Neoadjuvant treatment in non-small cell lung cancer: New perspectives with the incorporation of immunotherapy

Carlos Aguado, Luis Chara, Mónica Antoñanzas, Jose Maria Matilla Gonzalez, Unai Jiménez, Raul Hernanz, Xabier Mielgo-Rubio, Juan Carlos Trujillo-Reyes, Felipe Couñago

Abstract
The aim of neoadjuvant treatment in non-small cell lung cancer (NSCLC) is to eliminate micrometastatic disease to facilitate surgical resection. Neoadjuvant
chemotherapy (ChT) in localised NSCLC has numerous advantages over other therapeutic modalities and is considered standard treatment in resectable disease. Treatment with immune checkpoint inhibitors (ICI) improves long-term survival in advanced disease and has a better toxicity profile than conventional therapies. These immunotherapy agents (anti-PD1/PD-L1), administered with or without ChT, are currently being evaluated in the preoperative setting, with initial results showing better pathological response rates and more long-term benefits. Importantly, these drugs do not appear to increase the rate of severe adverse effects and/or postoperative complications. However, several questions still need to be resolved, including the identification of predictive biomarkers; comparative studies of immunotherapy alone vs combined treatment with ChT and/or radiotherapy; the optimal duration of treatment; the timing of surgery; the need for adjuvant treatment; appropriate radiologic evaluation and mediastinal staging; and the correlation between pathological response and survival outcomes. Here we review the current evidence for immunotherapy from a multidisciplinary perspective and discuss current and future controversies.

Key Words: Non-small cell lung cancer; Neoadjuvant; Immune checkpoint inhibitors; Immunotherapy; Anti-PD1; Anti-PD-L1; Complete pathological response

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Studies evaluating neoadjuvant immunotherapy in non-small cell lung cancer have reported extraordinary pathological response rates without any increase in postoperative complications. However, before immunotherapy is implemented in routine clinical practice, several issues still need to be resolved. This review analyses the current evidence for immunotherapy from a multidisciplinary perspective and discusses current and future controversies.

Citation: Aguado C, Chara L, Antoñanzas M, Matilla Gonzalez JM, Jiménez U, Hernanz R, Mielgo-Rubio X, Trujillo-Reyes JC, Couñago F. Neoadjuvant treatment in non-small cell lung cancer: New perspectives with the incorporation of immunotherapy. World J Clin Oncol 2022; 13(5): 314-322

URL: https://www.wjgnet.com/2218-4333/full/v13/i5/314.htm
DOI: https://dx.doi.org/10.5306/wjco.v13.i5.314

INTRODUCTION

Approximately 30% of patients with non-small cell lung cancer (NSCLC) are diagnosed with early-stage disease and most will undergo curative intent surgery. However, a substantial proportion of these patients will develop distant metastases, leading to a poor 5-year overall survival (OS) rate (< 35%) in patients with stage IIIA disease. Platinum-based adjuvant chemotherapy (ChT) has shown a marginal benefit in these patients, increasing 5-year survival rates by an additional 5%[1].

Multiple studies have directly compared adjuvant to neoadjuvant (preoperative) treatment, but have failed to demonstrate differences in efficacy between these two strategies. Nonetheless, neoadjuvant treatment has several advantages over adjuvant therapy, including: (1) A reduction in tumour volume and disease stage (thus increasing the potential for complete surgical resection); (2) early treatment of micrometastatic disease; (3) assessment of in vivo response to systemic therapy; and (4) improvement in the patient’s preoperative performance status, which may increase adherence to the therapeutic plan.

The introduction of immune checkpoint inhibitors (ICI), which have been shown to substantially prolong survival in many patients, has radically altered the therapeutic landscape in advanced NSCLC. By contrast, the role of ICIs in localised disease is poorly understood. In this context, the aim of this article is to provide a detailed review, from a multidisciplinary perspective, of the current status of neoadjuvant therapy and the future of immunotherapy in locally-advanced NSCLC.

CONTRIBUTION OF NEOADJUVANT TREATMENT TO SURGERY IN STAGE III NSCLC

Numerous studies have evaluated the role of neoadjuvant therapy—mainly ChT—in surgically-treated patients with stage IIIA NSCLC. However, this approach remains controversial, in part due to the contradictory findings. Randomised studies have failed to demonstrate a clear advantage for neoadjuvant ChT followed by surgery vs definitive chemoradiotherapy (CRT). It seems likely that these
conflicting results are due to the wide heterogeneity in study designs (patient selection, treatment regimens, and treatment duration periods). Moreover, the type of surgery can also have a large influence on the outcomes. For example, in the Intergroup 0139 trial[2], neoadjuvant therapy significantly improved 5-year survival compared to CRT, but only in the lobectomy arm, mainly due to the high postoperative mortality rate (26%) in the pneumonectomy arm. Similarly, a subgroup analysis of the EORTC 08941 trial[3] also found that lobectomy was a predictor of better survival. That trial also included patients with unresectable disease, many of whom were treated with sequential CRT. By contrast, the ESPATUE trial failed to confirm these differences in survival outcomes according to type of treatment or surgical procedure, finding no significant differences in 5-year OS between the neoadjuvant and CRT arms (44% vs 40%)[4].

CRT has also been compared to induction ChT alone in the neoadjuvant setting[5], with no clear differences between these approaches in stage IIIA disease. Several studies have found that CRT does not significantly increase mortality or postoperative complications, even in patients undergoing pneumonectomy[6,7]. A major limitation of neoadjuvant treatment is the increased surgical complexity caused by the presence of thoracic adhesions and fibrosis, although complications associated with these treatments have decreased in recent years[8].

NEW HORIZONS FOR PREOPERATIVE RADIOThERAPY

Radiotherapy (RT) continues to play a fundamental role in the management of localised NSCLC, either as radical-intent monotherapy [e.g., stereotactic body radiation therapy (SBRT)] or combined (pre- or postoperatively) with ChT. In advanced disease, palliative RT can help manage symptoms such as hemoptysis, pain, and dyspnea. For this reason, it is crucial to determine the optimal timing and treatment modality.

Although the immune system will trigger an effective innate response when it detects the presence of cancer cells, in some cases tumours may become resistant to this immune response[9,10]. Exposure to ionising radiation induces changes in the tumour microenvironment, triggering the release of antigens that stimulate the immune system through a “vaccine” effect. In this clinical scenario, immunotherapy can trigger both a local response as well as a systemic response against tumour cells located outside the irradiation field, known as the “abscopal effect”[11,12]. However, several studies have shown that the real incidence of these responses in clinical practice is low.

Based on the results reported to date, the combination of radiotherapy and immunotherapy in NSCLC appears to be a promising strategy, but more robust data are needed to definitively establish the most appropriate treatment regimen for this combined approach, especially in localised disease. More specifically, studies are needed to evaluate this combination in the neoadjuvant setting in NSCLC.

REINVENTING SYSTEMIC TREATMENT: ROLE OF IMMUNOTHERAPY

General aspects

The main advantage of neoadjuvant immunotherapy is its capacity to stimulate the production and activation of T cells. In this therapeutic approach, the primary tumour cells are used as a source of antigen production, thus activating different types or clones of effector T cells, which may then act against tumour cells throughout the body (primary tumour, metastatic sites, circulation, etc.), thus allowing systemic elimination of micrometastases[13]. Compared to adjuvant therapy, the structure of the pulmonary lymphatic system before surgery remains intact, which enhances the potential for tumour cell-immune interaction. This ability to maximize antigen exposure to T cells not only permits a stronger initial response, but a longer lasting one. However, neoadjuvant immunotherapy also has several possible disadvantages, including the lack of long-term survival and safety data, and the potential impact on the timing of surgery and surgical complications.

Clinical evidence for neoadjuvant immunotherapy in NSCLC

Neoadjuvant therapy with ICI monotherapy: The first study to prospectively assess the role of neoadjuvant immunotherapy in NSCLC was a pilot study by Forde et al.[9], who evaluated 21 patients with stage I-IIIA NSCLC treated preoperatively with two cycles of the anti-PD-1 agent nivolumab. Of these, nine patients (45%) achieved a major pathological response (MPR) and two patients (10%) a pathological complete response (pCR). By RECIST criteria, most patients (85%) had stable disease and 10% showed a partial response. A stage reduction was observed in eight patients (40%). At a median follow-up of 18 mo, the disease-free survival (DFS) rate was 73%.

The phase II LCMC3 trial[14] was performed to evaluate the effects of two cycles of atezolizumab followed by surgery in stage IB-IIIB disease. Of the 181 patients included, 159 underwent surgery. In the surgically-treated patients without a known EGFR/ALK mutation, MPR was observed in 20% (30/147) and pCR in 7% (10/147). In 43% of patients (66/155), the tumour was downstaged. At 18 mo of follow-
up, the DFS and OS rates in patients with stage I-II disease were 79% and 91%, respectively, vs 77% and 87% in stage III patients.

Other anti-PD-1 or anti-PD-L1 agents have also been investigated in recent years. One study evaluated sintilimab in 40 patients with stage IA-IIIB NSCLC, with 40% of patients achieving MPR and 16% pCR[15]. Most patients (70%) in that study had stable disease on radiologic assessment. In contrast to many studies, the tumour histology in most patients (80%) was squamous cell carcinoma. Another study evaluated the effects of two cycles of pembrolizumab, another anti-PD-1 agent, in stage II-IIIA NSCLC, with similar results (MPR, 27% and pCR, 13%)[16].

In the phase II IONESCO trial[17], patients with stage IIB-IIIA NSCLC received three cycles of durvalumab. The preliminary results (n = 46) showed an MPR and pCR of 18% and 7%, respectively, with an objective response rate (ORR) of 8%. Despite promising 12-mo DFS and OS (78% and 89%, respectively), the trial was closed early due to high postoperative mortality (9%).

The combination of nivolumab and ipilimumab was evaluated in the phase II NEOSTAR trial[18]. In the 37 surgically-treated patients, combined therapy achieved higher MPR (50% vs 24%) and pCR (38% vs 10%) rates than nivolumab alone. There were no significant between-group differences in severe (≥ grade 3) toxicity (13% vs 10%).

Neoadjuvant therapy: immune checkpoint inhibitors combined with chemotherapy: Several studies have been performed (or are currently underway) to evaluate immunotherapy combined with ChT in an attempt to further improve the survival and pathologic response rates observed with ICI monotherapy. In a single-arm open label trial, Shu et al[19] preoperatively administered four cycles of atezolizumab plus carboplatin + nab-paclitaxel in patients with stage IB-IIIA NSCLC (77% stage IIIA). The MPR, pCR, and ORR rates were 57%, 33%, and 63%, respectively, all of which are higher than typically achieved with monotherapy. Median OS has not yet been reached due to the short follow-up.

The phase II NADIM trial[20] evaluated the combination of carboplatin + paclitaxel + nivolumab for three cycles in 46 patients with stage IIIA disease followed by adjuvant nivolumab for six months. In the 41 patients who underwent surgery, the MPR, pCR, and ORR were 83%, 63%, and 76%, respectively. No cases of disease progression were observed during neoadjuvant treatment. At 2-years of follow-up, DFS and OS were 77% and 90%, respectively. Adverse events ≥ grade 3 were observed in 30% of patients, but not associated with delays in surgery or death.

The findings of the phase II SAKK 16/14 trial in patients (n = 62) with stage IIIa NSCLC[21] were recently reported. In that study, patients received three cycles of cisplatin + docetaxel followed by two cycles of durvalumab and one-year of postoperative durvalumab maintenance therapy. The MPR, pCR, and overall response rates were 60%, 18%, and 58%, respectively. At 12 mo, the DFS was 73.4% (Table 1).

Unresolved questions

Assessment of response to immunotherapy: The ORR is a key indicator for evaluating the antitumour activity of neoadjuvant therapy; however, postoperative pathological findings are not always consistent with the radiologic response[22]. For this reason, fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) [23] remains the gold standard for assessing response to neoadjuvant therapy. FDG-PET-CT imaging measures tumour metabolic activity to assess response and rule out distant disease. However, in some cases, neoadjuvant immunotherapy modifies the peritumoral inflammatory environment, and it can be difficult to determine whether there is a tumour response (increase or decrease) due to the presence of lymphocytic infiltrates. This phenomenon was described in the NEOSTAR trial[24] as “nodal immune flare”, which was observed in 11% of cases with proven histological pCR after surgical resection. Several of the aforementioned studies have reported this phenomenon.

Correlation with long-term survival: One of the most striking results of immunotherapy is the marked increase in the MPR and/or pCR rates; in fact, some authors[25] have proposed using these parameters as surrogates for OS. For this reason, the systematic, standardised evaluation of surgical specimens should be prioritised. Various algorithms have been proposed[26] and several groups have also published consensus statements aimed at standardising assessment of pathological response after systemic therapy (including immunotherapy)[27,28]. Given the higher pathological response rates observed in phase II trials[20], it seems highly likely that, when long-term data become available, OS rates should increase; however, this expected benefit needs to be confirmed in prospective randomised trials, many of which are still ongoing.

Biomarkers: The neoadjuvant scenario is an excellent context in which to explore biomarkers that may predict the benefit of immunotherapy. As in metastatic disease, PD-L1 expression and tumour mutational burden are the two most well-documented biomarkers in clinical trials of ICI[29]. Higher pretreatment PD-L1 expression levels have been associated with a greater probability of achieving MPR [18] or pCR[20]. However, no association has been observed between elevated PD-L1 expression and longer survival, and a substantial proportion of patients without PD-L1 expression also achieve MPR.
Table 1 Clinical evidence for neoadjuvant immunotherapy in non-small cell lung cancer

| Study                  | Phase | Stages | Treatment                                      | Cycles | Patients included | Main endpoint      | ORR | MPR  | pCR  |
|------------------------|-------|--------|-----------------------------------------------|--------|-------------------|---------------------|-----|------|------|
| Forde et al[8]         | I     | I-IIIA | Nivolumab                                     | 2      | 21                | Safety and feasibility | 10% | 45%  | 10%  |
| LCMC3[14]              | II    | IB-IIIB| Atezolizumab                                  | 2      | 181               | MPR                 | 7%  | 20%  | 7%   |
| NEOSTAR[18]            | II    | I-IIIA | Nivolumab vs nivolumab + ipilimumab           | 3      | 44                | MPR                 | 22% vs 19% | 24% vs 50% | 10% vs 38% |
| Gao et al[15]          | IB    | IA-III | Sintilimab                                    | 2      | 40                | Safety              | 20% | 40%  | 16%  |
| NEOMUN[16]             | II    | II-III | Pembrolizumab                                 | 2      | 15                | Safety and feasibility | 28% | 27%  | 13%  |
| JONESCO[17]            | II    | IB-IIIA| Durvalumab                                    | 3      | 46                | % R0                | 8%  | 18%  | 7%   |
| Shu et al[19]          | II    | IB-IIIA| Atezolizumab + carboplatin + nab-paclitaxel   | 4      | 30                | MPR                 | 63% | 57%  | 33%  |
| NADIM[20]              | II    | IIIA   | Nivolumab + carboplatin + paclitaxel          | 3      | 46                | DFS 24 mo           | 76% | 83%  | 63%  |
| SAK 16/14[21]          | II    | IIIA   | Cisplatin + docetaxel followed by durvalumab  | 2      | 62                | DFS 12 mo           | 58% | 60%  | 18%  |

1Nivolumab x3 cycles with or without a single dose of ipilimumab.
2Cisplatin + docetaxel x3 cycles followed by 2 cycles of durvalumab. ORR: Objective response rate; MPR: Major pathological response; pCR: Pathological complete response; % R0: % complete resection; DFS 24 mo: Progression-free survival at 24 mo; DFS 12 mo: Disease-free survival at 12 mo.

A higher density of tumour infiltrating lymphocytes–especially CD3+, CD8+, and CD103+–has been described as a prognostic factor associated with longer survival. The NEOSTAR and LCMC3 trials both assessed the influence of these lymphocytes[30], finding that resected tumours in patients with MPR presented a higher level of infiltration by effector-memory T-cells (CD3+, CD8+, CD45RO+) compared to those without MPR, suggesting a possible predictive capacity.

Other predictive biomarkers in peripheral blood are being evaluated: T-cell receptor, circulating tumour DNA, and somatic mutations (KEAP, STK11, RB1)[20], although these all need to be validated in prospective trials.

**Beyond immunotherapy: the role of targeted therapy**

In patients with metastatic NSCLC with certain molecular alterations (EGFR mutations, ALK rearrangements), treatment with tyrosine kinase inhibitors has shown a large benefit. Preoperative administration of drugs such as erlotinib[31] and crizotinib[32] improves ORR, but not OS, and postoperative recurrence rate after treatment discontinuation is high[33]. In this regard, prolonged treatment after surgery will probably be needed to reduce the likelihood of recurrence. Several studies are currently exploring this strategy, including the phase III NeoADAURA trial (NCT04351555), which is evaluating neoadjuvant osimertinib as monotherapy or combined with ChT.

**NEW CHALLENGES: CHANGES FROM THE SURGICAL PERSPECTIVE**

The high MPR and pCR rates obtained in clinical trials with neoadjuvant immunotherapy, with or without ChT, suggest that more patients with stage II-III disease will be candidates for surgery, even with the same operability and resectability criteria.

However, immunotherapy can induce atypical radiologic response patterns (*i.e.*, pseudoprogression, hyperprogression), which can make it more challenging to identify patients with negativization of the mediastinal nodes and therefore ideal candidates for surgical resection. Traditional response assessment criteria may not be optimal to adequately classify patients after immunotherapy, especially with regard to mediastinal evaluation. For this reason, new protocols with specific restaging criteria need to be developed and validated.

In current treatment algorithms, the indication for surgery depends on the presence or absence of contrast uptake on the PET-CT scan after neoadjuvant therapy, considered together with the findings of invasive diagnostic tests. However, high mediastinal uptake on PET-CT images should not immediately rule out surgery in these patients, since this finding is more common after immunotherapy than induction ChT or radiotherapy. For this reason, the introduction of new PET-CT response criteria[34] is expected to lead to an increase in invasive testing. However, the diagnostic efficacy of these invasive
Table 2 Ongoing clinical trials of neoadjuvant therapy

| Treatment strategy | Study number (name) | Phase | Treatment |
|--------------------|--------------------|-------|-----------|
| Anti-PD-1 + chemotherapy | NCT03838159 (NADIM II) | Phase 2 randomised | 3 cycles of carboplatin + paclitaxel +/- nivolumab → surgery → 6 mo of adjuvant nivolumab (experimental arm) |
| Anti-PD-1 + chemotherapy | NCT04728724 Grupo A: sintilimab 2-4 cycles → surgery; Group B: sintilimab + chemotherapy (carboplatin + pemetrexed/gemcitabine) 2-4 cycles → surgery |
| Anti-PD-1 + chemotherapy | NCT04326153 | Phase 2 | 2-4 cycles of camrelizumab + apatinib or camrelizumab + chemotherapy (carboplatin + pemetrexed/gemcitabine) → surgery |
| Anti-PD-1 + chemotherapy | NCT04061590 | Phase 2 | 2 cycles of pembrolizumab + chemotherapy (cisplatin + pemetrexed) → surgery |
| Anti-PD-1 + chemotherapy | NCT04638582 | Phase 2 | 3 cycles of pembrolizumab +/- chemotherapy (carboplatin + pemetrexed/paclitaxel) → surgery |
| Anti-PD-1 + chemotherapy | NCT04025879 | Phase 3 | chemotherapy +/- nivolumab → surgery → adjuvant nivolumab (experimental arm) |
| Anti-PD-L1 + anti-CTLA-4 | NCT02986528 (CheckMate 816) | Phase 3 | 2 cycles of chemotherapy (platinum doublet) + nivolumab → surgery +/- adjuvant chemotherapy (one experimental arm) |
| Anti-PD-L1 + anti-CTLA-4 | NCT02986528 (CheckMate 816) | Phase 3 | 3 cycles of chemotherapy (platinum-based + nab-paclitaxel) + durvalumab → surgery → durvalumab 1 yr |
| Anti-PD-1 | NCT03197467 (NEOMUN) | Phase 2 | 2 cycles of pembrolizumab → surgery |
| Anti-PD-1 + anti-LAG3 | NCT04205552 (NEOpredict) | Phase 2 | 2 cycles of nivolumab +/- relatlimab → surgery |
| Anti-PD-L1 + radiotherapy | NCT04245314 | Phase 2 | 3 cycles of chemotherapy → 1 cycle durvalumab + radiotherapy → surgery → durvalumab 1 yr |
| Anti-PD-L1 + radiotherapy | NCT03257377 | Phase 2 | 2 cycles of durvalumab +/- tremelimumab (antiCTLA-4) + radiotherapy → surgery → adjuvant chemotherapy |
| Anti-PD-L1 + radiotherapy | NCT03871153 | Phase 2 | Carboplatin + paclitaxel + radiotherapy + durvalumab → surgery → durvalumab 1 yr |

Other questions surrounding immunotherapy include the potential interference with the timing of surgery. In patients treated with monotherapy, surgery can be performed earlier (1-2 wk after treatment); by contrast, after combined treatment (immunotherapy and ChT), surgery will need to be delayed by 4-6 wk. Nevertheless, major changes in the timing of surgery are not expected.

Another issue is that the surgical procedure may be more technically challenging due to the possible presence of multiple inflamed lymph nodes induced by neoadjuvant immunotherapy. While thoracotomy is the most common route of access, minimally invasive surgery is generally indicated when an optimal resection is considered feasible. Nonetheless, several studies have reported a high conversion rate to open surgery (23%-54%) [36,37]. Minimally-invasive techniques are expected to become more standardised and reproducible as surgical teams gain more experience.

CONCLUSION

The emergence of immunotherapy with ICIs has radically altered the course of disease in advanced NSCLC. The results reported to date for neoadjuvant immunotherapy—demonstrating significant increases in major and complete pathological response rates—suggest that patients with localised disease could also benefit from ICIs, potentially increasing cure rates and prolonging survival in these patients.

The currently available pre- and postoperative safety data support the use of this therapeutic strategy. However, many open questions remain: (1) Does combined chemo-immunotherapy provide greater long-term benefits than immunotherapy alone? (2) Are there any predictive biomarkers of response? (3) What is optimal treatment duration and timing of surgery? (4) Is adjuvant treatment necessary in all patients? and (5) Are new protocols needed for re-evaluation and restaging?

Several ongoing studies are evaluating different therapeutic strategies (Table 2), and will allow us to answer these and other questions that may emerge in the future.
Aguado C et al. Neoadjuvant treatment advances in NSCLC with immunotherapy

FOOTNOTES

Author contributions: Aguado C, Chara LE, Antoñanzas M, Matilla JM, Jiménez U and Hernanz R drafted the manuscript; Couñago F, Trujillo JC and Mielgo-Rubio X critically revised the content of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests related to this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Spain

ORCID number: Carlos Aguado 0000-0002-5624-8035; Luis Chara 0000-0001-5143-7331; Mónica Antoñanzas 0000-0002-7434-9059; Jose María Matilla González 0000-0002-6157-0758; Unai Jiménez 0000-0001-5034-4723; Raul Hernanz 0000-0002-7161-8321; Xabier Mielgo-Rubio 0000-0002-0985-6150; Juan Carlos Trujillo-Reyes 0000-0002-3370-0869; Felipe Couñago 0000-0001-7233-0234.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

REFERENCES

1 Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T; LACE Collaborative Group. Lung adenocarcinoma evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-3559 [PMID: 18506026 DOI: 10.1200/JCO.2007.13.9030]

2 Albain KS, Rusch VW, Crowley JJ, Rice TW, Turrisi AT 3rd, Weck JK, Lonchyna VA, Presant CA, McKenna RJ, Gandara DR. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995; 13: 1880-1892 [PMID: 7636530 DOI: 10.1200/JCO.1995.13.1880]

3 van Meerbeeck JP, Kramer GW, Van Schil PE, Legrand C, Smit EF, Schramel F, Tjens Heijn VN, Biesma B, Debruyne C, van Zandwijk N, Splinter TA, Giaccone G; European Organisation for Research and Treatment of Cancer-Lung Cancer Group. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007; 99: 442-450 [PMID: 17374834 DOI: 10.1093/jnci/djk093]

4 Eberhardt WE, Pöttgen C, Gauer TC, Friedel G, Velt S, Heinrich V, Welter S, Budach W, Spegler W, Kimmich M, Fischer B, Schmidberger H, De Ruyscher S, Belka C, Cordes S, Hopp R, Lütke-Brisentrup D, Lehnmann N, Schuler M, Jöckel KH, Stamatis G, Stuschke M. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE). J Clin Oncol 2015; 33: 4194-4201 [PMID: 26527789 DOI: 10.1200/JCO.2015.62.6812]

5 NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014; 383: 1561-1571 [PMID: 24576776 DOI: 10.1016/S0140-6736(13)62159-5]

6 Couñago F, Rodríguez de Dios N, Montemuiño S, Jove-Teixidó J, Martín M, Calvo-Crespo P, López-Mata M, Samper-Ots MP, López-Guerra JL, García-Cabihanó T, Díaz-Díaz V, de Ingunza-Barón L, Murcia-Mejía M, Alcántara P, Corona J, Ébezúñez U and Hernanz R drafted the manuscript.

7 Stupp R, Mayer M, Kann R, Weder W, Zouhair A, Betticher DC, Roth AD, Stahel RA, Zouhair A, Betticher DC, Roth AD, Stahel RA, Majno SB, Peters S, Jost L, Furrer Eberhardt WE, Chakravarty PK, Alfieri A, Thomas EK, Beri V, Tanaka KE, Vikram B, Guha C. Fli3-ligand administration after neoadjuvant treatment followed by surgery versus definitive chemoradiation in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2009; 101: 785-793 [PMID: 19604722 DOI: 10.1093/jnci/djp071]

8 Forde PM, Chaft JE, Smith KN, Anagnostou T, Cottrell TR, Hellmann MD, Zahurak M, Yang SC, Jones DR, Broderick S, Battafarano RJ, Velez MJ, Rekhtman N, Olah Z, Naidoo J, Marrone KA, Verde F, Guo H, Zhang J, Caushi JX, Chan HY, Sidhoo JW, Scharpf RB, White J, Gabrielson E, Wang H, Rosner GL, Rusch V, Wolchok JD, Merghoub T, Taube JM, Velceucescu Y, Topalian SL, Brahmer JR, Pardoll DM. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med 2018; 378: 1976-1986 [PMID: 29658848 DOI: 10.1056/NEJMoa1716078]

9 Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 2002; 331: 1565-1570 [PMID: 12143644 DOI: 10.1126/science.1086386]

10 Koechler CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ, Schreiber RD. Adaptive immunity maintains occult cancer in an equilibrium state. Nature 2007; 450: 903-907 [PMID: 18026089 DOI: 10.1038/nature06309]

11 Chakravarty PK, Alfieri A, Thomas EK, Beri V, Tanaka KE, Vikram B, Guha C. Fli3-ligand administration after....
radiation therapy prolongs survival in a murine model of metastatic lung cancer. *Cancer Res* 1999; 59: 6028-6032 [PMID: 10627874]

12 Tetzl-Tennenbaum S, Li Q, Rynkwicz S, Ito F, Davis MA, McGinn CJ, Chang AE. Radiotherapy potentiates the therapeutic efficacy of intratumoral dendritic cell administration. *Cancer Res* 2003; 63: 8466-8475 [PMID: 14679011]

13 Versluis JH, Long GV, Blank CU. Learning from clinical trials of neoadjuvant checkpoint blockade. *Nat Med* 2020; 26: 475-484 [PMID: 32376288 DOI: 10.1038/s41591-020-0820-9]

14 Lee J, Chaft J, Nicholas A, Patterson A, Waqar S, Toloza E, Haura E, Raz D, Reckamp K, Merritt R, Owen D, Finley D, Mccnamee C, Blasberg J, Garon E, Mitchell J, Doebele R, Bacciwiecz N, Nagasaka M, Pass A, Schulze K, Phan S, Johnson A, Bunn P, Johnson B, Kris M, Kwiatkowski D, Wistuba I, Carbone D, Rusch V. PS01.05 Surgical and Clinical Outcomes With Neoadjuvant Atezolizumab in Resectable Stage IB–IIIB NSCLC: LCMC3 Trial Primary Analysis. *J Thorac Oncol* 2021; 16 [DOI: 10.1016/j.jto.2021.01.320]

15 Gao S, Li N, Gao S, Xue Q, Ying J, Wang S, Tao X, Zhao J, Mao Y, Wang B, Shao K, Lei W, Wang D, Lv F, Zhao L, Zhang F, Zhao Z, Su K, Tan F, Gao Y, Sun N, Wu D, Yu Y, Ling Y, Wang Z, Duan C, Tang W, Zhang L, He S, Wu N, Wang J, He J. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. *J Thorac Oncol* 2020; 15: 816-826 [PMID: 32036071 DOI: 10.1016/j.jto.2020.01.017]

16 Eichhorn F, Klotz LV, Kriegsmann M, Bischoff H, Schneider MA, Muley T, Kriegsmann K, Haberkorn U, Heussel CP, Savai R, Zoemig I, Jaeger D, Thomas M, Hoffmann H, Winter H, Eichhorn ME. Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: First clinical experience. *Lung Cancer* 2021; 153: 150-157 [PMID: 33529989 DOI: 10.1016/j.lungcan.2021.01.018]

17 Wislez M, Mazieres J, Lavole A, Zalcman G, Carre O, Egenod T, Caliandro R, Gervais R, Jeannin G, Molinier O, Massiani MA, Langlais A, Morin F, Le Fimpeec Barthes F, Brouchet L, Assouad J, Milleron B, Dammot D, Antoine M, Westeel V. Neoadjuvant durvalumab in resectable non-small cell lung cancer (NSCLC): Preliminary results from a multicenter study (IFCT-1601 IONESCO). *Ann Oncol* 2021; 32: S794 [DOI: 10.1093/annonc/mdab241 2021.09.14.16]

18 Cascone T, Williams WJ Jr, Weissferdt A, Leung CH, Lin HY, Pater A, Godoy MB, Carter BW, Federico L, Reuben A, Khan MAJ, Doebele R, Fujiwara Y, Solis LM, Fujimoto J, Tan HT, Kalhor N, Fossella FV, Mott FE, Tsao AS, Blumemserich G Jr, Le X, Zhang J, Skouldils F, Kurie JM, Altan M, Lu C, Glisson BS, Byers LA, Elamin YY, Mehran RJ, Rice DC, Walsh GL, Fisetier WT, Roth JA, Antonoff MB, Kada M, Haymaker C, Berchuck A, Ajami NJ, Jenq RR, Sharma P, Allison JP, Futele A, Wajstala II, Swisher SG, Lee JH, Gibbons DL, Vaporiyin CAA, Heymach JV, Sepesi B. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2020; 21: 786-795 [PMID: 32386568 DOI: 10.1016/S1470-2045(20)30140-6]

19 Provencio M, Nadel E, Insu A, Garcia-Campelo MR, Casal-Rubio J, Domine M, Majein M, Rodriguez-Abruze D, Martínez-Martí A, De Castro Carpeo J, Cobo M, López Vivanco G, Del Barco E, Bernalde Caro R, Viholas N, Barneto Aranda I, Viteri S, Rogerie A, Casarrubios M, Salas Antón C, Parra ER, Wistuba I, Calvo V, Laza-Briviesca R, Romero A, Massuti B, Cruz-Bermúdez A. 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 [PMID: 32979984 DOI: 10.1016/S1470-2045(20)30453-8]

20 Rothchild SI, Zippelius A, Eobulet EL, Savic Prince S, Betticher D, Bettini A, Führ M, Joerger M, Britschgi C, Peters S, Mark MF, Ohschenbein AF, Janthur WD, Wambel C, Mach N, Gonzalez M, Frosch MR, Gudar G, Rusterholz C, Ples M. SAKK 16/14: Anti-PD-L1 antibody durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA (N2) non-small cell lung cancer (NSCLC) – A multicenter single-arm phase 2 trial. *Lancet Oncol* 2020; 31: S803-S804 [DOI: 10.1016/S1470-2045(20)30810-8]

21 Nishino M, Hataha H, Hodi FS. Imaging of Cancer Immunotherapy: Current Approaches and Future Directions. *Radiology* 2019; 290: 9-22 [PMID: 30457485 DOI: 10.1148/radiol.2018181349]

22 Liang W, Cai K, Chen C, Chen H, Chen Q, Fu J, Hu J, Jiang T, Jiao W, Li S, Liu C, Liu D, Liu W, Liu Y, Ma H, Pan X, Qiao G, Tian H, Wei L, Zhang Y, Zhao S, Zhao X, Zhuo C, Zhu Y, Zhong R, Li F, Rosell R, Provencio M, Massarelli E, Antonoff MB, Hida T, de Perrot M, Lin SH, Di Maio M, Ross A, De Ruyscher D, Ramirez RA, Denpeke WCM, Camidge DR, Guibert N, Califano R, Wang Q, Ren S, He J. Expert consensus on neoadjuvant immunotherapy for non-small cell lung cancer. *Transl Lung Cancer Res* 2020; 9: 2696-2715 [PMID: 33489828 DOI: 10.21037/tlcr-2020-63]

23 Sepesi B, Godoy M, William V, Vaporiyin C, Lin H, Leung C, Lee J, Mitchell K, Weissferdt A, Le X, Lam V, Fossella F, Swisher S, Heymach J, Cascone T. Nodal Immune Flare (NIF) Following Neoadjuvant Anti-PD-1 and Anti-CTLA-4 Therapy (NIF) Following Neoadjuvant Anti-PD-1 and Anti-CTLA-4 Therapy. *J Thorac Oncol* 2019; 14: 5745 [DOI: 10.1016/j.jto.2019.08.1599]

24 Hellmann MD, Chaft JE, William WN Jr, Rusch V, Pisters KM, Kalhor N, Pater A, Travis WD, Swisher SG, Kris MG; University of Texas MD Anderson Lung Cancer Collaborative Group. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *Lancet Oncol* 2014; 15: e2-e50 [PMID: 24334493 DOI: 10.1016/S1470-2045(14)73344-6]

25 Travis WD, Dacic S, Wistuba I, Sholl L, Adusumpli P, Bubendorf L, Bunn P, Cascone T, Chaft J, Chen G, Chou TY, Cooper W, Erasmus JJ, Ferreira CG, Goo JM, Heymach J, Hirsch FR, Horinouchi H, Kerr K, Kris M, Jain D, Kim YT, Lopez-Rios F, Lu S, Mitsudomi T, Moreira A, Motisi N, Nicholson AG, Oliveira R, Papotti M, Pasturino U, Paz-Ares L, Pelosi G, Poleri C, Provencio M, Roden AC, Scagliotti G, Swisher SG, Tsumura E, Tsaos MS, Vansteenkiste J, Weder W, Yatabe Y. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. *J Thorac Oncol* 2020; 15: 709-740 [PMID: 32040713 DOI: 10.1016/j.jto.2020.01.005]

26 Weissferdt A, Pater A, Vaporiyin AA, Correa AM, Sepesi B, Moran CA, Wistuba II, Roth JA, Shewale JB, Heymach JV, Kalhor N, Cascone T, Hofstetter WL, Lee JH, Swisher SG. Agreement on Major Pathological Response in NSCLC Patients Receiving Neoadjuvant Chemotherapy. *Clin Lung Cancer* 2020; 21: 341-348 [PMID: 32279936 DOI: 10.1016/j.clincr.2019.11.003]
Aguado C et al. Neoadjuvant treatment advances in NSCLC with immunotherapy

28 Cottrell TR, Thompson ED, Forde PM, Stein JE, Duffield AS, Anagnostou V, Rekhtman N, Anders RA, Cuda JD, Illei PB, Gabrielson E, Askin FB, Niknafs N, Smith KN, Velez MJ, Sauter JL, Isbell JM, Jones DR, Battafarano RJ, Yang SC, Danilova L, Wolchok JD, Topalian SL, Velculescu VE, Pardoll DM, Brahmer JR, Hellmann MD, Chaft JE, Cimino-Mathews A, Taube JM. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (iPRC). Ann Oncol 2018; 29: 1853-1860 [PMID: 29982279 DOI: 10.1093/annonc/mdy218]

29 Pradhan M, Chocry M, Gibbons DL, Sepesi B, Cascone T. Emerging biomarkers for neoadjuvant immune checkpoint inhibitors in operable non-small cell lung cancer. Transl Lung Cancer Res 2021; 10: 590-606 [PMID: 33569339 DOI: 10.21037/tlcr-20-573]

30 Kwiatkowski DJ, Rusch VW, Chaft JE, Johnson BE, Nicholas A, Wistuba II, Merritt R, Lee JM, Bunn PA, Tang Y, Phan SC, Wagar SN, Patterson A, Haura EB, Toloza EM, Reckamp KL, Raz D, Schulze K, Johnson A, Carbone DP. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). J Clin Oncol 2019; 37 (15_suppl): 8503 [DOI: 10.1200/JCO.2019.37.15_suppl.8503]

31 Zhong WZ, Chen KN, Chen C, Gu CD, Wang J, Yang XN, Mao WM, Wang Q, Qiao GB, Cheng Y, Xu L, Wang CL, Chen MW, Kang X, Yan W, Yan HH, Liao RQ, Yang JJ, Zhang X, Zhou Q, Wu YL. Erlotinib Versus Gemcitabine Plus Cisplatin as Neoadjuvant Treatment of Stage IIIA-N2 EGFR-Mutant Non-Small-Cell Lung Cancer (EMERGING-CTONG 1103): A Randomized Phase II Study. J Clin Oncol 2019; 37: 2235-2245 [PMID: 31194613 DOI: 10.1200/JCO.19.00075]

32 Zhang C, Li SL, Nie Q, Dong S, Shao Y, Yang XN, Wu YL, Yang Y, Zhong WZ. Neoadjuvant Crizotinib in Resectable Locally Advanced Non-Small Cell Lung Cancer with ALK Rearrangement. J Thorac Oncol 2019; 14: 726-731 [PMID: 30408570 DOI: 10.1016/j.jtho.2018.10.161]

33 Reyes R, Reguart N. Neoadjuvant treatment of stage IIIA-N2 in EGFR-Mutant/ALK-rearranged non-small cell lung cancer. Transl Lung Cancer Res 2021; 10: 607-621 [PMID: 33569340 DOI: 10.21037/tlcr-20-780]

34 Decazes P, Bohn P. Immunotherapy by Immune Checkpoint Inhibitors and Nuclear Medicine Imaging: Current and Future Applications. Cancers (Basel) 2020; 12 [PMID: 32041105 DOI: 10.3390/cancers12020371]

35 Lainez S, Tissot C, Cottier M, Vergnon JM. EBUS-TBNA Can Distinguish Sarcoid-Like Side Effect of Nivolumab Treatment from Tumor Progression in Non-Small Cell Lung Cancer. Respiration 2017; 94: 518-521 [PMID: 28910804 DOI: 10.1159/000480155]

36 Yang CJ, McSherry F, Mayne NR, Wang X, Berry MF, Tong B, Harpole DH Jr, D’Amico TA, Christensen JD, Ready NE, Klapper JA. Surgical Outcomes After Neoadjuvant Chemotherapy and Ipiulinumab for Non-Small Cell Lung Cancer. Ann Thorac Surg 2018; 105: 924-929 [PMID: 29258674 DOI: 10.1016/j.athoracsur.2017.09.030]

37 Bott MJ, Yang SC, Park BJ, Adasumilli PS, Rusch VW, Isbell JM, Downey RJ, Brahmer JR, Battafarano R, Bush E, Chaft J, Forde PM, Jones DR, Broderick SR. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg 2019; 158: 269-276 [PMID: 30718052 DOI: 10.1016/j.jtcvs.2018.11.124]
