CV301	NCT02840994		Phase I	Completed	[30]
	NEO-PV-01	NCT02897765		Phase I	Completed	[31]
Durvalumab						
Additional Treatment	Drug Type	NCT/EU Identifier	Trial Name	Phase	Status	Reference
Immune Checkpoint Inhibitors	Tremelimumab	NCT02000947		Phase I	Completed	[32]
		NCT03373760		Phase	Completed	[33]

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	Tremelimumab +/- chemotherapy	NCT03057106		Phase II	Active, not recruiting	[34]
Anti-Angiogenic	Ramucirumab	NCT02572687		Phase Ia/b	Completed	[35]
Other	Gefitinib	NCT02088112		Phase I	Completed	[36]
	LY3022855	NCT02718911		Phase Ia/b	Completed	[37]
	AZD4635	NCT02740985		Phase I	Active, not recruiting	[38]
	Osimertinib	NCT02454933	CAURAL	Phase III	Active, not recruiting	[39]
Atezolizumab						
Additional Treatment	Drug Type	NCT/EU Identifier	Trial Name	Phase	Status	Reference
Chemotherapy	Carboplatin and paclitaxel or carboplatin and nab-paclitaxel	NCT02367794	iMpower131	Phase III	Completed	[40]
	Vinorelbine	NCT03801304	VinMetAtezo	Phase II	Completed	[41]
	Carboplatin and paclitaxel with bevacizumab	NCT02366143	iMpower150	Phase III	Completed	[18]
	Carboplatin and nab-paclitaxel	NCT02367781	iMpower130	Phase III	Completed	[42]
	Pemetrexed and either cisplatin or carboplatin	NCT02657434	iMpower132	Phase III	Completed	[43]
Immune Checkpoint Inhibitors	Ipilimumab	NCT02174172		Phase Ib	Completed	[44]
Other	Navoximod	NCT02471846		Phase I	Completed	[45]
Pembrolizumab						

Additional Treatment	Drug Type	NCT/EU Identifier	Trial Name	Phase	Status	Reference
Chemotherapy	Chemotherapy agents	NCT02039674	KEYNOTE-021	Phase I/II	Completed	[46]
		NCT01840579	KEYNOTE-011	Phase I	Completed	[47]
	Pemetrexed/platinum chemotherapy	NCT02578680	KEYNOTE-189	Phase III	Active, not recruiting	[48]
	Docetaxel	NCT02574598		Phase II	Completed	[49]
Immune Checkpoint Inhibitors	Ipilimumab	NCT02039674	KEYNOTE-021	Phase I/II	Completed	[46]
Anti-Angiogenic	Ramucirumab	NCT02443324		Phase I	Completed	[50]
		NCT03971474		Phase II	Active, not recruiting	[51]
	Lenvatinib	NCT02501096		Phase I/II	Completed	[52]
		NCT03006887		Phase I	Completed	[53]
Other	Pegilodecakin	NCT02009449		Phase I	Active, not recruiting	[54]
	Necitumumab	NCT02451930		Phase I	Completed	[55]
	Oral Azacitidine	NCT02546986		Phase II	Active, not recruiting	[56]
	Afatinib	NCT03157089	LUX-Lung-10	Phase II	Completed	[57]
	Eprenetapopt	NCT04383938		Phase I/II	Completed	[58]
	Niraparib	NCT04475939	JASPER	Phase II	Active, not recruiting	[59]
	Stereotactic body radiotherapy (SBRT)	NCT02608385		Phase I	Active, not recruiting	[60]

with 5-year OS. In February 2018, the FDA approved the use of durvalumab for patients with unresectable stage III NSCLC whose disease had not progressed following concurrent platinum-based chemotherapy and radiation therapy. This was the first approval of an immunotherapy agent for the treatment of earlier stage NSCLC and was based on the results of the phase III PACIFIC trial, which demonstrated prolonged PFS and OS in patients treated

with 1 year of consolidation durvalumab versus a placebo [9]. In recent years, much effort has also centred around designing effective uses of immunotherapy for the treatment of resectable NSCLC (**Table 3**).

In October 2021, the FDA approved atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II and IIIA NSCLC whose tumours have a PD-L1 expression of greater than/equal 1% of tumour cells. This approval came about following the Impower010 trial which demonstrated a DFS benefit with atezolizumab versus best supportive care after adjuvant chemotherapy [61]. This was the first phase III trial to demonstrate a benefit from immunotherapy in patients with early-stage resectable NSCLC. In 2023, the KEYNOTE-091/PEARLS trial investigated pembrolizumab for adjuvant treatment of early-stage NSCLC following resection and optional platinum-based chemotherapy for patients with stage IB-III A NSCLC. This is approved for this indication, independent of tumoural PD-L1 expression [62].

Table 3. Clinical trials investigating ICIs in resectable NSCLC.

Drug Name	Additional Drug/Treatment	NCT/EU Identifier	Status	Trial Name	Phase	Reference
Nivolumab	Ipilimumab	NCT02259621	Recruiting	NA_00092076	Phase II (neoadjuvant)	[63]
	Ipilimumab	NCT03158129	Active, not recruiting	NEOSTAR	Phase II	[64]
	Platinum based-Chemotherapy	NCT02998528	Active, not recruiting	CheckMate 816	Phase III (neoadjuvant)	[65]
	Neoadjuvant Chemotherapy	NCT03081689	Active, not recruiting	NADIM phase II trial	Phase II (neoadjuvant)	[66]
	Neoadjuvant Chemotherapy	NCT04025879	Active, not recruiting	Checkmate 77T	Phase III (neoadjuvant)	[67]
Pembrolizumab		NCT03197467	Active, not recruiting	NEOMUN	Phase II (neoadjuvant)	[68]
		NCT02504372	Active, not recruiting	KEYNOTE-091/PEARLS	Phase II (neoadjuvant)	[68]
Ipilimumab	Chemotherapy	NCT01820754	Completed	TOP1201 IPI	Phase II (neoadjuvant)	[69]
Durvalumab	Neoadjuvant chemotherapy	NCT02572843	Active, not recruiting	SAKK 16/14	Phase II (adjuvant and neoadjuvant)	[70]
		NCT03030131	Terminated	IoNESCO trial	Phase II (neoadjuvant)	[71]

Drug Name	Additional Drug/Treatment	NCT/EU Identifier	Status	Trial Name	Phase	Reference
	Chemotherapy Olecumab/ monailiziumab/ danvatirsen	NCT03800134 NCT03794544	Active, not recruiting Completed	AEGEAN Trial NEOCOAST	Phase III (adjuvant and neoadjuvant) Phase II (Neoadjuvant)	[72] [73]
Atezolizumab	Platinum-based chemotherapy	NCT02486718	Active, not recruiting	Impower010	Phase III (adjuvant)	[61]
		NCT02927301	Active, not recruiting		Phase II	[74]

NSCLC. The chemotherapy results were significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone. Similar results have also been observed in the NADIM trial, for patients with resectable stage IIIA NSCLC [72]. The trial compares the effect of nivolumab with chemotherapy against chemotherapy as a monotherapy. While the trial is still ongoing, current results show an improved overall survival in patients treated with chemo-immunotherapy compared with chemotherapy alone, with overall survival at 24 months showing 85.3% vs. 64.8%.

In March 2022, the Checkmate-816 data led to the FDA approval of neoadjuvant nivolumab and platinum-doublet chemotherapy for the treatment of early-stage resectable NSCLC. The NEOSTAR trial was also performed in the neoadjuvant setting, examining the effect of nivolumab or nivolumab and ipilimumab followed by surgery in patients with resectable NSCLC. The data from this trial indicate that neoadjuvant nivolumab and ipilimumab-based therapy enhances pathological response, tumour immune infiltrates and immunological memory [70].

For patients with resectable NSCLC, the goal of therapy is cure. In the context of a curable disease, ICIs are used to reduce the risk of relapse, but it is critical that they do not interfere with the curative portion of the treatment paradigm, that is, surgery. This is a particular challenge for patients being treated in the neoadjuvant setting (e.g., CHECKMATE-816) in which the use of neoadjuvant therapy could be associated with delays to surgery. Encouragingly, an increased risk of surgical complications has not been observed in most neoadjuvant studies involving ICIs and NSCLC. For example, in the CHECKMATE-816 study, the authors reported surgical complications of 41.6% in the nivolumab plus chemotherapy arm and 46.7% in the chemotherapy arm [75]. Encouragingly, only 3.4% of patients had delayed surgery in the nivolumab plus chemotherapy arm and 5.1% in the chemotherapy alone arm.

For patients in the adjuvant setting (e.g., PEARLS/IMPower010), different challenges emerge compared with the neoadjuvant setting [61][76]. Given that the cancer is already surgically resected, irAEs will not interfere with patients' curative procedure. However, unlike in the metastatic setting, it is researcher's expectation that the majority of these patients will be cured of their disease. In this regard, the risk of inducing a chronic or multi-organ toxicity may be associated with significant and long-term impact on patients' quality-of-life. The risks and benefits of such adjuvant therapy pose challenges in weighing the low risk of long-term toxicity versus the survival benefit of disease control. Decisions regarding the most appropriate treatment option need to be made in a collaborative manner between patients and the multidisciplinary team.

Adjuvant/neoadjuvant studies in resectable NSCLC have to date demonstrated impressive event-free/disease-free survival for patients, which researchers hope will translate to an overall survival benefit. Long-term follow-up and further studies will provide more data on the efficacy of adjuvant/neoadjuvant ICI and the risks of delays to surgical resection/long-term toxicity. Researchers eagerly await the publication of further studies in this field and long-term follow-up.

3. Future Outlook for the Use of Immunotherapy in Non-Small Cell Lung Cancer

ICIs have established efficacy in advanced and early-stage NSCLC, and it is unlikely that PD-1/PD-L1 monotherapy will improve on the already established benefit for patients. As mentioned previously in this research, recent interest lies in combining ICIs with novel combination strategies which could include radiation, novel ICIs or other novel systemic therapies. For example, neoadjuvant durvalumab was investigated with or without sub-ablative stereotactic radiotherapy (SBRT) in patients with resectable NSCLC [77]. In this research patients received two cycles of neoadjuvant durvalumab +/- 3 fractions of SBRT (8 Gy * 3), followed by surgery. In the NEOCOAST study, the authors investigated neoadjuvant durvalumab +/- novel agents for resectable stage I-IIIa NSCLC [78]. These novel agents included the anti-CD73 agent oleclumab, the anti-NKG2A monalizumab or the anti-STAT3 antisense oligonucleotide danavatirsen. Finally, the inhibition of novel checkpoints as a monotherapy or in combination with pre-existing ICIs is an emerging strategy in this field. LAG-3 suppresses T cell activation and cytokine secretion [79]. Inhibitors of LAG-3 have already reached phase II and phase III clinical trials and relatlimab has been approved in combination with nivolumab for advanced melanoma [80]. In NSCLC, the RELATIVITY study has commenced accrual and is exploring the combination of relatlimab and nivolumab and chemotherapy in the advanced setting [81].

Another critical area of research in this field is utilising 'liquid biopsy' assays to identify patients not responding to therapy at an early stage in their treatment paradigm so that therapy plans can be adapted thereafter. 'Liquid Biopsy' generally refers to the use of blood based (but can use other body fluids, e.g., breath) biomarkers to identify tumour-based signatures which could include cfDNA, ctDNA, circulating tumour cells (CTCs) and others [82]. In an investigation of 67 patients with stage IV NSCLC, a ctDNA 'molecular response' in plasma 9 weeks post starting ICI was associated with a durable clinical benefit (defined as an ongoing response at 6 months post IO, 3.5% vs. 49.4%, $p < 0.001$). This research demonstrates the potential for ctDNA dynamics to identify responders to therapy.

In summary, it is likely that the future of ICIs in NSCLC will involve their combination with other systemic/local therapy but advances in therapeutics will be combined with novel diagnostics/biomarkers (e.g., liquid biopsy) to improve patient selection for therapy.

References

1. Topalian, S.L.; Hodi, F.S.; Brahmer, J.R.; Gettinger, S.N.; Smith, D.C.; McDermott, D.F.; Powderly, J.D.; Carvajal, R.D.; Sosman, J.A.; Atkins, M.B.; et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* 2012, 366, 2443–2454.
2. Brahmer, J.; Reckamp, K.L.; Baas, P.; Crinò, L.; Eberhardt, W.E.E.; Poddubskaya, E.; Antonia, S.; Pluzanski, A.; Vokes, E.E.; Holgado, E.; et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* 2015, 373, 123–135.
3. Borghaei, H.; Paz-Ares, L.; Horn, L.; Spigel, D.R.; Steins, M.; Ready, N.E.; Chow, L.Q.; Vokes, E.E.; Felip, E.; Holgado, E. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *New Engl. J. Med.* 2015, 373, 1627–1639.
4. Borghaei, H.; Gettinger, S.; Vokes, E.E.; Chow, L.Q.; Burgio, M.A.; de Castro Carpeno, J.; Pluzanski, A.; Arrieta, O.; Frontera, O.A.; Chiari, R. Five-year outcomes from the randomized, phase III trials checkmate 017 and 057: Nivolumab versus docetaxel in previously treated non–small-cell lung cancer. *J. Clin. Oncol.* 2021, 39, 723.
5. Herbst, R.S.; Baas, P.; Kim, D.-W.; Felip, E.; Pérez-Gracia, J.L.; Han, J.-Y.; Molina, J.; Kim, J.-H.; Arvis, C.D.; Ahn, M.-J.; et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet* 2016, 387, 1540–1550.
6. Reck, M.; Rodríguez-Abreu, D.; Robinson, A.G.; Hui, R.; Csőszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N. Engl. J. Med.* 2016, 375, 1823–1833.
7. Fehrenbacher, L.; Spira, A.; Ballinger, M.; Kowanetz, M.; Vansteenkiste, J.; Mazieres, J.; Park, K.; Smith, D.; Artal-Cortes, A.; Lewanski, C. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016, 387, 1837–1846.
8. Rittmeyer, A.; Barlesi, F.; Waterkamp, D.; Park, K.; Ciardiello, F.; Von Pawel, J.; Gadgeel, S.M.; Hida, T.; Kowalski, D.M.; Dols, M.C.; et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017, 389, 255–265.
9. Antonia, S.J.; Villegas, A.; Daniel, D.; Vicente, D.; Murakami, S.; Hui, R.; Yokoi, T.; Chiappori, A.; Lee, K.H.; de Wit, M.; et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *N. Engl. J. Med.* 2017, 377, 1919–1929.
10. Hellmann, M.D.; Paz-Ares, L.; Bernabe Caro, R.; Zurawski, B.; Kim, S.-W.; Carcereny Costa, E.; Park, K.; Alexandru, A.; Lupinacci, L.; de la Mora Jimenez, E.; et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* 2019, 381, 2020–2031.

11. Gogishvili, M.; Melkadze, T.; Makharadze, T.; Giorgadze, D.; Dvorkin, M.; Penkov, K.; Laktionov, K.; Nemsadze, G.; Nechaeva, M.; Rozhkova, I.; et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: A randomized, controlled, double-blind phase 3 trial. *Nat. Med.* 2022, 28, 2374–2380.
12. Johnson, M.L.; Cho, B.C.; Luft, A.; Alatorre-Alexander, J.; Geater, S.L.; Laktionov, K.; Kim, S.W.; Ursol, G.; Hussein, M.; Lim, F.L.; et al. Durvalumab with or without Tremelimumab in Combination with Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J. Clin. Oncol.* 2023, 41, 1213–1227.
13. Lynch, T.J.; Bondarenko, I.; Luft, A.; Serwatowski, P.; Barlesi, F.; Chacko, R.; Sebastian, M.; Neal, J.; Lu, H.; Cuillerot, J.M.; et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study. *J. Clin. Oncol.* 2012, 30, 2046–2054.
14. Callahan, M.K.; Kluger, H.; Postow, M.A.; Segal, N.H.; Lesokhin, A.; Atkins, M.B.; Kirkwood, J.M.; Krishnan, S.; Bhole, R.; Horak, C.; et al. Nivolumab Plus Ipilimumab in Patients with Advanced Melanoma: Updated Survival, Response, and Safety Data in a Phase I Dose-Escalation Study. *J. Clin. Oncol.* 2018, 36, 391–398.
15. Reck, M.; 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 with two cycles of chemotherapy versus chemotherapy alone (four cycles) in metastatic non-small cell lung cancer: CheckMate 9LA 2-year patient-reported outcomes. *Eur. J. Cancer* 2023, 183, 174–187.
16. Gandhi, L.; Rodríguez-Abreu, D.; Gadgeel, S.; Esteban, E.; Felip, E.; De Angelis, F.; Domine, M.; Clingan, P.; Hochmair, M.J.; Powell, S.F. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N. Engl. J. Med.* 2018, 378, 2078–2092.
17. Paz-Ares, L.; Luft, A.; Vicente, D.; Tafreshi, A.; Gümüş, M.; Mazières, J.; Hermes, B.; Çay Şenler, F.; Csőszi, T.; Fülöp, A. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N. Engl. J. Med.* 2018, 379, 2040–2051.
18. 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.
19. de Goeje, P.L.; Poncin, M.; Bezemer, K.; Kaijen-Lambers, M.E.H.; Groen, H.J.M.; Smit, E.F.; Dingemans, A.C.; Kunert, A.; Hendriks, R.W.; Aerts, J. Induction of Peripheral Effector CD8 T-cell Proliferation by Combination of Paclitaxel, Carboplatin, and Bevacizumab in Non-small Cell Lung Cancer Patients. *Clin. Cancer Res.* 2019, 25, 2219–2227.
20. Govindan, R.; Szczesna, A.; Ahn, M.J.; Schneider, C.P.; Gonzalez Mella, P.F.; Barlesi, F.; Han, B.; Ganea, D.E.; Von Pawel, J.; Vladimirov, V.; et al. Phase III Trial of Ipilimumab Combined with

- Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* 2017, 35, 3449–3457.
21. Formenti, S.C.; Rudqvist, N.P.; Golden, E.; Cooper, B.; Wennerberg, E.; Lhuillier, C.; Vanpouille-Box, C.; Friedman, K.; Ferrari de Andrade, L.; Wucherpennig, K.W.; et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat. Med.* 2018, 24, 1845–1851.
 22. Chalmers, A.W.; Patel, S.; Boucher, K.; Cannon, L.; Esplin, M.; Luckart, J.; Graves, N.; Van Duren, T.; Akerley, W. Phase I Trial of Targeted EGFR or ALK Therapy with Ipilimumab in Metastatic NSCLC with Long-Term Follow-Up. *Target Oncol.* 2019, 14, 417–421.
 23. Zucali, P.A.; Lin, C.C.; Carthon, B.C.; Bauer, T.M.; Tucci, M.; Italiano, A.; Iacovelli, R.; Su, W.C.; Massard, C.; Saleh, M.; et al. Targeting CD38 and PD-1 with isatuximab plus cemiplimab in patients with advanced solid malignancies: Results from a phase I/II open-label, multicenter study. *J. Immunother. Cancer* 2022, 10, e003697.
 24. Hellmann, M.D.; Rizvi, N.A.; Goldman, J.W.; Gettinger, S.N.; Borghaei, H.; Brahmer, J.R.; Ready, N.E.; Gerber, D.E.; Chow, L.Q.; Juergens, R.A. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. *Lancet Oncol.* 2017, 18, 31–41.
 25. 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.
 26. Clarke, J.M.; Patel, J.D.; Robert, F.; Kio, E.A.; Thara, E.; Camidge, D.R.; Dunbar, M.; Nuthalapati, S.; Dinh, M.H.; Bach, B.A. Veliparib and nivolumab in combination with platinum doublet chemotherapy in patients with metastatic or advanced non-small cell lung cancer: A phase 1 dose escalation study. *Lung Cancer* 2021, 161, 180–188.
 27. Rizvi, N.A.; Hellmann, M.D.; Brahmer, J.R.; Juergens, R.A.; Borghaei, H.; Gettinger, S.; Chow, L.Q.; Gerber, D.E.; Laurie, S.A.; Goldman, J.W.; et al. Nivolumab in Combination with Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* 2016, 34, 2969–2979.
 28. Ready, N.; Hellmann, M.D.; Awad, M.M.; Otterson, G.A.; Gutierrez, M.; Gainor, J.F.; Borghaei, H.; Jolivet, J.; Horn, L.; Mates, M.; et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. *J. Clin. Oncol.* 2019, 37, 992–1000.
 29. Gettinger, S.N.; Redman, M.W.; Bazhenova, L.; Hirsch, F.R.; Mack, P.C.; Schwartz, L.H.; Bradley, J.D.; Stinchcombe, T.E.; Leighl, N.B.; Ramalingam, S.S.; et al. Nivolumab Plus Ipilimumab vs. Nivolumab for Previously Treated Patients with Stage IV Squamous Cell Lung Cancer: The Lung-MAP S1400I Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2021, 7, 1368–1377.

30. Rajan, A.; Gray, J.E.; Devarakonda, S.; Birhiray, R.; Korchin, B.; Menius, E.; Donahue, R.N.; Schlom, J.; Gulley, J.L. Phase 1 trial of CV301 in combination with anti-PD-1 therapy in nonsquamous non-small cell lung cancer. *Int. J. Cancer* 2023, 152, 447–457.
31. Ott, P.A.; Hu-Lieskovan, S.; Chmielowski, B.; Govindan, R.; Naing, A.; Bhardwaj, N.; Margolin, K.; Awad, M.M.; Hellmann, M.D.; Lin, J.J.; et al. A Phase Ib Trial of Personalized Neoantigen Therapy Plus Anti-PD-1 in Patients with Advanced Melanoma, Non-small Cell Lung Cancer, or Bladder Cancer. *Cell* 2020, 183, 347–362.e324.
32. Antonia, S.; Goldberg, S.B.; Balmanoukian, A.; Chaft, J.E.; Sanborn, R.E.; Gupta, A.; Narwal, R.; Steele, K.; Gu, Y.; Karakunnel, J.J.; et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: A multicentre, phase 1b study. *Lancet Oncol.* 2016, 17, 299–308.
33. Leighl, N.B.; Redman, M.W.; Rizvi, N.; Hirsch, F.R.; Mack, P.C.; Schwartz, L.H.; Wade, J.L.; Irvin, W.J.; Reddy, S.C.; Crawford, J.; et al. Phase II study of durvalumab plus tremelimumab as therapy for patients with previously treated anti-PD-1/PD-L1 resistant stage IV squamous cell lung cancer (Lung-MAP substudy S1400F, NCT03373760). *J. Immunother. Cancer* 2021, 9, e002973.
34. Leighl, N.B.; Laurie, S.A.; Goss, G.D.; Hughes, B.G.M.; Stockler, M.; Tsao, M.S.; Hwang, D.M.; Joubert, P.; Kulkarni, S.; Blais, N.; et al. CCTG BR34: A Randomized Phase 2 Trial of Durvalumab and Tremelimumab with or without Platinum-Based Chemotherapy in Patients with Metastatic NSCLC. *J. Thorac. Oncol.* 2022, 17, 434–445.
35. Bang, Y.J.; Golan, T.; Dahan, L.; Fu, S.; Moreno, V.; Park, K.; Geva, R.; De Braud, F.; Wainberg, Z.A.; Reck, M.; et al. Ramucirumab and durvalumab for previously treated, advanced non-small-cell lung cancer, gastric/gastro-oesophageal junction adenocarcinoma, or hepatocellular carcinoma: An open-label, phase Ia/b study (JVDJ). *Eur. J. Cancer* 2020, 137, 272–284.
36. Creelan, B.C.; Yeh, T.C.; Kim, S.W.; Nogami, N.; Kim, D.W.; Chow, L.Q.M.; Kanda, S.; Taylor, R.; Tang, W.; Tang, M.; et al. A Phase 1 study of gefitinib combined with durvalumab in EGFR TKI-naive patients with EGFR mutation-positive locally advanced/metastatic non-small-cell lung cancer. *Br. J. Cancer* 2021, 124, 383–390.
37. Falchook, G.S.; Peeters, M.; Rottey, S.; Dirix, L.Y.; Obermannova, R.; Cohen, J.E.; Perets, R.; Frommer, R.S.; Bauer, T.M.; Wang, J.S.; et al. A phase 1a/1b trial of CSF-1R inhibitor LY3022855 in combination with durvalumab or tremelimumab in patients with advanced solid tumors. *Investig. New Drugs* 2021, 39, 1284–1297.
38. Lim, E.A.; Bendell, J.C.; Falchook, G.S.; Bauer, T.M.; Drake, C.G.; Choe, J.H.; George, D.J.; Karlix, J.L.; Ulahannan, S.; Sachsenmeier, K.F.; et al. Phase Ia/b, Open-Label, Multicenter Study of AZD4635 (an Adenosine A2A Receptor Antagonist) as Monotherapy or Combined with Durvalumab, in Patients with Solid Tumors. *Clin. Cancer Res.* 2022, 28, 4871–4884.

39. Yang, J.C.; Shepherd, F.A.; Kim, D.W.; Lee, G.W.; Lee, J.S.; Chang, G.C.; Lee, S.S.; Wei, Y.F.; Lee, Y.G.; Laus, G.; et al. Osimertinib Plus Durvalumab versus Osimertinib Monotherapy in EGFR T790M-Positive NSCLC following Previous EGFR TKI Therapy: CAURAL Brief Report. *J. Thorac. Oncol.* 2019, 14, 933–939.
40. Jotte, R.; Cappuzzo, F.; Vynnychenko, I.; Stroyakovskiy, D.; Rodríguez-Abreu, D.; Hussein, M.; Soo, R.; Conter, H.J.; Kozuki, T.; Huang, K.-C.; et al. Atezolizumab in Combination with Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results from a Randomized Phase III Trial. *J. Thorac. Oncol.* 2020, 15, 1351–1360.
41. Vergnenegre, A.; Monnet, I.; Bizieux, A.; Bernardi, M.; Chiapa, A.M.; Léna, H.; Chouaid, C.; Robinet, G. Open-label Phase II trial to evaluate safety and efficacy of second-line metronomic oral vinorelbine-atezolizumab combination for stage-IV non-small-cell lung cancer—VinMetAtezo trial, (GFPC(‡) 04-2017). *Future Oncol.* 2020, 16, 5–10.
42. 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.
43. Nishio, M.; Barlesi, F.; West, H.; Ball, S.; Bordoni, R.; Cobo, M.; Longeras, P.D.; Goldschmidt, J., Jr.; Novello, S.; Orlandi, F.; et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results from the Randomized Phase 3 IMpower132 Trial. *J. Thorac. Oncol.* 2021, 16, 653–664.
44. Blank, C.U.; Wong, D.J.; Ho, T.H.; Bauer, T.M.; Lee, C.B.; Bene-Tchaleu, F.; Zhu, J.; Zhang, X.; Cha, E.; Sznol, M. Phase Ib Study of Atezolizumab Plus Interferon- α with or without Bevacizumab in Patients with Metastatic Renal Cell Carcinoma and Other Solid Tumors. *Curr. Oncol.* 2021, 28, 5466–5479.
45. Jung, K.H.; LoRusso, P.; Burris, H.; Gordon, M.; Bang, Y.J.; Hellmann, M.D.; Cervantes, A.; Ochoa de Olza, M.; Marabelle, A.; Hodi, F.S.; et al. Phase I Study of the Indoleamine 2,3-Dioxygenase 1 (IDO1) Inhibitor Navoximod (GDC-0919) Administered with PD-L1 Inhibitor (Atezolizumab) in Advanced Solid Tumors. *Clin. Cancer Res.* 2019, 25, 3220–3228.
46. Langer, C.J.; Gadgeel, S.M.; Borghaei, H.; Papadimitrakopoulou, V.A.; Patnaik, A.; Powell, S.F.; Gentzler, R.D.; Martins, R.G.; Stevenson, J.P.; Jalal, S.I. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016, 17, 1497–1508.
47. Kurata, T.; Nakagawa, K.; Satouchi, M.; Seto, T.; Sawada, T.; Han, S.; Homma, M.; Noguchi, K.; Nogami, N. Phase 1 study of pembrolizumab plus chemotherapy as first-line treatment in Japanese patients with advanced NSCLC. *Cancer Treat. Res. Commun.* 2021, 29, 100458.

48. Gadgeel, S.; Rodríguez-Abreu, D.; Speranza, G.; Esteban, E.; Felip, E.; Dómine, M.; Hui, R.; Hochmair, M.J.; Clingan, P.; Powell, S.F.; et al. Updated Analysis from KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J. Clin. Oncol.* 2020, 38, 1505–1517.
49. Arrieta, O.; Barrón, F.; Ramírez-Tirado, L.A.; Zatarain-Barrón, Z.L.; Cardona, A.F.; Díaz-García, D.; Ramos, M.Y.; Mota-Vega, B.; Carmona, A.; Álvarez, M.P.P.; et al. Efficacy and Safety of Pembrolizumab Plus Docetaxel vs Docetaxel Alone in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer: The PROLUNG Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020, 6, 856–864.
50. Herbst, R.S.; Arkenau, H.T.; Santana-Davila, R.; Calvo, E.; Paz-Ares, L.; Cassier, P.A.; Bendell, J.; Penel, N.; Krebs, M.G.; Martin-Liberal, J.; et al. Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): A multicohort, non-randomised, open-label, phase 1a/b trial. *Lancet Oncol.* 2019, 20, 1109–1123.
51. Reckamp, K.L.; Redman, M.W.; Dragnev, K.H.; Minichiello, K.; Villaruz, L.C.; Faller, B.; Al Baghdadi, T.; Hines, S.; Everhart, L.; Highleyman, L.; et al. Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non-Small-Cell Lung Cancer Previously Treated with Immunotherapy-Lung-MAP S1800A. *J. Clin. Oncol.* 2022, 40, 2295–2306.
52. Taylor, M.H.; Lee, C.H.; Makker, V.; Rasco, D.; Dutcus, C.E.; Wu, J.; Stepan, D.E.; Shumaker, R.C.; Motzer, R.J. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients with Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. *J. Clin. Oncol.* 2020, 38, 1154–1163.
53. Kitano, S.; Fujiwara, Y.; Shimizu, T.; Iwasa, S.; Yonemori, K.; Kondo, S.; Shimomura, A.; Koyama, T.; Ebata, T.; Ikezawa, H.; et al. A feasibility study of lenvatinib plus pembrolizumab in Japanese patients with advanced solid tumors. *Cancer Chemother. Pharmacol.* 2022, 90, 523–529.
54. Naing, A.; Wong, D.J.; Infante, J.R.; Korn, W.M.; Aljumaily, R.; Papadopoulos, K.P.; Autio, K.A.; Pant, S.; Bauer, T.M.; Drakaki, A.; et al. Pegilodecakin combined with pembrolizumab or nivolumab for patients with advanced solid tumours (IVY): A multicentre, multicohort, open-label, phase 1b trial. *Lancet Oncol.* 2019, 20, 1544–1555.
55. Besse, B.; Lopez, P.G.; Puente, J.; Cortot, A.; Garcia, M.E.O.; Perol, M.; Gil, M.; Chao, G.; Shahidi, J.; Bennouna, J. Efficacy and safety of necitumumab and pembrolizumab combination therapy in patients with stage IV non-small cell lung cancer (NSCLC). *Ann. Oncol.* 2017, 28, v466.
56. Levy, B.P.; Giaccone, G.; Besse, B.; Felip, E.; Garassino, M.C.; Gomez, M.D.; Garrido, P.; Piperdi, B.; Ponce-Aix, S.; Menezes, D.; et al. Randomised phase 2 study of pembrolizumab plus CC-486

- versus pembrolizumab plus placebo in patients with previously treated advanced non-small cell lung cancer. *Eur. J. Cancer* 2019, 108, 120–128.
57. Levy, B.; Barlesi, F.; Paz-Ares, L.; Bennouna, J.; Erman, M.; Felip, E.; Isla, D.; Kim, H.R.; Kim, S.W.; Madelaine, J.; et al. Phase II study of afatinib plus pembrolizumab in patients with squamous cell carcinoma of the lung following progression during or after first-line chemotherapy (LUX-Lung-IO). *Lung Cancer* 2022, 166, 107–113.
58. Park, H.; Shapiro, G.I.; Gao, X.; Mahipal, A.; Starr, J.; Furqan, M.; Singh, P.; Ahrorov, A.; Gandhi, L.; Ghosh, A.; et al. Phase Ib study of eprenetapopt (APR-246) in combination with pembrolizumab in patients with advanced or metastatic solid tumors. *ESMO Open* 2022, 7, 100573.
59. Ramalingam, S.S.; Thara, E.; Awad, M.M.; Dowlati, A.; Haque, B.; Stinchcombe, T.E.; Dy, G.K.; Spigel, D.R.; Lu, S.; Iyer Singh, N.; et al. JASPER: Phase 2 trial of first-line niraparib plus pembrolizumab in patients with advanced non-small cell lung cancer. *Cancer* 2022, 128, 65–74.
60. Xiao, A.; Luke, J.J.; Partouche, J.; Karrison, T.; Chmura, S.J.; Al-Hallaq, H.A. Evaluation of Dose Distribution to Organs-at-Risk in a Prospective Phase 1 Trial of Pembrolizumab and Multisite Stereotactic Body Radiation Therapy (SBRT). *Pract. Radiat. Oncol.* 2022, 12, 68–77.
61. Felip, E.; Altorki, N.; Zhou, C.; Csősz, T.; Vynnychenko, I.; Goloborodko, O.; Luft, A.; Akopov, A.; Martinez-Marti, A.; Kenmotsu, H.; et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIa non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. *Lancet* 2021, 398, 1344–1357.
62. O'Brien, M.; Paz-Ares, L.; Marreaud, S.; Dafni, U.; Oselin, K.; Havel, L.; Esteban, E.; Isla, D.; Martinez-Marti, A.; Faehling, M.; et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIa non-small-cell lung cancer (PEARLS/KEYNOTE-091): An interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol.* 2022, 23, 1274–1286.
63. 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.; Broderick, S.; et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *N. Engl. J. Med.* 2018, 378, 1976–1986.
64. 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.
65. Forde, P.M.; Spicer, J.; Lu, S.; Provencio, M.; Mitsudomi, T.; Awad, M.M.; Felip, E.; Broderick, S.R.; Brahmer, J.R.; Swanson, S.J.; et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N. Engl. J. Med.* 2022, 386, 1973–1985.

66. 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.
67. 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.
68. 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.
69. Yi, J.S.; Ready, N.; Healy, P.; Dumbauld, C.; Osborne, R.; Berry, M.; Shoemaker, D.; Clarke, J.; Crawford, J.; Tong, B.; et al. Immune Activation in Early-Stage Non-Small Cell Lung Cancer Patients Receiving Neoadjuvant Chemotherapy Plus Ipilimumab. *Clin. Cancer Res.* 2017, 23, 7474–7482.
70. Rothschild, S.I.; Zippelius, A.; Eboulet, E.I.; Savic Prince, S.; Betticher, D.; Bettini, A.; Früh, M.; Joerger, M.; Lardinois, D.; Gelpke, H.; et al. SAKK 16/14: Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage IIIA(N2) Non-Small-Cell Lung Cancer-A Multicenter Single-Arm Phase II Trial. *J. Clin. Oncol.* 2021, 39, 2872–2880.
71. Wislez, M.; Mazieres, J.; Lavole, A.; Zalcman, G.; Carre, O.; Egenod, T.; Caliandro, R.; Dubos-Arvis, C.; Jeannin, G.; Molinier, O.; et al. Neoadjuvant durvalumab for resectable non-small-cell lung cancer (NSCLC): Results from a multicenter study (IFCT-1601 IONESCO). *J. Immunother. Cancer* 2022, 10, e005636.
72. Heymach, J.V.; Mitsudomi, T.; Harpole, D.; Aperghis, M.; Jones, S.; Mann, H.; Fouad, T.M.; Reck, M. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients with Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial. *Clin. Lung Cancer* 2022, 23, e247–e251.
73. Campelo, R.G.; Forde, P.; Weder, W.; Spicer, J.; He, P.; Hamid, O.; Martinez, P.; Cascone, T. P2. 04-28 NeoCOAST: Neoadjuvant Durvalumab Alone or with Novel Agents for Resectable, Early-Stage (I–IIIA) Non-Small Cell Lung Cancer. *J. Thorac. Oncol.* 2019, 14, S719.
74. Chaft, J.E.; Oezkan, F.; Kris, M.G.; Bunn, P.A.; Wistuba, I.I.; Kwiatkowski, D.J.; Owen, D.H.; Tang, Y.; Johnson, B.E.; Lee, J.M.; et al. Neoadjuvant atezolizumab for resectable non-small cell lung cancer: An open-label, single-arm phase II trial. *Nat. Med.* 2022, 28, 2155–2161.
75. Forde, P.M.; Spicer, J.; Lu, S.; Provencio, M.; Mitsudomi, T.; Awad, M.M.; Felipe, E.; Broderick, S.; Brahmer, J.; Swanson, S.J. 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 Res.* 2021, 81, CT003.
76. Paz-Ares, L.; Hasan, B.; Dafni, U.; Menis, J.; De Maio, E.; Oselin, K.; Albert, I.; Faehling, M.; Van Schil, P.; O'Brien, M.E.R. A randomized, phase 3 trial with anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (EORTC/ETOP 1416-PEARLS). *Ann. Oncol.* 2017, 28, ii23.
77. Altorki, N.; Borczuk, A.; Saxena, A.; Port, J.; Stiles, B.; Lee, B.; Sanfilippo, N.; Ko, E.; Scheff, R.; Pua, B.; et al. P2.04-92 Neoadjuvant Durvalumab with or without Sub-Ablative Stereotactic Radiotherapy (SBRT) in Patients with Resectable NSCLC (NCT02904954). *J. Thorac. Oncol.* 2019, 14, S746.
78. Spicer, J.; Cascone, T.; Kar, G.; Zheng, Y.; Blando, J.; Tan, T.; Cheng, M.; Mager, R.; Hamid, O.; Soo-Hoo, Y.; et al. 929MO—Platform study of neoadjuvant durvalumab (D) alone or combined with novel agents in patients (pts) with resectable, early-stage non-small cell lung cancer (NSCLC): Pharmacodynamic correlates and circulating tumor DNA (ctDNA) dynamics in the NeoCOAST study. *Ann. Oncol.* 2022, 33, S971.
79. Long, L.; Zhang, X.; Chen, F.; Pan, Q.; Phiphatwatchara, P.; Zeng, Y.; Chen, H. The promising immune checkpoint LAG-3: From tumor microenvironment to cancer immunotherapy. *Genes Cancer* 2018, 9, 176–189.
80. Tawbi, H.A.; Schadendorf, D.; Lipson, E.J.; Ascierto, P.A.; Matamala, L.; Castillo Gutiérrez, E.; Rutkowski, P.; Gogas, H.J.; Lao, C.D.; De Menezes, J.J.; et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N. Engl. J. Med.* 2022, 386, 24–34.
81. Morgensztern, D.; Chaudhry, A.; Iannotti, N.; Acevedo, A.; Balaburski, G.; Balogh, A.; Peters, S. 1359TiP RELATIVITY-104: First-line relatlimab (RELA) + nivolumab (NIVO) with chemotherapy vs nivo with chemotherapy in stage IV or recurrent non-small cell lung cancer (NSCLC): A phase II, randomized, double-blind study. *Ann. Oncol.* 2021, 32, S1030.
82. Alix-Panabières, C.; Pantel, K. Liquid biopsy: From discovery to clinical implementation. *Mol. Oncol.* 2021, 15, 1617–1621.

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