Resectable IIIA-N2 NSCLC

Locally advanced non-small cell lung cancer accounts for one third of non-small cell lung cancer (NSCLC) at the time of initial diagnosis and presents with a wide range of clinical and pathological heterogeneity. To date, the combined multimodality approach involving both local and systemic control is the gold standard for these patients, since occult distant micrometastatic disease should always be suspected. With the rapid increase in treatment options, the need for an interdisciplinary discussion involving oncologists, surgeons, radiation oncologists and radiologists has become essential. Surgery should be recommended to patients with non-bulky, discrete, or single-level N2 involvement and be included in the multimodality treatment. Resectable stage IIIA patients have been the subject of a number of clinical trials and retrospective analysis, discussing the efficiency and survival benefits on patients treated with the available therapeutic approaches. However, most of them have some limitations due to their retrospective nature, lack of exact pretreatment staging, and the involvement of heterogeneous populations leading to the awareness that each patient should undergo a tailored therapy in light of the nature of his tumor, its extension and his performance statu

1. Introduction

Locally advanced (LA) non-small cell lung cancer (NSCLC) accounts for one third of NSCLC at the time of initial diagnosis and presents with a wide range of clinical and pathological heterogeneity. Typically, LA NSCLC refers to stage III disease which represents a heterogeneous group of patients according to the most recent version of the IASLC/UICC TNM staging system (8th edition) [1]. A distinction between stage IIIA and IIIB must be carried out given the different prognosis and different diagnostic and multidisciplinary treatment approach which should be discussed case by case. Stage IIIA includes small tumors (T1a-T2b) with N2 involvement, large tumors (T3-T4) with N1 involvement and T4N0. In particular, N2 disease includes border-zone situations in which radical surgery could be predicted and suggested in a multimodality setting, along with others in which radical resection cannot be achieved and other treatment options should be evaluated. Survival of patients with stage IIIA NSCLC is poor: only half of them survive at 24 months (55%) and 5-years survival rate is only of 36% according to clinical staging [1][2]. When dealing with stage IIIA(N2), occult distant micrometastatic disease should always be suspected giving the rational for a combined multimodality approach which is the gold standard for LA tumors, since the addiction of systemic treatment to radiotherapy or surgery allows a better local and systemic control. These considerations emphasize the need for discussing every case within a multidisciplinary tumor board in which oncologist, surgeon, radiation oncologist and radiologist (at least) agree on diagnostic and therapeutic approach in order to optimize the treatment options and give the patient the best chance of cure and survival.

To date, there are still some controversies regarding the role of surgery in stage IIIA(N2) NSCLC [3][4][5], whether patients considered eligible for resection should be restaged surgically to determine operability [3][4][6][7] and whether induction regimens should include radiation therapy (RT). Although no widely agreed-upon definition of resectability exists [8][9], patients with non-bulky (defined as less than 3 cm), discrete, or single-level N2 involvement may be the best candidates to undergo resection as part of a multimodality approach. Resectable stage IIIA patients have been the subject of a number of clinical trials and retrospective analysis. Most of the published studies have some limitations due to their retrospective nature, lack of exact pretreatment staging, and the involvement of heterogeneous populations.

Given the fundamental role of surgery in managing these tumors, this review aims to discuss the main controversial points regarding the treatment of resectable stage IIIA(N2) NSCLC by searching in Literature to assess the state-of-the-art of treatment, along with new evidences and advances.

2. Local Control: Surgery or Radiotherapy?

The use of chemotherapy or chemoradiotherapy (CR) plus surgery should be suggested in two different subsets of stage IIIA NSCLC patients. The first subset involves patients with low tumor burden of N2 disease, considered resectable at diagnosis; in these cases, the aim of systemic therapy is to optimize distant disease control, allowing better patient tolerance and compliance. The second subset includes patients with advanced local tumors initially not amenable of surgical resection, for whom definitive CR (dCR) is the standard of care. In these cases, it is notable that by resecting the residual disease, some of these patients could be rendered disease free. The central role of chemotherapy in the setting of a multimodality therapy has been well established: Radiation Therapy Oncology Group (RTOG) 8808 study compared CR vs radiation alone in patients with stage IIIA NSCLC not amenable for surgery, a significant improvement in median survival was found with CR [10]. Moreover, two phase II trials comparing chemotherapy plus surgery to surgery alone found a similar significant improvement in median survival with chemotherapy [11][12]. In the last years, clinicians' attention has shifted to the role of surgery following neoadjuvant therapy, since no published study has established the superiority of this approach over dCR, yet and the main concern is the potential for increase surgical morbidity and mortality [13]. Definitive concurrent CR is the standard treatment, as shown in a metanalysis by Auperin et al. [14]; by comparing six randomized trials about outcomes of concomitant over sequential dCR in patients with locally advanced NSCLC, concomitant combination increases 3-years overall survival (OS) of a 5.7% and 5-years OS of a 4.5%.

One of the limits of dCR is the high rate of local recurrence ranging between 20% and 50% [15]. A study by Caglar et al. [16] in stage IIIA-IIIB patients found out that local recurrence rates for patients who received CR plus surgery or dCR were 50% vs 7%. When examining how outcomes had changed when the dose of radiation was increased, they found no difference, although some retrospective analysis [17][18] have shown increased rates of OS for higher radiation doses, even beyond 80 Gy.

These high local recurrence rates have proved to be significantly lower when surgical resection was added after neoadjuvant therapy [5][19][20]. The role of surgical resection in the management of stage IIIA patients after induction therapy is subject of intense debate. To date, only few randomized trials comparing surgery versus radiotherapy after neoadjuvant chemotherapy have been conducted [5][20][21][22], and their results have been widely discussed in two recent meta-analyses [23][24]. None of them showed any improvement in 2- and 4-years OS; moreover, when radiotherapy was added to the neoadjuvant treatment [5][21] only 3-years progression free survival (PFS) significantly increased. Interestingly, median survival and 5-years OS rates increased over the years, starting from 19.4 vs 17.4 months in the earliest published study [22] to 49.4 vs 34.6 months in the latest [21]. These results can be explained looking at the different improvements achieved over the last years both in the surgical and radiation oncology fields. As previously described, modern radiation techniques allow a more precise targeting and higher radiation dosage in conjunction with chemotherapy, thereby avoiding irradiation to the adjacent structures as lung, esophagus, heart, and spinal cord and reducing radiation-related adverse events.

On the other hand, clinicians have started performing a better patient selection for resection procedures, by implementing preoperative studies and performing pneumonectomies only in highly selected patients [25]. It is well known, indeed, that particularly right pneumonectomy is affected by high mortality and morbidity rates [5]. Moreover, performing sleeve lobectomy can potentially reduce the surgical mortality among patients who would otherwise have required a pneumonectomy [26]. Additionally, the importance of the mediastinal clearance has been elucidated: tumors responding to neoadjuvant chemotherapy achieving a complete mediastinal response, may behave more like as de novo stage I or II disease and reflect favorable systemic chemosensitivity [27][28][29]. Factors associated with a better prognosis in patients who undergo surgery are: confirmation of a complete response of the mediastinal disease (pN0), achieving a complete resection, and confirmation of a complete pathological response.

Moreover, to achieve the best outcome, it is important to respect the perfect timing between the induction therapy and surgery which should be up to 6–8 weeks from the end of the induction treatment [30].

The most recent studies about this topic are retrospective analyses [31][32][33]. Aggarwal et al. [31] compared surgical treatment and dCR: lobectomy conferred a survival benefit over dCR alone (39 vs 22 months, $p = 0.038$) while pneumonectomy did not (28 vs 22 months, $p = 0.534$). Darling et al. [32] also found significant differences in median survival when comparing induction chemoradiation (iCR) plus surgery and dCR (50.4 vs 20.4 months) and higher rates of loco-regional recurrence for dCR approach (33.7% vs 51.4%). Haque et al. [34] performed a large analysis on 28,379 patients to evaluate short-term mortality following trimodality vs bimodality approaches and found a 30-day mortality rate higher in the trimodality cohort (3.4% vs 0.8%); when analyzing data per surgical technique, only pneumonectomies experienced higher 30-day mortality rates, while the lobectomies reported similar rates to those of the bimodality group.

Moreover, they also compared post-treatment mortality between patients treated with dCR and those receiving iCR plus S using a video-assisted thoracoscopic surgery (VATS) approach; no significant difference in either 30- and 90-days mortality was found.

All these results suggest a potential role of trimodality approach in the treatment of certain LA NSCLC. More randomized trials are needed to explore the technical advances achieved in the last years. Moreover, the right patient selection for one specific treatment plan is peculiar in order to guarantee the best outcome; indeed, it has been already elsewhere proposed that patients requiring pneumonectomy may proportionally benefit more from up-front surgery followed by adjuvant CR than from neoadjuvant therapy [21][34]. New clinical trials should take account also for this selection criterion.

3. The Perfect Timing: Neoadjuvant or Adjuvant Chemotherapy?

The role of chemotherapy has been well established, and a large number of trials reported a good impact on survival in the perioperative setting, both neoadjuvant or postoperative delivery.

Few retrospective studies and no phase III study have been published about a direct comparison of outcomes of induction versus adjuvant chemotherapy delivery in stage IIIA(N2) patients and the proper timing still remains an unsolved question [35][36]. Although not direct comparison, the available systematic reviews and metanalyses reported an average 5-year survival rate of 24% for patients treated with induction therapy and 36% for those treated with adjuvant therapy [37]. Lim et al. [38] published a meta-analysis to perform an indirect comparison of the impact of preoperative vs postoperative chemotherapy in patients with operable lung cancer. They included 32 trials (22 with postoperative and 10 with peri- or preoperative chemotherapy) comprising patients with stage IA-IV NSCLC. Overall results showed no differences in OS (hazard ratio (HR) 0.80 vs 0.81) and disease-free survival (DFS) (HR 0.80 vs 0.76); this result was confirmed also when considering only stage IIIA(N2) patients. A similar analysis was performed by Berghmans et al. [35]: when comparing induction versus adjuvant therapy in addiction to standard surgical procedure, they found no statistical differences in OS for stage III patients (HR 0.65 vs 0.85). They also found that fully planned neoadjuvant chemotherapy could be administered in 71 to 100% of patients, while adjuvant chemotherapy only could be in 23.5 to 85.2%. This is important and shines a light on considering the performance of the patient at the time of diagnosis to decide the better timing of chemotherapy delivery. Previous studies have shown that pulmonary function and quality of life are at their lowest levels 4 weeks after surgery, which is exactly the time when adjuvant chemotherapy should be delivered. While young and fit patients would be able to start adjuvant treatment, older patients could not, and they would better tolerate neoadjuvant treatments.

Koshy et al. [39] published one of the largest cohorts of 11,242 stage IIIA(N2) NSCLC patients who underwent five different treatment strategies from 1998 to 2004, including iCR plus lobectomy or pneumonectomy, lobectomy or pneumonectomy plus adjuvant therapy and dCR. Among patients who underwent surgical resection, 90-day mortality was higher in the adjuvant groups (2.46% and 1.97% vs 1.6% and 0% for pneumonectomies and lobectomies respectively). The 5-years survival rates were 33.5% and 20.8%, for iCR plus lobectomy or pneumonectomy, 20.3% and 13.4% for lobectomy or pneumonectomy plus adjuvant therapy, and 10.9% and for dCR, respectively. This work, however, is biased by the pretreatment selection of patients; those with better prognostic factors and improved performance status were more likely selected to undergo neoadjuvant chemoradiation followed by surgery. However, even when this analysis was adjusted for comorbidities, the relationship between treatment and survival remained unaltered.

Boffa et al. [40] published the results of a retrospective analysis on 2,005 clinical stage III NSCLC patients who underwent surgical resection plus adjuvant or neoadjuvant treatment. A simple unadjusted survival analysis showed that preoperative and postoperative chemotherapy did not significantly impact on 5-years OS (47% vs 42%, p = 0.15), while preoperative CR was associated with better survival than postoperative CR (44% vs 32%, p < 0.001). These results may be affected by some biases which have to be considered; this analysis in fact, included clinical stage III patients, but only 32% of treated patients were confirmed to have pathologic N2 disease, leading to the presence of significant overstaging both in the preoperative and postoperative cohorts. Moreover, to adjust for potential confounders, a multivariate analysis failed to demonstrate a survival difference between preoperative and postoperative chemotherapy, with or without radiation.

4. Induction Therapy: Should Radiotherapy Be Included?

The majority of randomized controlled trials and meta-analyses have proven that neoadjuvant or adjuvant therapy improves survival compared with surgery alone [41][42][43][44]. Induction therapy has several advantages: it allows pathological downstaging (which is the best prognostic factor related to overall survival), it enables better local control facilitating radical surgery by decreasing the tumor volume, it may eradicate clinically undetected micrometastatic disease and it is better tolerated compared to adjuvant chemotherapy with higher full dose and cycles administration [45][46][47]. The

main limit is the risk of disease progression during treatment losing the possibility of surgery. Although the role of induction chemotherapy (iC) is well established, the use of induction chemoradiation (iCR) remains controversial, since it allows better locoregional control rates and nodal downstaging, but not always leading to subsequent survival benefits with 5-year survival rates ranging from 21 to 41% [48][49][50][51][52][53]. Moreover, the most effective timing of combining the three therapeutic modalities remains unclear and one main concern is the potential toxicity, often related to higher rates of surgical complications [54]. In the 1990s, many phase II studies have been performed comparing iC and iCR outcomes of patients with stage III NSCLC, demonstrating higher pathologic complete response (pCR) rates after iCR compared to iC (26–79% vs 17–53%), even if it did not translate in overall survival (OS) benefit (27–40% vs 23–56%) [55]. In the last 20 years, only few randomized trials have been performed comparing outcomes after neoadjuvant chemotherapy or chemoradiotherapy in stage IIIA(N2) NSCLC, all with same limitations including the small sample sizes and the diculty to enroll only stage IIIA(N2) patients (Table 2). Interestingly, when comparing response rates, according to the WHO and Response Evaluation Criteria in Solid Tumors (RECIST) criteria [56][57], the dierence was significant, in favor of the iCR in almost all cases. Moreover, like previous published findings, these recent studies confirm the trend for iCR to increase resectability rates and to decrease recurrence rate, even if these dierences have not proven to be statistically significant. Despite that, none of the analyzed studies showed a statistically significant dierence in OS and progression free survival (PFS) when comparing the two induction approaches. Krantz et al. [58] found that RT was associated with more than double of mortality rate at 30 and 90 days, confirming the high toxicity and proinflammatory eect of radiotherapy. Indeed, it can lead to radiation-induced pneumonitis and pulmonary fibrosis, which may delay surgical resection or interfere with the administration of preoperative chemotherapy [59]. Postoperative survival and OS could also be aected by several variables, including the type of surgery performed. In the series published by Albain et al. [60], in fact, mortality rates after iCR were 26% vs 1% when either pneumonectomy or lobectomy were performed. Thomas et al. [51] reported a postoperative mortality rate of 14% vs 6% after pneumonectomy following iCR or iC alone. In the analyzed series of patients (Table 1), perioperative mortality ranged from 0% to 6%; comparing these data to those from previous published studies (ranging from 4% to 9%), they are significantly lower maybe due to surgical and anesthesiological improvements and changed therapy patterns over time [61][62][63][64]. Additionally, radiation dose and modality matter. A study by Seder et al. [63] showed no dierence in complications when patients received either 44 Gy or 60 Gy in the neoadjuvant setting. This could be interesting considering that response rate can also be related to the radiation dose; better response rates, in fact, they are typically related to higher radiation doses (>45 Gy) and hyperfractionated accelerated RT; it seems that classical fractionated RT with a total dose of 45 Gy is suboptimal in achieving local control [64][65][66][67]. In a recent study by Sher et al. [65], pathological and surgical outcomes in patients with stage IIIA NSCLC treated with dierential doses of iCR (high-dose, 55–74 Gy; low-dose, 36–44 Gy; standard-dose 45–54 Gy) were compared. They found that patients treated with standard-dose RT, experienced significantly prolonged survival in comparison with those treated with lower or higher doses (p = 0.0089) and they were less likely to have a prolonged hospital stay. On the other hand, patients who received high-dose RT experienced the lowest probability of residual lymph-nodes disease. Additionally, hyperfractionated-accelerated RT may shorten the interval between iCR and surgery, given the reduced risk of pulmonary fibrosis [67]. Recently, results from the NRG Oncology RTOG 0617 trial demonstrated that, when associated to preoperative chemotherapy, delivery of preoperative intensity-modulated RT (IMRT) instead of three-dimensional RT (3DCRT) may boost radiation coverage of tumors by reducing normal tissues exposition leading to reduced morbidity and mortality [68]. Park et al. [69] retrospectively analyzed data about stage IIIA patients who underwent iCR followed by surgery. When performing the multivariate analysis, they found out that downstaging to pN0-1 together with age <60 years at the time of the diagnosis were independent prognostic factors for OS. Similar findings were reported by Krantz et al. [70]; their multivariate analysis, in fact, revealed older age (>65 years), male sex, comorbidity index >2 as significant risk factors for mortality. One of the main indications for iCR is the treatment of superior sulcus tumors, as indicated by guidelines, [71]since the control of local tumor regression is the key to achieve complete resection. It has been proved, in fact, that after iCR, these tumors register high rates of complete resection and OS [72][73]. Taking into account all these parameters, it can be stated that in highly selected patients with good performance status, young age and LA disease requiring volume reduction to achieve complete resection, combined neoadjuvant chemoradiotherapy oers better outcomes in terms of pathological downstaging, even if it oers no significant improvement in terms of overall survival when compared with bimodality treatment.

5. Adjuvant Therapy: Should Radiation Be Included?

Completely resected IIIA(N2) stage patients have OS rates ranging from 7 to 34% and even after adjuvant chemotherapy, locoregional recurrence can be as high as 40%, independently correlating with worse OS. Several randomized trials have extensively discussed and confirmed the benefit of postoperative chemotherapy (POCT) in the subset of IIIA(N2) stage patients and it still is considered the standard of care [74][75][76]. Adding to POCT the postoperative radiotherapy (PORT) to improve locoregional control for patients with advanced NSCLC has been the subject of debate for many years, since its

eect on survival has not been yet defined. Since the late 1990s many randomized trials have been conducted to prove the ecacy of PORT, until the PORT meta-analysis Trialists Group published a meta-analysis of nine randomized trials demonstrating that, when compared to surgery alone, PORT added a 21% of risk of death [77]. Although PORT detrimental eect was higher for N0 and N1 diseases, its use for N2 disease remained discretionary and it drastically felt down being applied to less than one third of the population. However, all the studies included in the PORT meta-analysis are nowadays obsolete since old data and techniques, non-standard treatment schedules and outmoded equipment as two-dimensional RT or cobalt-based RT and imprecise dosimetry were employed [78]. The Adjuvant Navelbine International Trialist Association (ANITA) trial, the results of which were published in 2008, suggested a potential benefit in median survival in patient with stage I-IIIA NSCLC when PORT was added both to the chemotherapy (47.4 vs 23.8 months) or to the observation arm (22.7 vs 12.7 months) [128]. This study, however, has several limitations: in the ANITA trial the decision to perform PORT was not randomized and its delivery was not homogeneous in the dierent centers. In the Surveillance, Epidemiology, and End Results (SEER) trial, instead, no details about radiotherapy and chemotherapy delivery were given. Both studies are now obsolete because of their treatment protocols and techniques. Similar results were described by Lally et al. [79] by using data from the Surveillance, Epidemiology and End Results (SEER) database about stage III patients; they observed a significant dierence in 5-years OS in favor of the PORT group (27 vs 20%, p = 0.008); however, the SEER database did not add any information about the delivery of POCT.

In this review we looked at published evidence about the feasibility and the potential advantages of postoperative chemo-radiotherapy (POCRT) when compared to POCT alone. Studies reporting the outcomes of completely resected pN2 patients treated with POCRT or POCT alone over the last 20 years are outlined in Table 3. The main limit of these studies is their retrospective nature. Median survival rates range from 28 to 45.6 months for POCT and from 34 to 53.1 months for POCRT. Five-years survival rates range from 22.2 to 41.0% and from 30.5 to 57.5%. DFS ranging from 9.3 to 18.8% and from 14.4 to 30.3%. When comparing POCT vs POCRT rates, most of them were significantly dierent, confirming the potential advantage of adding the RT to the postoperative treatment. Interestingly, almost all studies which reported local relapse or local recurrence-free survival confirmed the leading role of RT in preventing local failures.

One of the main concerns about PORT is the high rate of toxicity-related disease. As a consequence of PORT, pneumonitis may occur in 1–28% of patients, as well as alterations in pulmonary function, decrease in di usion capacity and FEV1, cardiac diseases, and esophagitis [80]. Methodological advances, as well as the use of linear accelerators and 3D-CRT, tried to limit the excess of toxic deaths, and modern PORT seems to confer an OS advantage in the treatment of N2 disease. Kepka et al. [81] conducted a prospective study comparing patients treated with PORT delivered with 3D-CRT systems and patients who did not receive PORT; they found out that the PORT group did not result in an increase of cardiopulmonary morbidity or in decrease of quality of life. Moreover, radiation doses can make the di erence in toxicity; some studies demonstrated that patient receiving standard doses of PORT (45–54 Gy) after margin-negative resection, had higher survival rates than those receiving excessive doses. This highlights the importance of the preoperative and multidisciplinary evaluation of the patient, to identify the better therapeutic window in delivering PORT (patient characteristics and comorbidities, doses, techniques, and timing).

Current research aims to identify and stratify high risk patients who could benefit from PORT. Wang et al. [82], in a recent retrospective analysis on 3377 stage IIIA(N2) patients from the SEER database, compared outcomes of those treated with PORT associated or not to POCT. In a subset analysis of patients classified by the number of positive lymph nodes (n < 3 and n > 3), they found that the use of PORT significantly improves survival in patients with > 3 lymph nodes, while no benefit in survival was registered in patients with < 3 positive lymph nodes. Another recent study by Yuan et al. compared stage IIIA(N2) patients treated with or without PORT, demonstrating that PORT could improve OS in single N2 station involved patients (65.7% vs 54.1%, p = 0.04), but not the well known that patients with pathologic single station N2 diseases are those who could get more benefit in survival from upfront surgery followed by adjuvant therapy . Moreover, Zhang et al. [83] recently tried to establish whether the type of lymph node metastasis (skip or non-skip) could be predictive for prognosis in stage IIIA NSCLC treated with POCT with or without radiation. Although not significant, a trend toward improved PFS, OS and distant recurrence free survival was found in both skip and non-skip metastasis when PORT was added even if this trend was more evident in the skip metastases group. Similar findings were reported by Zou et al. who found that the absence of N1 nodal involvement (skip metastases) was a good prognostic factor for both OS and DFS. Another recent study [84] evaluated the safety and e cacy of PORT plus POCT after pneumonectomy for 119 patients with stage IIIA(N2) NSCLC, demonstrating that PORT is feasible and safe in this subset. When comparing the PORT with the non-PORT group, the median OS and DFS significantly improved in the first subset of patients, as well as locoregional failure significantly decreased in PORT group; moreover, no treatment-related complication was registered.

Another concern is that, given the lack of a consensus on the definition of the proper extent of clinical target volume (CTV), significant heterogeneity still a ects all reported studies. Generally, PORT CTV includes stump, ipsilateral hilum, the initially involved lymph nodes and subcarinal lymph nodes. On margin negative patients, PORT target volume is mainly delineated at lymph node drainage area, mostly mediastinum. Several studies have tried to investigate the locoregional patterns of recurrence after surgery to plan the optimal tailored PORT CTV; it seems, in fact, that this pattern varies depending on the location of the primary tumor [85][86][87] As result, CTV should always include the bronchial stump, the ipsilateral hilum and positive lymph nodes; station 4 and 7 should always be included due to their high incidence of relapse. Moreover, right-sided tumors generally recur unilaterally at the ipsilateral superior mediastinal nodes while left-sided lung cancers recur more frequently in the bilateral superior mediastinal nodes [85][86][87][88]. Given the advantages linked both to PORT and POCT, their optimal sequencing after surgery has been not extensively discussed and POCT-first strategy has always been first adopted even if some evidences suggest that the correct timing may play a role in survival. Lee et al. [89] published the first retrospective study on 105 patients receiving PORT-first therapy, starting from four to six weeks after surgical resection and subsequent POCT starting three to four weeks after the completion of PORT. When comparing PORT plus POCT and POCT alone, they found higher rates of 5-years OS and DFS when PORT was added (61.3% vs 29.2%, p < 0.001; 49.6% vs 30.5%, p = 0.0049). These rates are comparable to those of retrospective reports of stage IIIA(N2) patients treated with PORT. However, Lee et al. speculated that an appropriate sequence of the postoperative therapy could maximize the therapeutic eects; delaying PORT may aect the locoregional control, while PORT-first strategy can minimize the overall delay since treatment time of PORT (5–6 weeks) is shorter than that of POCT (12–16 weeks). Sura et al. [90] recently performed a retrospective analysis to determine whether the timing between postoperative chemotherapy and radiotherapy could aect outcomes. Then, 1629 patients were divided in two groups on the basis of PORT delivery time after surgery: early time to radiation (<8 weeks) and late time to radiation (>8 weeks). After propensity score analysis, median survival time was longer in the late group (48.3 vs 38.1 months, p = 0.006) and when analyzing whether to add concurrent or sequential POCT, results suggested that sequential chemotherapy with a late delivery of PORT led to better survival compared with concurrent POCT and/or sequential POCT with early PORT. This could be explained by the positive role of postoperative therapy delay; it may allow, in fact, a decrease in rates of toxicity and a longer time for postoperative healing.

6. Induction/Adjuvant Therapy: Looking at the Target-Therapy

Adjuvant chemotherapy has indisputable advantages on IIIA(N2) NSCLC, while bringing along high rates of treatment-related toxicity which may delay or force treatment discontinuation. From the necessity to improve patients' compliance to therapies, great attention has been given in the last years to alternative therapies with better tolerability. Overall, 10% of patients with NSCLC in the United States and 35% in Asia have tumor-associated epidermal growth factor receptors (EGFR) mutations, which are predictive of response to EGFR-tyrosine kinase inhibitors (TKIs) [91]. EGFR-TKIs as first-line treatment have proved to significantly improve OS and DFS compared to chemotherapy in LA EGFR mutation-positive NSCLC [92][93][94][95][96], particularly in patients who are never-smokers, female, or present with adenocarcinoma histology with lepidic growth pattern [97][98][99]. Checkpoint inhibitors work by aecting the interactions between the immune system and the tumor. Because curative treatments remove or ablate the macroscopic tumor, timing of immunotherapy around curative treatment may influence its efficacy.

Since 2007, many retrospective and case reports have hypothesized that neoadjuvant EGFR-TKI therapy could result in N2 downstaging and better survival rates in stage IIIA patients, although they provided short follow-up terms and no definitive answer [100][101][102][103]. The available studies, support erlotinib as the best option for neoadjuvant therapy in this subset of patients, while currently no data support the use of second- or third-generation EGFR TKIs. The trial performed by Zhong et al. [104] analyzed 24 IIIA(N2) patients assigned either to the iC or the EGFR-TKI neoadjuvant arm. They found a significant better trend in the response rate (25% vs 58.1%; p = 0.18) favoring erlotinib, while median OS (57.3 vs 25.5 months, p = 0.162) and median PFS (28.9 vs 8.6 months; p = 0.018) were significantly higher for the iC group. As previous studies suggested, also in this case, the most common failure pattern in the erlotinib arm was distant metastasis which could be explained by a rebound effect after discontinuing TKI therapy before surgery [105]. This may promote potential residual circulating tumor cells acceleration, thus resulting in more aggressive disease, which imply that a possible better strategy could be the addition of TKI treatment to neoadjuvant chemotherapy and eventually prolonging it in adjuvant setting [106][107].

A recent phase II trial conducted by Xiong et al. [108] evaluated ecacy of erlotinib as neoadjuvant therapy in patients with resectable IIIA(N2) EGFR mutation-positive NSCLC. Although, in the small cohort of patients analyzed they found that erlotinib improved the likelihood for surgery, associated with good resection rates and favorable tolerability without life-

threatening toxicities when compared with iC. The recent EMERGING-CTONG 1103 randomized phase II trial analyzed outcomes of 72 resectable stage IIIA(N2) patients undergoing either neoadjuvant erlotinib or gemcitabine plus cisplatin. Median PFS was significantly longer in the erlotinib arm vs iC (21.5 vs 11.4 months, p < 0.001).

Response rate (54.1% vs 34.3%), complete resection (73% vs 63%), and nodal downstaging (10.8% vs 2.9%) did not dier significantly; however, a better trend towards improved outcomes was registered in the erlotinib arm. The hypothesis to use EGFR-TKI in the adjuvant setting has been investigated in the last 20 years, even if the first results fromtheSWOGS0023 trial [109] and BR16 study [110] in which either unresectable stage III patients or IB-IIIA NSCLC patients received adjuvant gefitinib compared to placebo, did not show any improvement in OS or disease-free survival. Over the years, other trials [111][112] and retrospective studies [113][114] have analyzed the role of EGFR-TKIs in the adjuvant setting for early-stage NSCLC patients, and their positive results in terms of survival and clinical benefits have inspired further researches in the subset of LA NSCLC.

The prospective phase II trial conducted by Li et al. [115] has been the first examining the efficacy and safety of adding EGFR-TKI as adjuvant therapy to pemetrexed-cisplatin in IIIA(N2) NSCLC patients. When comparing adjuvant C followed by gefitinib and adjuvant C alone, they found DFS (39.8 vs 27.9 months, p = 0.014) and 2-years overall survival (92.4% vs 77.4%, p = 0.07) to be significantly longer in the gefitinib group. One of the main concerns about this therapy is the best scheduling of the EGFR-TKI relative to chemotherapy. In this study, in fact, gefitinib was delivered for 6 months immediately after chemotherapy and upon disease recurrence, eight patients received further gefitinib, achieving a good postrecurrence response rate. This may lead to review the schedule of the gefitinib, as 6 months after chemotherapy could not be enough. The recent EVAN trial [148] focused on 102 IIIA (N2) EGFR mutation-positive patients treated either with adjuvant 4 cycles of vinorelbine or 2 years of erlotinib. The results showed that 3-year disease-free survival (54.2% vs 19.8%; p = 0.046) and OS (51% vs 20%, p < 0.001) were significantly longer for the EGFR-TKI group. Moreover, when stratifying patients for their characteristics, they found that there was a dierence in survival and, consequently, a higher response rate to erlotinib, when patients were non-smokers, when they had EGFR mutation type exon 19 and adenocarcinomas. Moreover, the prolonged use of the erlotinib for two years did not lead to higher grades of adverse eects and toxicity in comparison of chemotherapy.

7. Neoadjuvant Immune Checkpoint Inhibitors: An Area of Active Research

The last years have seen a great exploit of the immune checkpoint inhibitors (ICI) and their use could potentially revolutionize lung cancer treatment, being highly selective, safe, and well tolerated. Immunotherapy drugs targeting the programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) block the cancer-derived inhibitory signal on eector T-cells and remove residual cancer cells. The rationale for using these therapies before surgical resection is to release neoantigens from dying tumor cells while stimulating the expansion of neoantigen-specific T-cells, producing a stronger tumor-specific CD8+ T-cell response. The activity of neoadjuvant immunotherapy activity is substantially measured on major pathological response (MPR) as defined as a proportion of cancer cells in the resected tumors and lymph nodes below 10%. Forde et al. [116], in fact, have been among the firsts to test the use of nivolumab in the neoadjuvant setting for patients with stages I, II, and IIIA NSCLC. Their protocol included the delivery of two doses of nivolumab every two weeks and the surgery to be performed approximately 4 weeks after the first dose. Of the 22 patients enrolled, 23% suered adverse events and only in one case it was of grade 3; 80% of patients survived after the first 12 months and 45% and 15% of all tumors showed a major or complete pathological response respectively. In no case the neoadjuvant therapy led to a delay in the planned surgery. Similar findings are those described by Bott et al. [117] who analyzed results on 22 patients with stage IB-IIIA NSCLC treated with the same neoadjuvant protocol as the one described previously. The pathological analysis after surgical resection showed that the major pathological response reached 45% and 10% experienced complete pathological remission. Preliminary data from ongoing Phase II trials confirm these results [118]. Moreover, to boost their effect, some trials have associated the ICIs with chemotherapy or to a second ICI. The experience from the ongoing NEOSTAR trial, [119] in fact, compared the e cacy of nivolumab monotherapy with nivolumab plus ipilimumab dual therapy; their results show an MPR of 17% vs 33% in favor of the dual therapy. Recently, Shu et al. [120] described a trial to test the activity of the PD-L1 inhibitor atezolizumab together with platin-based chemotherapy in the neoadjuvant setting for resectable stage IB-IIIA NSCLC. Their protocol included the delivery of atezolizumab on days 1, 8 and 15 and carboplatin on day 1 of each 21-day cycle for four cycles before performing surgery. On 30 selected patients, 77% had a stage IIIA NSCLC at presentation; 57% and 33% had a major and complete pathological response, respectively. Pathological responses were observed regardless of tumor PD-L1 expression, while histological type and genetic mutations were found to be predictive of the response. Squamous cell carcinoma proved to better response to these therapies than adenocarcinomas; moreover, patients with STK11 tumor mutations did not have significant radiographic or pathological responses.

Overall, neoadjuvant immunotherapy can induce significant pathological remissions, and it has the potential for continued anti-tumor immunity. Although these promising results prove the safety and effectiveness of neoadjuvant immunotherapy, larger studies are needed to determine its best planning in terms of duration and dose. Current studies demonstrate that choosing one or another immunotherapy drug is of paramount importance, since different drugs may lead to significant difference in the MPR rates, as well as the protocol used, the timing before surgery and the association with chemotherapy regimens. Moreover, although high PD-L1 expression seems to be linked to better responses to ICIs, also PD-L1 negative patients may respond; for this reason, assessing expression in patients can contribute only minimally to clinical decision-making about suitability for treatment.

One possible explanation could be the lack of standardization in testing methods with regard to antibodies used, cutoffs/thresholds for a given antibody, and differences in scoring algorithm and test sites. Finally, no trial has yet focused specifically on IIIA-N2 stage NSCLC and no shared indication for choosing the right patients who could benefit the most of these therapies has been proposed yet.

References

1. Goldstraw, P.; Crowley, J.; Chansky, K.; Giroux, D.J.; Groome, P.A.; Rami-Porta, R.; Postmus, P.E.; Rusch, V.; Sobin, L. International Association for the Study of Lung Cancer International Staging Committee, Participating Institutions. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J. Thorac. Oncol. 2007, 2, 706–714, doi:10.1097/JTO.0b013e31812f3c1a.

2. Groome, P.A.; Bolejack, V.; Crowley, J.J.; Kennedy, C.; Krasnik, M.; Sobin, L.H.; Goldstraw, P. IASLC International Staging Committee, Cancer Research and Biostatistics, Observers to the Committee, Participating Institutions (2007). The IASLC Lung Cancer Staging Project: Validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J. Thorac. Oncol. 2007, 2, 694–705, doi:10.1097/JTO.0b013e31812d05d5.

3. Ettinger, D.S.; Akerley, W.; Bepler, G.; Blum, M.G.; Chang, A.; Cheney, R.T.; Chirieac, L.R.; D'Amico, T.A.; Demmy, T.L.; Ganti, A.K.; et al. NCCN Non-Small Cell Lung Cancer Panel Members. Non-small cell lung cancer. J. Natl. Compr. Cancer Netw. 2010, 8, 740–801, doi:10.6004/jnccn.2010.0056.

4. Atkins, B.Z.; D'Amico, T.A. Controversial issues regarding the use of induction chemotherapy for lung cancer. Semin. Thorac. Cardiovasc. Surg. 2005, 17, 191–194, doi:10.1053/j.semtcvs.2005.06.012.

5. Albain, K.S.; Swann, R.S.; Rusch, V.W.; Turrisi, A.T.; Shepherd, F.A.; Smith, C.; Chen, Y.; Livingston, R.B.; Feins, R.H.; Gandara, D.R.; et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. Lancet 2009, 374, 379–386, doi:10.1016/S0140-6736(09)60737-6.

6. Betticher, D.C.; Hsu Schmitz, S.F.; Tötsch, M.; Hansen, E.; Joss, C.; von Briel, C.; Schmid, R.A.; Pless, M.; Habicht, J.; Roth, A.D.; et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: A multicenter phase II trial. J. Clin. Oncol. 2003, 21, 1752–1759, doi:10.1200/JCO.2003.11.040.

7. Voltolini, L.; Luzzi, L.; Ghiribelli, C.; Paladini, P.; Di Bisceglie, M.; Gotti, G. Results of induction chemotherapy followed by surgical resection in patients with stage IIIA (N2) non-small cell lung cancer: The importance of the nodal down-staging after chemotherapy. Eur. J. Cardiothorac. Surg. 2001, 20, 1106–1112, doi:10.1016/s1010-7940(01)00984-8.

8. De Leyn, P.; Dooms, C.; Kuzdzal, J.; Lardinois, D.; Passlick, B.; Rami-Porta, R.; Turna, A.; Van Schil, P.; Venuta, F.; Waller, D.; et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur. J. Cardiothorac. Surg. 2014, 45, 787–798, doi:10.1093/ejcts/ezu028.

9. Ettinger, D.S.; Aisner, D.L.; Wood, D.E.; Akerley, W.; Bauman, J.; Chang, J.Y.; Chirieac, L.R.; D'Amico, T.A.; Dilling, T.J.; Dobelbower, M.; et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 5. J. Natl. Compr. Cancer Netw. 2018, 16, 807–821, doi:10.6004/jnccn.2018.0062.

10. Sause, W.; Kolesar, P.; Taylor, S., IV; Johnson, D.; Livingston, R.; Komaki, R.; Emami, B.; Curran, W., Jr.; Byhardt, R.; Rashid, D.A.; et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 2000, 117, 358–364., doi:10.1378/chest.117.2.358.

11. Rosell, R.; Gómez-Codina, J.; Camps, C.; Maestre, J.; Padille, J.; Cantó, A.; Mate, J.L.; Li, S.; Roig, J.; Olazábal, A. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N. Engl. J. Med. 1994, 330, 153–158, doi:10.1056/NEJM199401203300301.

12. Roth, J.A.; Fossella, F.; Komaki, R.; Ryan, M.B.; Putnam, J.B.; Lee, J.S.; Dhingra, H.; De Caro, L.; Chasen, M.; McGavran, M. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J. Natl. Cancer Inst. 1994, 86, 673–680, doi:10.1093/jnci/86.9.673.

13. Jeremic, B.; Casas, F.; Dubinsky, P.; Gomez-Caamano, A.; Cihoric, N.; Videtic, G.; Latinovic, M. Combined modality therapy in Stage IIIA non-small cell lung cancer: Clarity or confusion despite the highest level of evidence? J. Radiat. Res. 2017, 58, 267–272, doi:10.1093/jrr/rrx003.

14. Aupérin, A.; Le Péchoux, C.; Rolland, E.; Curran, W.J.; Furuse, K.; Fournel, P.; Belderbos, J.; Clamon, G.; Ulutin, H.C.; Paulus, R.; et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J. Clin. Oncol. 2010, 28, 2181–2190, doi:10.1200/JCO.2009.26.2543.

15. Vokes, E.E.; Herndon, J.E.; Kelley, M.J.; Cicchetti, M.G.; Ramnath, N.; Neill, H.; Atkins, J.N.; Watson, D.M.; Akerley, W.; Green, M.R. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. J. Clin. Oncol. 2007, 25, 1698–1704, doi:10.1200/JCO.2006.07.3569.

16. Caglar, H.B.; Baldini, E.H.; Othus, M.; Rabin, M.S.; Bueno, R.; Sugarbaker, D.J.; Mentzer, S.J.; Jänne, P.A.; Johnson, B.E.; Allen, A.M. Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. Cancer 2009, 115, 4156–4166, doi:10.1002/cncr.24492.

17. Rengan, R.; Rosenzweig, K.E.; Venkatraman, E.; Koutcher, L.A.; Fox, J.L.; Nayak, R.; Amols, H.; Yorke, E.; Jackson, A.; Ling, C.C.; et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. 2004, 60, 741–747, doi:10.1016/j.ijrobp.2004.04.013.

18. Kong, F.M.; Ten Haken, R.K.; Schipper, M.J.; Sullivan, M.A.; Chen, M.; Lopez, C.; Kalemkerian, G.P.; Hayman, J.A. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: Long-term results of a radiation dose escalation study. Int. J. Radiat. Oncol. Biol. Phys. 2005, 63, 324–333, doi:10.1016/j.ijrobp.2005.02.010.

19. Govindan, R.; Bogart, J.; Stinchcombe, T.; Wang, X.; Hodgson, L.; Kratzke, R.; Garst, J.; Brotherton, T.; Vokes, E.E. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J. Clin. Oncol. 2011, 29, 3120–3125, doi:10.1200/JCO.2010.33.4979.

20. van Meerbeeck, J.P.; Kramer, G.W.; Van Schil, P.E.; Legrand, C.; Smit, E.F.; Schramel, F.; Tjan-Heijnen, V.C.; Biesma, B.; Debruyne, C.; van Zandwijk, N.; et al. 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, doi:10.1093/jnci/djk093.

21. Eberhardt, W.E.; Pöttgen, C.; Gauler, T.C.; Friedel, G.; Veit, S.; Heinrich, V.; Welter, S.; Budach, W.; Spengler, W.; Kimmich, M.; et al. 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, doi:10.1200/JCO.2015.62.6812.

22. Johnstone, D.W.; Byhardt, R.W.; Ettinger, D.; Scott, C.B. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group. Int. J. Radiat. Oncol. Biol. Phys. 2002, 54, 365–369, doi:10.1016/s0360-3016(02)02943-7.

23. Ren, Z.; Zhou, S.; Liu, Z.; Xu, S. Randomized controlled trials of induction treatment and surgery versus combined chemotherapy and radiotherapy in stages IIIA-N2 NSCLC: A systematic review and meta-analysis. J. Thorac Dis. 2015, 7, 1414–1422, doi:10.3978/j.issn.2072-1439.2015.08.14.

24. Pöttgen, C.; Eberhardt, W.; Stamatis, G.; Stuschke, M. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC)—A cumulative meta-analysis of the randomized evidence. Oncotarget 2017, 8, 41670–41678, doi:10.18632/oncotarget.16471.

25. Johnson, D.H.; Rusch, V.W.; Turrisi, A.T. Scalpels, beams, drugs, and dreams: Challenges of stage IIIA-N2 non-small-cell lung cancer. J. Natl. Cancer Inst. 2007, 99, 415–418, doi:10.1093/jnci/djk107.

26. Deslauriers, J.; Grégoire, J.; Jacques, L.F.; Piraux, M.; Guojin, L.; Lacasse, Y. Sleeve lobectomy versus pneumonectomy for lung cancer: A comparative analysis of survival and sites or recurrences. Ann. Thorac. Surg. 2004, 77, 1152–1156, doi:10.1016/j.athoracsur.2003.07.040.

27. Albain, K.S.; Crowley, J.J.; Turrisi, A.T.; Gandara, D.R.; Farrar, W.B.; Clark, J.I., Beasley, K.R.; Livingston, R.B. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group phase II study, SWOG 9019. J. Clin. Oncol. 2002, 20, 3454–3460, doi:10.1200/JCO.2002.03.055.

28. Turrisi, A.T.; Scott, C.B.; Rusch, V.R.; Albain, K.S.; Shepherd, F.A.; Smith, C.; Chen, Y.; Livingston, R.; Gandara, D.R.; Darling, G.; et al. Randomized trial of chemo-radiotherapy to 61 Gy (no S) versus chemoradiotherapy to 45 Gy followed by surgery (S) using cisplatin etoposide in stage IIIa non-small cell lung cancer (NSCLC): Intergroup Trial 0139, RTOG (9309). Int. J. Radiat. Oncol. Biol. Phys. 2003, 57, 125–126.

29. Sonett, J.R.; Suntharalingam, M.; Edelman, M.J.; Patel, A.B.; Gamliel, Z.; Doyle, A.; Hausner, P.; Krasna, M. Pulmonary resection after curative intent radiotherapy (59 Gy) and concurrent chemotherapy in nonsmall-cell lung cancer. Ann. Thorac. Surg. 2004, 78, 1200–1206.

30. D'Angelillo, R.M.; Trodella, L.; Ciresa, M.; Cellini, F.; Fiore, M.; Greco, C.; Pompeo, E.; Mineo, T.C.; Paleari, L.; Granone, P.; et al. Multimodality treatment of stage III non-small cell lung cancer: Analysis of a phase II trial using preoperative cisplatin and gemcitabine with concurrent radiotherapy. J. Thorac. Oncol. 2009, 4, 1517–1523, doi:10.1097/JTO.0b013e3181b9e860.

31. Aggarwal, C.; Li, L.; Borghaei, H.; Mehra, R.; Somaiah, N.; Turaka, A.; Langer, C.J.; Simon, G.R. Multidisciplinary therapy of stage IIIA non-small-cell lung cancer: Long-term outcome of chemoradiation with or without surgery. Cancer Control. 2014, 21, 57–62, doi:10.1177/107327481402100108.

32. Darling, G.E.; Li, F.; Patsios, D.; Massey, C.; Wallis, A.G.; Coate, L.; Keshavjee, S.; Pierre, A.; De Perrot, M.; Yasufuku, K.; et al. Neoadjuvant chemoradiation and surgery improves survival outcomes compared with definitive chemoradiation in the treatment of stage IIIA N2 non-small-cell lung cancer. Eur. J. Cardiothorac. Surg. 2015, 48, 684–690, doi:10.1093/ejcts/ezu504.

33. Vyfhuis, M.; Bhooshan, N.; Burrows, W.M.; Turner, M.; Suntharalingam, M.; Donahue, J.; Nichols, E.M.; Feliciano, J.; Bentzen, S.M.; Badiyan, S.; et al. Oncological outcomes from trimodality therapy receiving definitive doses of neoadjuvant chemoradiation (≥60 Gy) and factors influencing consideration for surgery in stage III non-small cell lung cancer. Adv. Radiat. Oncol. 2017, 2, 259–269, doi:10.1016/j.adro.2017.07.009.

34. Haque, W.; Verma, V.; Butler, E.B.; Teh, B.S. Pathologic nodal clearance and complete response following neoadjuvant chemoradiation for clinical N2 non-small cell lung cancer: Predictors and long-term outcomes. Lung Cancer 2019, 130, 93–100, doi:10.1016/j.lungcan.2019.02.003.

35. Berghmans, T.; Paesmans, M.; Meert, A.P.; Mascaux, C.; Lothaire, P.; Lafitte, J.J.; Sculier, J.P. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: Results of a meta-analysis of the literature. Lung Cancer 2005, 49, 13–23, doi:10.1016/j.lungcan.2005.01.002.

36. Burdett, S.; Stewart, L.A.; Rydzewska, L. A systematic review and metaanalysis of the literature: Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J. Thorac. Oncol. 2006, 1, 611–621.

37. Ramnath, N.; Dilling, T.J.; Harris, L.J.; Kim, A.W.; Michaud, G.C.; Balekian, A.A.; Diekemper, R.; Detterbeck, F.C.; Arenberg, D.A. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013, 143, e314S–e340S.

38. Lim, E.; Harris, G.; Patel, A.; Adachi, I.; Edmonds, L.; Song, F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: Systematic review and indirect comparison meta-analysis of randomized trials. J. Thorac. Oncol. 2009, 4, 1380–1388, doi:10.1097/JTO.0b013e3181.

39. Koshy, M.; Fedewa, S.A.; Malik, R.; Ferguson, M.K.; Vigneswaran, W.T.; Feldman, L.; Howard, A.; Abdelhady, K.; Weichselbaum, R.R.; Virgo, K.S. Improved survival associated with neoadjuvant chemoradiation in patients with clinical stage IIIA(N2) non-small-cell lung cancer. J. Thorac. Oncol. 2013, 8, 915–922, doi:10.1097/JTO.0b013e31828f68b4.

40. Boffa, D.J.; Hancock, J.G.; Yao, X.; Goldberg, S.; Rosen, J.E.; Kim, A.W.; Moreno, A.; Detterbeck, F.C. Now or later: Evaluating the importance of chemotherapy timing in resectable stage III (N2) lung cancer in the National Cancer Database. Ann. Thorac. Surg. 2015, 99, 200–208, doi:10.1016/j.athoracsur.2014.08.040.

41. Pass, H.I.; Pogrebniak, H.W.; Steinberg, S.M.; Mulshine, J.; Minna, J. Randomized trial of neoadjuvant therapy for lung cancer: Interim analysis. Ann. Thorac. Surg. 1992, 53, 992–998.

42. Depierre, A.; Milleron, B.; Moro-Sibilot, D.; Chevret, S.; Quoix, E.; Lebeau, B.; Braun, D.; Breton, J.L.; Lemarie, E.; Gouva, S.; et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J. Clin. Oncol. 2002, 20, 247–253, doi:10.1200/JCO.2002.20.1.247.

43. Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: Two meta-analyses of individual patient data. Lancet 2010, 375, 1267–1277.

44. 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.

45. Martin, J.; Ginsberg, R.J.; Venkatraman, E.S.; Bains, M.S.; Downey, R.J.; Korst, R.J.; Kris, M.G.; Rusch, V.W. Long-term results of combined-modality therapy in resectable non-small cell lung cancer. J. Clin. Oncol. 2002, 20, 1989–

1995.

46. Adelstein, D.J.; Rice, T.W.; Rybicki, L.A.; Greskovich, J.F.; Ciezki, J.P.; Carrol, M.A.; De Camp, M.M. Accelerated hyperfractionated radiation, concurrent paclitaxel/cisplatin chemotherapy and surgery for stage III non-small cell lung cancer. Lung Cancer 2002, 36, 167–174.

47. Bueno, R.; Richards, W.G.; Swanson, S.J.; Jaklitsch, M.T.; Lukanich, J.M.; Mentzer, S.J.; Sugarbaker, D.J. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Ann. Thorac. Surg. 2000, 70, 1826–1831.

48. Yang, C.F.; Gulack, B.C.; Gu, L.; Speicher, P.J.; Wang, X.; Harpole, D.H.; Onaitis, M.W.; D'Amico, T.A.; Berry, M.F.; Hartwig, M.G. Adding radiation to induction chemotherapy does not improve survival of patients with operable clinical N2 non-small cell lung cancer. J. Thorac. Cardiovasc. Surg. 2015, 150, 1484–1493, doi:10.1016/j.jtcvs.2015.06.062.

49. Ripley, R.T.; Rusch, V.W. Role of induction therapy: Surgical resection of non-small cell lung cancer after induction therapy. Thorac. Surg. Clin. 2013, 23, 273–285.

50. Katayama, H.; Ueoka, H.; Kiura, K.; Tabata, M.; Kozuki, T.; Tanimoto, M.; Fujiwara, T.; Tanaka, N.; Date, H.; Aoe, M.; et al. Preoperative concurrent chemoradiotherapy with cisplatin and docetaxel inpatients with locally advanced non-small-cell lung cancer. Br. J. Cancer 2004, 90, 979–984.

51. Ettinger, D.S.; Akerley, W.; Borghaei, H.; Chang, A.C.; Cheney, R.T.; Chirieac, L.R.; D'Amico, T.A.; Demmy, T.L.; Ganti, A.K.; Govindan, R.; et al. Non-small cell lung cancer. J. Natl. Compr. Cancer Netw. 2012, 10, 1236–1271.

52. Thomas, M.; Rube, C.; Hoffknecht, P.; Macha, H.N.; Freitag, L.; Linfer, A.; Willich, N.; Hamm, M.; Sybrecht, G.W.; Ukena, D.; et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: A randomised trial in stage III non-small-cell lung cancer. Lancet Oncol. 2008, 9, 636–648.

53. Shah, A.A.; Berry, M.F.; Tzao, C.; Gandhi, M.; Worni, M.; Pietrobon, R.; D'Amico, T.A. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. Ann. Thorac. Surg. 2012, 93, 1807–1812.

54. Stamatis, G.; Djuric, D.; Eberhardt, W.; Pöttken, C.; Zaboura, G.; Fechner, S.; Fujimoto, T. Postoperative morbidity and mortality after induction chemoradiotherapy for locally advanced lung cancer: An analysis of 350 operated patients. Eur. J. Cardiothorac. Surg. 2002, 22, 292–297, doi:10.1016/s1010-7940(02)00266-x.

55. Higgins, K.; Chino, J.P.; Marks, L.B.; Ready, N.; D'Amico, T.A.; Clough, R.W.; Kelsey, C.R. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. 2009, 75, 1462–1467, doi:10.1016/j.ijrobp.2009.01.069.

56. WHO. Handbook for Reporting Results of Cancer Treatment; World Health Organization offset Publication: Geneva, Switzerland, 1979; No. 48.

57. Nishino, M.; Jackman, D.M.; Hatabu, H.; Yeap, B.Y.; Cioffredi, L.A.; Yap, J.T.; Jänne, P.A.; Johnson, B.E.; Van den Abbeele, A.D. New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: Comparison with original RECIST and impact on assessment of tumor response to targeted therapy. Am. J. Roentgenol. 2010, 195, W221–W228.

58. Krantz, S.B.; Mitzman, B.; Lutfi, W.; Kuchta, K.; Wang, C.H.; Howington, J.A.; Kim, K.W. Neoadjuvant Chemoradiation Shows No Survival Advantage to Chemotherapy Alone in Stage IIIA Patients. Ann. Thorac. Surg. 2018, 105, 1008–1016, doi:10.1016/j.athoracsur.2017.10.056

59. Kong, F.M.; Ten Haken, R.; Eisbruch, A.; Lawrence, T.S. Nonsmall cell lung cancer therapy-related pulmonary toxicity: Anupdate on radiation pneumonitis and fibrosis. Semin. Oncol. 2005, 32, S42–S54.

60. Albain, K.S. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage III A (pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309) [ASTRO Abstract]. J. Clin. Oncol. 2005, 23, 7014.

61. Semik, M.; Riesenbeck, D.; Linder, A.; Schmid, C.; Hoffknecht, P.; Heinecke, A.; Scheld, H.H.; Thomas, M.; The German Lung Cancer Cooperative Group. Preoperative chemotherapy with and without additional radiochemotherapy: Benefit and risk for surgery of stage III non-small cell lung cancer? Eur. J. Cardiothorac. Surg. 2004, 26, 1205–1210.

62. Van Schil, P.; Van Meerbeeck, J.; Kramer, G.; Splinter, T.; Legrand, C.; Giaccone, G.; Manegold, C.; van Zandwijk, N. Morbidity and mortality in the surgery arm of EORTC 08941 trial. Eur. Respir. J. 2005, 26, 192–197.

63. Seder, C.W.; Allen, M.S.; Cassivi, S.D.; Deschamps, C.; Nichols, F.C.; Olivier, K.R.; Shen, K.R.; Wigle, D.A. Stage IIIA non-small cell lung cancer: Morbidity and mortality of three distinct multimodality regimens. Ann. Thorac. Surg. 2013, 95, 1708–1716.

64. Choi, N.C.; Carey, R.W.; Daly, W.; Mathisen, D.; Wain, J.; Wright, C.; Lynch, T.; Grossbard, M.; Grillo, H. Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. J. Clin. Oncol. 1997, 15, 712–722.

65. Eberhardt, W.; Wilke, H.; Stamatis, G.; Stuschke, M.; Harstrick, A.; Menker, H.; Krause, B.; Müeller, M.R.; Stahl, M.; Flasshove, M.; et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: Mature results of a phase II trial. J. Clin. Oncol. 1998, 16, 622–634.

66. Thomas, M.; Rübe, C.; Semik, M.; von Eiff, M.; Freitag, L.; Macha, H.N.; Wagner, W.; Klinke, F.; Scheld, H.H.; Willich, N.; et al. Impact of preoperative bimodality induction including twice-daily radiation on tumor regression and survival in stage III non-small-cell lung cancer. J. Clin. Oncol. 1999, 17, 1185–1193.

67. Pöttgen, C.; Eberhardt, W.E.; Gauler, T.; Krbek, T.; Berkovic, K.; Jawad, J.A.; Korfee, S.; Teschler, H.; Stamatis, G.; Stuschke, M. Intensified high-dose chemoradiotherapy with induction chemotherapy in patients with locally advanced non-small-cell lung cancer-safety and toxicity results within a prospective trial. Int. J. Radiat. Oncol. Biol. Phys. 2010, 76, 809–815.

68. Chun, S.G.; Hu, C.; Choy, H.; Komaki, R.U.; Timmerman, R.D.; Schild, S.E.; Bogart, J.A.; Dobelbower, M.C.; Bosch, W.; Galvin, J.M.; et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J. Clin. Oncol. 2017, 35, 56–62, doi:10.1200/JCO.2016.69.1378.

69. Park, B.B.; Park, J.O.; Kim, H.; Ahn, Y.C.; Choi, Y.S.; Kim, K.; Kim, J.; Shim, Y.M.; Ahn, J.S.; Park, K. Is trimodality approach better then bimodality in stage IIIA, N2 positive non-small cell lung cancer? Lung Cancer 2006, 53, 323–330, doi:10.1016/j.lungcan.2006.05.024.

70. Krantz, S.B.; Mitzman, B.; Lutfi, W.; Kuchta, K.; Wang, C.H.; Howington, J.A.; Kim, K.W. Neoadjuvant Chemoradiation Shows No Survival Advantage to Chemotherapy Alone in Stage IIIA Patients. Ann. Thorac. Surg. 2018, 105, 1008–1016, doi:10.1016/j.athoracsur.2017.10.056.

71. Postmus, P.E.; Kerr, K.M.; Oudkerk, M.; Senan, S.; Waller, D.A.; Vansteenkiste, J.; Escriu, C.; Peters, S.; ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 2017, 28, iv1–iv21, doi:10.1093/annonc/mdx222.

72. Rusch, V.W.; Giroux, D.J.; Kraut, M.J.; Crowley, J.; Hazuka, M.; Johnson, D.; Goldberg, M.; Detterbeck, F.; Shepherd, F.; Burkes, R.; et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: Long-term results of Southwest Oncology Group trial 9416 (Intergroup trial 0160). J. Clin. Oncol. 2007, 25, 313–318.

73. Kunitoh, H.; Kato, H.; Tsuboi, M.; Shibata, T.; Asamura, H.; Ichinose, Y.; Katakami, N.; Nagai, K.; Mitsudomi, T.; Matsumura, A.; et al. Phase II trial of preopeperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: Report of Japan Clinical Oncology Group trial 9806. J. Clin. Oncol. 2008, 26, 644–649.

74. Arriagada, R.; Bergman, B.; Dunant, A.; Le Chevalier, T.; Pignon, J.P.; Vansteenkiste, J.; International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N. Engl. J. Med. 2004, 350, 351–360.

75. Winton, T.; Livingston, R.; Johnson, D.; Rigas, J.; Johnston, M.; Butts, C.; Cormier, Y.; Goss, G.; Inculet, R.; Vallieres, E.; et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N. Engl. J. Med. 2005, 352, 2589–2597.

76. Douillard, J.Y.; Rosell, R.; De Lena, M.; Carpagnano, F.; Ramlau, R.; Gonzáles-Larriba, J.L.; Grodzki, T.; Pereira, J.R.; Le Groumellec, A.; Lorusso, V.; et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): A randomised controlled trial. Lancet Oncol. 2006, 7, 719–727.

77. PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small-cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet 1998, 352, 257–263.

78. Bekelman, J.E.; Rosenzweig, K.E.; Bach, P.B.; Schrag, D. Trends in the use of postoperative radiotherapy for resected non-small-cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. 2006, 66, 492–499, doi:10.1016/j.ijrobp.2006.04.032.

79. Lally, B.E.; Zelterman, D.; Colasanto, J.M.; Haffty, B.G.; Detterbeck, F.C.; Wilson, L.D. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J. Clin. Oncol. 2006, 24, 2998–3006, doi:10.1200/JCO.2005.04.6110.

80. Saynak, M.; Higginson, D.S.; Morris, D.E.; Marks, L.B. Current status of postoperative radiation for non-small-cell lung cancer. Semin. Radiat. Oncol. 2010, 20, 192–200, doi:10.1016/j.semradonc.2010.01.008.

81. Kępka, L.; Bujko, K.; Bujko, M.; Matecka-Nowak, M.; Salata, A.; Janowski, H.; Rogowska, D.; Cieślak-Żerańska, E.; Komosińska, K.; Zawadzka, A. Target volume for postoperative radiotherapy in non-small cell lung cancer: Results from a prospective trial. Radiother. Oncol. 2013, 108, 61–65.

82. Wang, S.; Ma, Z.; Yang, X.; Wang, Y.; Xu, Y.; Xia, W.; Chen, R.; Qiu, M.; Jiang, F.; Yin, R.; et al. Choice of postoperative radiation for stage IIIA pathologic N2 non-small cell lung cancer: Impact of metastatic lymph node number. Radiat. Oncol. 2017, 12, 207, doi:10.1186/s13014-017-0946-1

83. Zheng, D.; Ye, T.; Hu, H.; Zhang, Y.; Sun, Y.; Xiang, J.; Chen, H. Upfront surgery as first-line therapy in selected patients with stage IIIA non–small cell lung cancer. J. Thorac. Cardiovasc. Surg. 2018, 155, 1814–1822

84. Wang, W.; Men, Y.; Wang, J.; Zhou, Z.; Chen, D.; Xiao, Z.; Feng, Q.; Lv, J.; Liang, J.; Gao, S.; et al. Postoperative radiotherapy is effective in improving survival of patients with stage pIII-N2 non-small-cell lung Cancer after pneumonectomy. BMC Cancer 2019, 19, 478, doi:10.1186/s12885-019-5692-3.

85. Yue, D.; Xu, S.; Wang, Q.; Li, X.; Shen, Y.; Zhao, H.; Chen, C.; Mao, W.; Liu, W.; Liu, J.; et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): A randomised, open-label, phase 2 trial. Lancet Respir. Med. 2018, 6, 863–873, doi:10.1016/S2213-2600(18)30277-7.

86. Spoelstra, F.O.; Senan, S.; Le Péchoux, C.; Ishikura, S.; Casas, F.; Ball, D.; Price, A.; De Ruysscher, D.; van Sörnsen de Koste, J.R.; Lung Adjuvant Radiotherapy Trial Investigators Group. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: Analysis of an international contouring study. Int. J. Radiat. Oncol. Biol. Phys. 2010, 76, 1106–1113.

87. Kelsey, C.R.; Light, K.L.; Marks, L.B. Patterns of failure after resection of non-small-cell lung cancer: Implications for postoperative radiation therapy volumes. Int. J. Radiat. Oncol. Biol. Phys. 2006, 65, 1097–1105.

88. Feng, W.; Fu, X.L.; Cai, X.W.; Yang, H.J.; Wu, K.L.; Fan, M.; Xiang, J.Q.; Zhang, Y.W.; Chen, H.Q. Patterns of local-regional failure in completely resected stage IIIA(N2) non-small cell lung cancer cases: Implications for postoperative radiation therapy clinical target volume design. Int. J. Radiat. Oncol. Biol. Phys. 2014, 88, 1100–1107, doi:10.1016/j.ijrobp.2013.12.048.

89. Lee, H.W.; Noh, O.K.; Oh, Y.T.; Choi, J.H.; Chun, M.; Kim, H.I.; Heo, J.; Ahn, M.S.; Park, S.Y.; Park, R.W.; et al. Radiation Therapy-First Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer. Int. J. Radiat. Oncol. Biol. Phys. 2016, 94, 621–627, doi:10.1016/j.ijrobp.2015.11.020.

90. Sura, K.; Grills, I.S.; Vu, C.C.; Stevens, C.W.; Ye, H.; Guerrero, T.M. Improved Survival with Increased Time-To-Radiation and Sequential Chemotherapy After Surgery for pN2 Non-Small-cell Lung Cancer. Clin. Lung Cancer 2018, 19, e185–e194, doi:10.1016/j.cllc.2017.10.011.

91. Zhong, W.Z.; Chen, K.N.; Chen, C.; Gu, C.D.; Wang, J.; Yang, X.N.; Mao, W.M.; Wang, Q.; Qiao, G.B.; Cheng, Y.; et al. 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, doi:10.1200/JCO.19.00075.

92. Fukuoka, M.; Wu, Y.L.; Thongprasert, S.; Sunpaweravong, P.; Leong, S.S.; Sriuranpong, V.; Chao, T.Y.; Nakagawa, K.; Chu, D.T.; Saijo, N.; et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J. Clin. Oncol. 2011, 29, 2866–2874.

93. Inoue, A.; Kobayashi, K.; Maemondo, M.; Sugawara, S.; Oizumi, S.; Isobe, H.; Gemma, A.; Harada, M.; Yoshizawa, H.; Kinoshita, I.; et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naıve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann. Oncol. 2013, 24, 54–59.

94. Zhou, C.; Wu, Y.L.; Chen, G.; Feng, J.; Liu, X.Q.; Wang, C.; Zhang, S.; Wang, J.; Zhou, S.; Ren, S.; et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011, 12, 735–742.

95. Wu, Y.L.; Zhou, C.; Liam, C.K.; Wu, G.; Liu, X.; Zhong, Z.; Lu, S.; Cheng, Y.; Han, B.; Chen, L.; et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE study. Ann. Oncol. 2015, 26, 1883–1889.

96. Wu, Y.L.; Zhou, C.; Hu, C.P.; Feng, J.; Lu, S.; Huang, Y.; Li, W.; Hou, M.; Shi, J.H.; Lee, K.Y.; et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): An open-label, randomised phase 3 trial. Lancet Oncol. 2014, 15, 213–222.

97. Shepherd, F.A.; Rodrigues Pereira, J.; Ciuleanu, T.; Tan, E.H.; Hirsh, V.; Thongprasert, S.; Campos, D.; Maoleekoonpiroj, S.; Smylie, M.; Martins, R.; et al. Erlotinib in previously treated non-small-cell lung cancer. N. Engl. J. Med. 2005, 353, 123–132.

98. Sakurada, A.; Shepherd, F.A.; Tsao, M.S. Epidermal growth factor receptor tyrosine kinase inhibitors in lung cancer: Impact of primary or secondary mutations. Clin. Lung Cancer 2006, 7, 138–144.

99. Ellis, P.M.; Morzycki, W.; Melosky, B.; Butts, C.; Hirsh, V.; Krasnoshtein, F.; Murray, N.; Shepherd, F.A.; Soulieres, D.; Tsao, M.S.; et al. The role of the epidermal growth factor receptor tyrosine kinase inhibitors as therapy for advanced, metastatic, and recurrent non-small-cell lung cancer: A Canadian national consensus statement. Curr. Oncol. 2009, 16, 27–48.

100. Hishida, T.; Nagai, K.; Mitsudomi, T.; Yokoi, K.; Kondo, H.; Horinouchi, H.; Akiyama, H.; Nagayasu, T.; Tsuboi, M.; Japan Clinical Oncology Group. Salvage surgery for advanced non-small cell lung cancer after response to gefitinib. J. Thorac. Cardiovasc. Surg. 2010, 140, e69–e71.

101. Kappers, I.; Klomp, H.M.; Burgers, J.A.; Van Zandwijk, N.; Haas, R.L.; van Pel, R. Neoadjuvant (induction) erlotinib response in stage IIIA non-small-cell lung cancer. J. Clin. Oncol. 2008, 26, 4205–4207.

102. Takamochi, K.; Suzuki, K.; Sugimura, H.; Funai, K.; Mori, H.; Bashar, A.H.; Kazui, T. Surgical resection after gefitinib treatment in patients with lung adenocarcinoma harboring epidermal growth factor receptor gene mutation. Lung Cancer 2007, 58, 149–155.

103. Wang, Q.; Wang, H.; Li, P.; Zhu, H.; He, C.; Wei, B.; Ma, J.; Ma, Z. Erlotinib-based perioperative adjuvant therapy for a case of unresectable stage IIIA (N2) nonsmall cell lung cancer. Am. J. Med. Sci. 2010, 340, 321–325.

104. Zhong, W.; Yang, X.; Yan, H.; Zhang, X.; Su, J.; Chen, Z.; Liao, R.; Nie, Q.; Dong, S.; Zhou, Q.; et al. Phase II study of biomarker-guided neoadjuvant treatment strategy for IIIA-N2 non-small cell lung cancer based on epidermal growth factor receptor mutation status. J. Hematol. Oncol. 2015, 8, 54, doi:10.1186/s13045-015-0151-3.

105. Riely, G.J.; Kris, M.G., Zhao, B.; Akhurst, T.; Milton, D.T.; Moore, E.; Tyson, L.; Pao, W.; Rizvi, N.A.; Schwartz, L.H.; et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin. Cancer Res. 2007, 13, 5150–5155.

106. Chaft, J.E.; Oxnard, G.R.; Sima, C.S.; Kris, M.G.; Miller, V.A.; Riely, G.J. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: Implications for clinical trial design. Clin. Cancer Res. 2011, 17, 6298–6303.

107. Zhou, Q.; Cheng, Y.; Yang, J.J.; Zhao, M.F.; Zhang, L.; Zhang, X.C.; Chen, Z.H.; Yan, H.H.; Song, Y.; Chen, J.H.; et al. Pemetrexed versus gefitinib as a second-line treatment in advanced nonsquamous nonsmall-cell lung cancer patients harboring wild-type EGFR (CTONG0806): A multicenter randomized trial. Ann. Oncol. 2014, 25, 2385–2391.

108. Xiong, L.; Li, R.; Sun, J.; Lou, Y.; Zhang, W.; Bai, H.; Wang, H.; Shen, J.; Jing, B.; Shi, C.; et al. Erlotinib as Neoadjuvant Therapy in Stage IIIA (N2) EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Prospective, Single-Arm, Phase II Study. Oncologist 2019, 24, 157-e64, doi:10.1634/theoncologist.2018-0120.

109. Kelly, K.; Chansky, K.; Gaspar, L.E.; Albain, K.S.; Jett, J.; Ung, Y.C.; Lau, D.H.; Crowley, J.J.; Gandara, D.R. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J. Clin. Oncol. 2008, 26, 2450–2456.

110. Goss, G.D.; O'Callaghan, C.; Lorimer, I.; Tsao, M.S.; Masters, G.A.; Jett, J.; Edelman, M.J.; Lilenbaum, R.; Choy, H.; Khuri, F. Gefitinib versus placebo in completely resected non-small-cell lung cancer: Results of the NCIC CTG BR19 study. J. Clin. Oncol. 2013, 31, 3320–3326.

111. Kelly, K.; Altorki, N.K.; Eberhardt, W.E.; O'Brien, M.E.; Spigel, D.R.; Crinò, L.; Tsai, C.M.; Kim, J.H.; Cho, E.K.; Hoffman, P.C.; et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): A randomized, double-blind, phase III trial. J. Clin. Oncol. 2015, 33, 4007–4014.

112. Pennell, N.A.; Neal, J.W.; Chaft, J.E.; Azzoli, C.G.; Jänne, P.A.; Govindan, R.; Evans, T.L.; Costa, D.B.; Wakelee, H.A.; Heist, R.S.; et al. SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC. Proc. Am. Soc. Clin. Oncol. 2014, 32, 7514.

113. D'Angelo, S.P.; Janjigian, Y.Y.; Ahye, N.; Riely, G.J.; Chaft, J.E.; Sima, C.S.; Shen, R.; Zheng, J.; Dycoco, J.; Kris, M.G.; et al. Distinct clinical course of EGFR-mutant resected lung cancers: Results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J. Thorac. Oncol. 2012, 7, 1815–1822.

114. Janjigian, Y.Y.; Park, B.J.; Zakowski, M.F.; Ladanyi, M.; Pao, W.; D'Angelo, S.P.; Kris, M.G.; Shen, R.; Zheng, J.; Azzoli, C.G. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected lung adenocarcinomas that harbor EGFR mutations. J. Thorac. Oncol. 2011, 6, 569–575.

115. Li, N.; Ou, W.; Ye, X.; Sun, H.B.; Zhang, L.; Fang, Q.; Zhang, S.L.; Wang, B.X.; Wang, S.Y. Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIA-N2 non-small cell lung cancer harbouring EGFR mutations: A randomized, phase II study. Ann. Surg. Oncol. 2014, 21, 2091–2096, doi:10.1245/s10434-014-3586-9.

116. 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, doi:10.1056/NEJMoa1716078.

117. Bott, M.J.; Yang, S.C.; Park, B.J.; Adusumilli, P.S.; Rusch, V.W.; Isbell, J.M.; Downey, R.J.; Brahmer, J.R.; Battafarano, R.; Bush, E.; et al. 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.

118. Kwiatkowski, D.J.; Rusch, V.W.; Chaft, J.E.; Johnson, B.E.; Wistuba, I.I.; Merritt, R.; Lee, J.M.; Bunn, P.A.; Tang, Y.; Phan, S.C.; et al. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3). Proc. Am. Soc. Clin. Oncol. 2019, 37, 8503.

119. Cascone, T.; William, W.; Weissferdt, A.; Lin, H.Y.; Leung, C.H.; Carter, B.W.; Fossella, F.V.; Mott, F.; Papadimitrakopoulou, V.; Blumenschein, G.R.; et al. Neoadjuvant nivolumab (N) or nivolumab plus ipilimumab (NI) for resectable non-small-cell lung cancer (NSCLC): Clinical and correlative results from the NEOSTAR study. Proc. Am. Soc. Clin. Oncol. 2019, 37, 8504.

120. Shu, C.A.; Gainor, J.F.; Awad, M.M.; Chiuzan, C.; Grigg, C.M.; Pabani, A.; Garofano, R.F.; Stoopler, M.B.; Cheng, S.K.; White, A.; et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: An open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020, 21, 786–795, doi:10.1016/S1470-2045(20)30140-6.