Surgical Outcomes After Chemotherapy plus Nivolumab and Chemotherapy plus Nivolumab and Ipilimumab in Patients with Non-Small Cell Lung Cancer

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**ARM C: Nivo+CT**
- 90% R0
- 95% via thoracotomy
- 59% rated as more challenging than standard lobectomy

**ARM D: Ipi+ Nivo+CT**
- 95% R0
- 80% via thoracotomy
- 45% considered challenging

**Clavien-Dindo Complications**

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Surgical resection after Nivo+CT +/- Ipi

- Is safe ✔
- Is feasible ✔
- Demonstrates high R0 rates ✔
- But may be more challenging than standard lobectomy
Surgical Outcomes After Chemotherapy plus Nivolumab and Chemotherapy plus Nivolumab and Ipilimumab in Patients with Non-Small Cell Lung Cancer

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Running head: Surgical outcomes after immunotherapy

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Glossary of Terms

EBL- estimated blood loss

Ipi+Nivo+CT- Ipilimumab+Nivolumab+Chemotherapy

Nivo+CT- Nivolumab+Chemotherapy

NEOSTAR- Nivolumab With or Without Ipilimumab or Chemotherapy in Treating Patients With Previously Untreated Stage I-IIIA Non–Small Cell Lung Cancer

PA- Pulmonary Artery

PFTs- pulmonary function tests

PORT- Post operative radiation therapy

RIOT- return to indicated oncologic therapy

STAS- Spread through air spaces

TRAE- treatment related adverse events
Central Message: Surgical resection after neoadjuvant nivolumab plus chemotherapy with or without ipilimumab can be performed safely with acceptable morbidity and no 90-day mortality.

Perspective Statement: While surgical resection following neoadjuvant Nivo+CT +/-Ipi was both safe and feasible, some resections may be more challenging than routine anatomical resections either due to tumor or nodal responses to therapy or the actual extent and location of the intra-thoracic disease.

Structured Abstract (250/250 words):

Objective: Chemotherapy plus nivolumab is the standard of care neoadjuvant treatment for patients with resectable stage IB-IIIA non-small cell lung cancer. The influence of dual checkpoint blockade with chemotherapy on surgical outcomes remains unknown. We aimed to determine operative complexity and perioperative outcomes associated with neoadjuvant chemotherapy (CT) and nivolumab (Nivo) with or without ipilimumab (Ipi).

Methods: 44 patients with Stage IB (≥4 cm)-IIIA NSCLC were treated on sequential platform arms of the NEOASTAR trial. 22 patients were treated with Nivo+CT and 22 were treated with Ipi+Nivo+CT. Safety of surgical resection following neoadjuvant therapy was estimated using 30-day complication rates. Operative reports and surgeons' narratives were evaluated to determine procedural complexity and operative conduct.

Results: All 22/22 (100%) patients treated with Nivo+CT underwent surgical resection, 20 R0
(90.9%), 17 (77.3%) lobectomies, 1 wedge resection, 2 segmentectomies and 2 pneumonectomies. The majority, 21/22 (95%), were performed by thoracotomy. 13/22 (59.1%) were rated as challenging resections. 4/22 patients (18.2%) experienced ≥ grade 3 Clavien-Dindo complication.

20/22 (90.9%) patients treated with Ipi+Nivo+CT underwent surgical resection, 19 R0 (95%), 18 (90%) lobectomies, 1 pneumonectomy and 1 segmentectomy. 16/20 (80%) resections were performed via thoracotomy, 3/20 (15%) via robotics and 1/20 (5%) via thoracoscopy. 9/20 (45%) resections were considered challenging. 4/20 patients (20%) experienced ≥ grade 3 Clavien-Dindo complication.

**Conclusions:** Surgical resections are feasible and safe, with high rates of R0 following neoadjuvant chemotherapy and nivolumab with or without ipilimumab. Overall, approximately half of cases (22/42, 52.3%) were considered to be more challenging than a standard lobectomy (Figure 4).

**Central Image:** Classification of Surgical Complications for Arms C and D of the NEOSTAR Trial

**Keywords:** NSCLC, immunotherapy, clinical trial

**Trial Registration** ClinicalTrials.gov Identifier: NCT03158129

**Introduction**
Lung cancer remains the leading cause of cancer-related deaths worldwide, and accounts for nearly 1 in 4 cancer-related deaths in the United States. In recent years, there has been a rapid increase in the array of immunotherapy and targeted pharmacologic agents available for the treatment of this disease. The work is ongoing to evaluate the utility of these agents, previously shown to confer benefit in the metastatic setting, in the neoadjuvant setting for surgically operable disease. While the primary outcomes of many ongoing trials focus on pathological response and survival, it is essential to keep evaluating the potential surgical challenges that may arise when novel treatments are administered prior to planned surgical resection.

We have previously reported surgical outcomes from the randomized phase II NEOSTAR trial following neoadjuvant nivolumab (Nivo) or nivolumab plus ipilimumab (Ipi) and demonstrated that perioperative outcomes are comparable to neoadjuvant chemotherapy (CT) or upfront resections alone. Following the randomized arms of Nivo (Arm A) or Nivo plus Ipi (Arm B), the NEOSTAR trial evolved into a platform trial of sequential, single-center, single-arm, phase 2 studies with a modular design. Major pathological response (MPR, defined as ≤10% viable tumor in resected tumor specimens) rate in each individual arm was the primary endpoint, which was hypothesized to be greater than the rate to historical controls of neoadjuvant CT. 422 patients were enrolled on Arm C and received neoadjuvant Nivo+CT followed by 22 patients on Arm D who received Ipi+Nivo+CT. In the intention-to-treat population, the primary outcome of MPR was achieved in 32.1% of patients treated with Nivo+CT and 50% of patients treated with Ipi+Nivo+CT. These results suggest augmented anti-cancer benefit with the addition of Ipi to the neoadjuvant regimen of Nivo+CT.

Herein we report the surgical outcomes of NEOSTAR Arms C and D with focus on treatment-related surgical delays, intraoperative surgical complexities, and postoperative complications.
Patients treated on the NEOSTAR study were permitted to receive adjuvant therapy as indicated based on physicians’ judgement. Return to intended oncologic therapy (RIOT) has become an important measure associated with long-term oncologic outcomes. We have instead used this term to signify return to indicated oncologic therapy due to the use of adjuvant agents based on the result of tumor molecular profiling and intraoperative findings, and we have evaluated RIOT in our patient population. To our knowledge, this is the first study to safely complete the treatment arm using neoadjuvant Ipi+Nivo+CT and we compare in an exploratory fashion this cohort to patients treated with neoadjuvant Nivo+CT.

**Methods**

**Study Design**

NEOSTAR (NCT03158129) was a multi-arm study wherein the first two arms were randomized and assigned in parallel; the subsequent two arms were a platform study design. The two arms addressed in this manuscript are Arm C, in which patients received 3 cycles of Nivo+CT followed by curative-intent surgical resection and Arm D, in which patients received 3 cycles of Ipi+Nivo+CT with Ipi given on day one of therapy only (cycle 1) followed by curative-intent surgical resection. The trial arms were completed sequentially, with patients enrolled in Arm C from December 2018 to July 2019 and Arm D from December 2019 to December 2020. Prior to enrollment, all patients were provided with and signed informed consent. The study was approved by the institutional review board at the University of Texas MD Anderson Cancer Center (2016-0982 02/15/2017). Detailed platform trial design, inclusion/exclusion criteria and primary and selected secondary and exploratory outcomes of the NEOSTAR platform trial have been previously reported (Cascone Nat Med 2023).
Participants

Arms C and D of the platform NEOSTAR study are modular arms that were conducted sequentially after completion of the randomized trial portion of the study (Arms A and B).

Inclusion criteria for the study included: age 18 years of age and older, stage IB (≥ 4 cm) to IIIA NSCLC according to American Joint Commission on Cancer (AJCC) 7th edition staging system, only single mediastinal N2 station was permitted for enrollment. All patients had to have surgically resectable disease and Eastern Cooperative Group (ECOG) performance status (PS) 0-1, adequate organ function, and cardiopulmonary status. Patients were excluded from the study if they had autoimmune disease, immunodeficiency, or previously received immunotherapy for other disease, if they had active infectious disease requiring ongoing treatment or cancer within the last two years. Patients were screened, enrolled and treated on study at The University of Texas MD Anderson Cancer Center in the Departments of Thoracic/Head and Neck Medical Oncology and Thoracic and Cardiovascular Surgery. The neoadjuvant treatment consisted of nivolumab 360 mg IV every 3 weeks, cisplatin 75 mg/m² and docetaxel 75 mg/m² IV or pemetrexed 500 mg/m² IV every 3 weeks (docetaxel or pemetrexed were chosen based on histology of NSCLC). In Arm D, Ipilimumab 1 mg/kg IV was administered on cycle 1 (D1, day 1 of therapy only). Carboplatin was an option for use as a platinum agent in Arm D only.4

Procedures and Surgical Complexity

Surgical resection was recommended between 21 and 42 days after completion of neoadjuvant therapy. The extent of the resection as well as the surgical procedure (open versus minimally invasive) was up to the discretion of the surgeon. A total of 9 surgeons performed the 42 surgical resections completed under this trial protocol. Surgeons were asked to assess the difficulty of the surgical resection on a scale from 1-4,² with 2 representing a standard lobectomy, 1 being easier
than a normal resection, and 3-4 representing a resection that necessitated advanced technical maneuvers. Only five cases received a numerical difficulty score from the operating attending, however, all attendings described operative conduct diligently enough to extrapolate the level of complexity. For cases that did not receive a score from the operating surgeon (n=37), case reports were reviewed and those that were felt to be more challenging than a standard lobectomy were confirmed by a second provider. Additionally, operative reports were reviewed to identify the source of difficulty as well as how the operating surgeon managed the finding. Intraoperative findings that would be described as more challenging than a standard lobectomy include: scarring or fibrosis of the hilar structures, adhesions, large and central tumors. Evidence that a case was more challenging than a standard lobectomy was seen when there was a change in planned operative approach, a deviation from the planned resection, proximal pulmonary artery control, arterioplasty, sleeve resection of the artery or bronchus, or safe completion of the operation necessitated a second surgeon or intraoperative consultation (at the discretion of the operating surgeon).

Pathological evaluation

Surgical resection specimens from two cases from each arm were reviewed by a thoracic pathologist, with one sample representing a standard lobectomy and one representing a more complex resection. The pathologist was blinded to the intraoperative findings.

Outcomes

In both NEOSTAR study arms, we evaluated the resection rate, R0 rate, time to surgery, operative approach, operative time, estimated blood loss (EBL) and completeness of resection. 30 and 90-day postoperative complications were captured in a prospectively maintained
departmental database. Postoperative morbidities were reported individually and were
additionally classified according to the Clavien-Dindo system. Pulmonary function tests (PFTs)
prior to treatment and, when available, post treatment (but pre-surgery), were included in an
exploratory analysis. Time to receiving post-operative radiation therapy (PORT) or adjuvant
systemic therapy was captured in the cohort of patients deemed to warrant further treatment after
surgery per treating physicians’ judgement.

Statistical Analysis

We used descriptive statistics to summarize data. Analyses were performed using data from
patients who were treated and underwent surgical resection on trial. The normality of continuous
variables including time from the last dose of neoadjuvant therapy to operation, estimated blood
loss, operative time, and length of stay was assessed by Shapiro-Wilk test. Median (interquartile
range (IQR)) is reported for non-normally distributed variables and mean (standard deviation
(SD)) is reported for normally distributed variables. Continuous variables were compared
between two groups using a Mann Whitney U test. Paired data, such as pre- and post-treatment
PFTs, were compared using Wilcoxon signed-ranked test. A univariate logistic regression model
was used to assess the association between perioperative outcomes and treatment arm. A two-
sided p-value of 0.05 was considered significant. All statistical tests were performed in IBM
SPSS 24.0 (IBM Corp, Armonk, NY), SAS 9.4, and GraphPad Prism9.

Results

The primary clinical results of the NEOSTAR platform trial were reported previously. Briefly,
22 patients were treated with Nivo+CT, all of whom subsequently underwent surgical resection
and 22 patients were treated with Ipi+Nivo+CT, of whom 20/22 (90.9%) underwent surgical
resection (Figure 1). Here, we report surgical and perioperative outcomes in the population of resected patients. The majority of patients who underwent surgery after neoadjuvant therapy with Nivo+CT were female (n=12, 54.5%), with stage IIIA disease (n=11, 50%) and the most common histologic subtype was adenocarcinoma (n=16, 72.7%). The majority of patients who underwent surgery after neoadjuvant therapy with Ipi+Nivo+CT were male (n=13, 65%), with stage IIIA disease (n=11, 55%) and the most common histologic subtype was adenocarcinoma (n=11, 55%). (Table 1)

**Surgical procedures**

In the Nivo+CT arm, all 22 (100%) patients underwent surgical resection. R0 resection was achieved in 20/22 (90.9%) patients. One patient was found to have pleural metastases (R2), and one patient had a microscopically positive parenchymal margin due to spread through airspaces (STAS). Median time from the last dose of neoadjuvant therapy to operation was 33 days (IQR 26 – 37), with four (18%) operations being delayed beyond the recommended 6 weeks due to TRAEs in three patients and pulmonary embolism in one patient. The following resections were performed: 17 (77.3%) lobectomies, one (4.5%) wedge resection, two (9.1%) segmentectomies and two (9.1%) pneumonectomies (Figure 2). One procedure was performed via VATS, the remaining 21/22 (95.5%) were completed via open thoracotomy. Median estimated blood loss (EBL) was 175cc (IQR 100 – 300) and mean operative time was 144.6 minutes (SD 44.9).

In the Ipi+Nivo+CT arm, 20/22 (91%) patients underwent a surgical resection. One patient died of SARS-CoV-2 infection-related complications (non-treatment related) after the first cycle of neoadjuvant therapy. Another patient completed neoadjuvant therapy and demonstrated radiographic SD. However, due to the proximity of the tumor to the left internal mammary graft to left anterior descending artery and decreased patient’s exercise test performance a decision
was made to treat the patient with definitive concurrent chemoradiation therapy instead of surgery. The R0 resection rate was 95% (19/20); one patient had a microscopically positive bronchial margin and an intra-operative decision was made not to proceed with additional resection (bilobectomy), due to grossly positive N2 disease and need for adjuvant mediastinal radiation following mediastinal nodal dissection. The median time to operation was 28.5 days (IQR 26.5 – 36) with two patients undergoing delayed operations due to scheduling in one patient, and a positive preoperative SARS-CoV-2 test in another patient requiring at least 20 days of quarantine prior to operation. The following resections were performed: 18 (90%) lobectomies, 1 (5%) pneumonectomy and 1 (5%) segmentectomy (Figure 2). 16/20 (80%) resections were performed via open thoracotomy, 3/20 (15%) were performed via RATS and 1/20 via VATS (5%). No cases using minimally invasive technique required conversion to open.

Median EBL was 145cc (IQR 72.5 – 200) and median operative time was 159 minutes (IQR 116.5, 189).

**Postoperative Course**

Among patients treated with Nivo+CT followed by surgical resection, mean length of stay was 3.5 days (SD 1.2). The 30-day complication rate was 31.8% (7/22). Clavien Dindo grade ≥ 3 requiring postoperative intervention in four (18.2%) patients which included chest tube replacement for subcutaneous emphysema, cord injection for a vocal cord paralysis, bronchoscopy and antibiotics for lobar collapse, and pericardial drainage for a pericardial tamponade following intrapericardial pneumonectomy. The 90-day mortality rates were 0%.

(Table 2 and Supplemental Figure 1).

Among patients treated with Ipi+Nivo+CT followed by surgical resection, the median hospital length of stay was 4 days (IQR 3 – 5.5). The 30-day complication rate was 65% (13/20), which
was numerically higher than that in the Nivo+CT arm. Clavien Dindo grade ≥ 3 surgical complications occurred in 4 patients and included: a permanent pacemaker implantation for persistent arrhythmia, diagnostic thoracoscopy to rule out empyema, vocal cord injection for a paralyzed cord, and an endobronchial valve placement for persistent air leak. The 90-day mortality rates were 0%. (*Table 2* and *Supplemental Figure 1*).

**Surgical Complexity**

Of the 22 resections performed in patients who had undergone neoadjuvant treatment with Nivo+CT, 13 (59.1%) were rated as more difficult than a standard lobectomy. The source of operative difficulty in 6/13 (46.2%) was related to the extent of disease, including nodal involvement and large tumor size. In 5 cases (38.5%) the source of operative complexity was attributed to tumor or nodal response to therapy. Details pertaining to the intraoperative finding, source of difficulty as well as surgeon management have been provided in *Supplemental Table 1*.

Of the 20 resections performed in patients who had undergone neoadjuvant treatment with Ipi+Nivo+CT, 9 (45%) were rated as more difficult than a standard lobectomy. The source of operative difficulty in 5/9 (55.6%) was related to tumor and/or nodal response to therapy while 4/9 (44.4%) intraoperative challenges could be attributed to the extent of disease. Details pertaining to the intraoperative finding, source of difficulty as well as surgeon management have been provided in *Supplemental Table 2*. In cases performed following Ipi+Nivo+CT, an increased surgical complexity rating was associated with increased EBL (p=0.02) and increased operative time (p=0.049) (*Figure 3*).

**Return to Indicated Oncologic Therapy (RIOT)**
While adjuvant therapy was not part of the trial, we collected data on administered adjuvant therapy. Following treatment with Nivo+CT and subsequent surgical resection, 7 (31.8%) patients received adjuvant therapy. 3/7 (57.1%) were treated with PORT alone, 1 received PORT and Durvalumab, 2 (28.6%) received chemoradiation, and one patient (14.3%) received chemotherapy. One patient treated with PORT only had MPR, the remaining patients treated with adjuvant therapy did not demonstrate MPR on surgical pathology. Median time to initiation of therapy was 45 days (IQR 33 – 56) and there were no noted delays in starting therapy.

Among patients treated with Ipi+Nivo+CT, 9 (45%) received adjuvant therapy. 5/9 (55.6%) were treated with PORT, 2 (22.2%) received PORT and Osimertinib therapy, and 2 (22.2%) received Osimertinib only. Two patients treated with PORT had MPR on surgical pathology, the remaining patients treated with adjuvant therapy did not demonstrate MPR. The median time to initiation of therapy was 54 days (IQR 38 – 62). Again, there were no medical reasons for therapeutic delay in this cohort.

Pathological evaluation

In an exploratory analysis to evaluate potential associations between pathological findings and surgical complexity, a thoracic pathologist was asked to re-review four cases with distinct surgical complexity. Histologically, there was an increase in fibrotic changes, especially involving the hilar structures and/or pleural surfaces in the cases that were felt to be more complex than a standard lobectomy. However, it was felt that the findings were minor and could have easily been overlooked if not specifically searching for any differences in histologic appearance related to surgical complexity (Supplemental Figure 2).

Pulmonary Function Test Analyses
12/22 (54.5%) patients in arm C and 12/20 (60%) patients in arm D had both pre and post-therapy PFTs available for exploratory analyses. All post-therapy testing was completed prior to surgery. In both arms, there was no change in FEV or FVC following neoadjuvant therapy. However, we observed a clinically significant reduction in DLCO following neoadjuvant therapy with Nivo+CT that was not seen in patients treated with Ipi+Nivo+CT (Supplemental Figure 3a-c). Change in pulmonary function after neoadjuvant therapy was not meaningfully associated with increased operative complexity (Supplemental Figure 3d-f).

Discussion

In this neoadjuvant NEOSTAR platform study evaluating Nivo+CT or Ipi+Nivo+CT treatments we demonstrate that surgical resections, while subjectively somewhat more challenging, can be performed overall safely with encouraging perioperative outcomes. Postoperatively, patients were able to initiate additional indicated therapy for NSCLC in what was considered a timely fashion. As noted in the descriptions from the operative notes, successful completion of these operations may require adjustment in the intra-operative strategy depending on the circumstances encountered, and should raise thoracic surgeons’ awareness in this setting.

The field of multimodality therapy for operable NSCLC has changed significantly over the last three years thanks to several landmark phase III studies. ADAURA, Impower 010 and Keynote 091 changed the adjuvant paradigm, and CheckMate 816 changed the neoadjuvant paradigm.\(^8{}\text{-}11\) CheckMate 816 demonstrated both improved pathological complete responses and event free survival in patients treated with Nivo+CT as compared to chemotherapy alone. In this large international trial 83% of patients in the Nivo+CT arm proceeded to surgical resection and 83% underwent R0 resection. The median length of stay ranged from 4 to 11 days between North America and Asia, highlighting the differences in care around the world. There was an
interesting trend towards less pneumonectomy and more minimally invasive procedures performed in the Nivo+CT study arm.\textsuperscript{11} As such, our surgical results of NEOSTAR arm C with Nivo+CT are overall comparable to CheckMate 816 with high resectability and R0 rates (> 90%), although our study is a small, single-center study in the United States.

The novelty of our work comes from the study arm D, which tested neoadjuvant Ipi+Nivo+CT followed by surgical resection. We have shown that the addition of ipilimumab to the treatment regimen does not adversely impact surgical outcomes, yet it produced an MPR rate of 50% in the intention-to-treat population and 62.5% in patients without known \textit{EGFR/ALK} alterations.

Therefore, this regimen should be considered for further investigation, especially since we did not observe any significant postoperative adverse events. This stands in contrast to one study that closed enrollment utilizing nivolumab plus ipilimumab without chemotherapy due to toxicity,\textsuperscript{12} and a nivolumab plus ipilimumab arm of the CheckMate 816 trial which also abandoned further enrollment early, possibly due to a strong signal in nivolumab plus chemotherapy observed in the NADIM trial.\textsuperscript{11, 13}

Regarding the surgical complexity, overall, a larger percentage of cases was felt to be more challenging than a standard lobectomy in the Nivo+CT group when compared to the Ipi+Nivo+CT group (59.1% vs. 45%). However, the source of difficulty in the Ipi+Nivo+CT group was more often felt to be related to treatment response (55.6% versus 38.5%). This correlated with higher overall pathological tumor response rates and slightly higher reactive tissue response around hilar structures and/or pleural surfaces at a microscopic level. Eventually, the median residual tumor viability (RVT) after Ipi+Nivo+CT in the resected population was 4.5% versus 50.5% in the Nivo+CT arm, suggesting a numerically improved pathological regression with the addition of ipilimumab.\textsuperscript{4} There was numerically higher overall 30-day
complication rate in the Ipi+Nivo+CT cohort with more blood transfusions. The small number of
patients in both arms, however, limits firm conclusions about these trends. A study that included
a larger Ipi+Nivo+CT cohort would be needed to establish consistent trends in postoperative
complications.

The readout of select peri-operative phase III trials, including AEGEAN (NCT 03800134)\textsuperscript{14},
Neotorch (NCT04158440)\textsuperscript{15} and Keynote-671 (NCT 03425643),\textsuperscript{16} and the anticipation of
upcoming results from two additional large randomized studies testing perioperative immune-
based therapies, CheckMate 77T (NCT 04025879) and IMpower 030 (NCT 03456063), make the
concept of the RIOT (return to intended/indicated oncologic therapy) ever so important. These
trials were designed with up to four cycles of chemotherapy plus immunotherapy in the
neoadjuvant setting (with the exception of the Neotorch trial in which three cycles of
chemoimmunotherapy were administered in the neoadjuvant phase and one cycle in the adjuvant
phase) followed by surgery followed by adjuvant immunotherapy versus placebo for up to a
year. Although AEGEAN and Keynote-671 have both met their primary endpoints, it is
premature to speculate whether the benefit of improved event-free survival is driven by the
neoadjuvant or adjuvant component of these trials.\textsuperscript{14,17,18} However, if the future of
multimodality therapy for operable stage II and III lung cancer is to administer a year-long
therapy with surgical disease control following four cycles, the perioperative outcomes will have
to be excellent to allow for RIOT. Our results suggest that RIOT is possible within reasonable
timeframe following either Nivo+CT or Ipi+Nivo+CT, although patients in our trial received
only three and not four cycles of neoadjuvant therapy, and adjuvant therapy was not part of the
trial, rather was administered based on treating physicians’ judgement. The decision to use
PORT in this patient population is made on an individual basis for patients at high risk of local or
regional recurrence and is discussed in a multidisciplinary setting in order to elucidate the opinions of surgeons, thoracic oncologists, pathologists and radiation oncologists prior to recommending this therapy.

Our study has important limitations, including the modest number of patients in each arm, the single-center and its non-randomized nature, which is subject to selection bias. Due to the sequential nature of the study, there may be differences between populations in each treatment arm that may have contributed to the differences in observed outcomes between arms. However, both arms were rather similar in demographics and therefore comparisons, albeit purely exploratory, appear reasonable as we try to build experience and continue to improve outcomes for operable lung cancer patients.

Conclusions

Objective surgical outcomes following neoadjuvant chemotherapy and nivolumab with or without ipilimumab demonstrate that operations can be performed overall safely with acceptable morbidity and no 90-day mortality. Some operations may be more challenging than routine anatomical resections either due to tumor or nodal responses to therapy or the actual extent and location of the intra-thoracic disease. Patients were started on adjuvant therapies as indicated without delays. Considering the promising MPR rate and encouraging perioperative outcomes, the addition of CTLA-4 inhibition to the chemotherapy plus nivolumab regimen should be considered in future trials. Additional work will be required to evaluate the generalizability of these findings, as universally agreed upon benchmarks for safety and perioperative outcomes are lacking at this time in this population of patients, patients in this study were treated by a team of experienced surgeons in a quaternary care center and patient selection for future trials should take into account these factors, differences and challenges.
References


Table 1. Baseline Characteristics of Surgical Cohort

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>Nivo+CT (n=22)</th>
<th>Ipi+Nivo+CT (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years – mean (SD)</td>
<td></td>
<td>66.5 (8.4)</td>
<td>63.3 (9.9)</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td>Female</td>
<td>12 (54.55)</td>
<td>7 (35)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>10 (45.5)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Race – n (%)</td>
<td>Asian NOS</td>
<td>3 (13.6)</td>
<td>1 (5)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>0 (0)</td>
<td>3 (15)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>19 (86.4)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Smoking status – n (%)</td>
<td>Never smoker</td>
<td>5 (22.7)</td>
<td>5 (25)</td>
</tr>
<tr>
<td></td>
<td>Former smoker/ Current smoker</td>
<td>17 (77.3)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Stage – n (%)</td>
<td>Stage IB (≥4 cm) or II</td>
<td>11 (50)</td>
<td>8 (40)</td>
</tr>
<tr>
<td></td>
<td>Stage IIIA</td>
<td>11 (50)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Histology – n (%)</td>
<td>Squamous</td>
<td>5 (22.7)</td>
<td>4 (20)</td>
</tr>
<tr>
<td></td>
<td>Non-Squamous</td>
<td>17 (77.3)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>ECOG PS – n (%)</td>
<td>0</td>
<td>10 (45.5)</td>
<td>14 (70)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>12 (54.5)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Invasive mediastinal staging – n (%)</td>
<td>Yes with EBUS</td>
<td>21 (95.5)</td>
<td>20 (100)</td>
</tr>
<tr>
<td></td>
<td>Yes with mediastinoscopy</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type of platinum agent*</td>
<td>Cisplatin</td>
<td>22 (100)</td>
<td>10 (50)</td>
</tr>
</tbody>
</table>
Carboplatin  0 (0)  10 (50)

Nivo, nivolumab; Ipi, ipilimumab; CT, chemotherapy; EBUS, endobronchial ultrasound; ECOG, Eastern Cooperative Group; PS, performance status. *At the time of initiation of neoadjuvant treatment on trial.

Table 2. Perioperative Outcomes by Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>Nivo+CT (n = 22)</th>
<th>Ipi+Nivo+CT (n = 20)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 Resection</td>
<td>20 (90.9)</td>
<td>19 (95)</td>
<td>1.90 (0.16, 22.7)</td>
</tr>
<tr>
<td>90-Day mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>EBL, mL</td>
<td>175 (100, 300)</td>
<td>145 (72.5, 200)</td>
<td></td>
</tr>
<tr>
<td>Operative time, minutes</td>
<td>144.6 (44.9)</td>
<td>159 (116.5, 189)</td>
<td></td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>3.5 (1.2)</td>
<td>4 (3, 5.5)</td>
<td></td>
</tr>
<tr>
<td>Complication (Any)</td>
<td>7 (32)</td>
<td>13 (65)</td>
<td>4.59 (1.29, 16.3)</td>
</tr>
<tr>
<td>Clavien Complication ≥3</td>
<td>4 (18.2)</td>
<td>4 (20)</td>
<td>1.13 (0.24, 5.25)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4 (18.2)</td>
<td>6 (30)</td>
<td>1.69 (0.40, 7.07)</td>
</tr>
<tr>
<td>Home oxygen</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Discharged with chest tube</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lobe collapse</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypercarbic respiratory failure</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Reoperation to rule out bronchopleural fistula

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2.22 (0.36, 13.6)</th>
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</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>2 (9.1)</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation managed medically</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia managed with pacemaker</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>1 (5)</td>
<td>NA</td>
</tr>
<tr>
<td>Neurological</td>
<td>2 (9.1)</td>
<td>2 (10)</td>
<td>1.00 (0.13, 7.81)</td>
</tr>
<tr>
<td>Delirium</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Recurrent laryngeal nerve injury</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>pRBC transfusion</td>
<td>0</td>
<td>4 (20)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Nivo, nivolumab; Ipi, ipilimumab; CT, chemotherapy; CI, confidence interval; EBL, estimated blood loss; pRBC, packed red blood cell. Data are n(%), median (IQR) or mean (SD). The odds ratio was estimated in univariate logistic regression.

Figure 1. Flow diagram of patient disposition to surgery

Figure 2. Pie chart depicting types of resection performed in each arm of the trial

Figure 3. Surgical complexity. Box and whisker plots. Box extends from 25th to 75th percentile, line in the middle of the box set at median, whiskers drawn minimum to maximum. Each dot represents a single data point. A. EBL and surgical complexity, where a score of 2 indicates a procedure with complexity comparable to standard lobectomy while >2 indicates increased technical complexity. Two-sided p-value is from Mann Whitney U test comparing distributions of estimated blood loss between standard complexity and increased complexity in Ipi+Nivo+CT arm. B. Operative time and surgical complexity, where a score of 2 indicates a procedure with complexity comparable to standard lobectomy while >2 indicates increased technical complexity. Two-sided p-value is from Mann Whitney U test comparing distributions of
operative blood loss between standard complexity and increased complexity in Ipi+Nivo+CT arm.

Figure 4. Graphical Abstract

Supplemental Table 1. Arm C Complex Case Details

Supplemental Table 2. Arm D Complex Case Details

Supplemental Figure 1. Postoperative complications

Supplemental Figure 2. Pathology

a. Arm C Increased Difficulty: Bronchial wall with dense fibrotic changes (asterisk) (H&E x2).

b. Arm C Normal Resection: Bronchial wall without significant pathologic changes (H&E x4).

c. Arm D Increased Difficulty: Pleural surface showing prominent pleural fibrosis/adhesions (asterisk) (H&E x4).

d. Arm D Normal Resection: Lung parenchyma lined by unremarkable pleura (H&E x4).

Supplemental Figure 3: Change in PFTs (Pulmonary Function Tests) from pre to post-treatment.

A. Change in FEV (Forced Expiratory Volume) B. Change in FVC (Forced Vital Capacity) C. Change in DLCO (Diffusion Capacity of Lungs for Carbon Monoxide) D. FEV% change separated by surgical difficulty score where a score of 2 indicates a procedure with complexity comparable to standard lobectomy while >2 indicates increased technical complexity. E. FVC% change separated by surgical difficulty score. F. DLCO% change separated by surgical difficulty score.
Clavien Dindo Complications

Proportion of resected patients (%)

Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Nivo+Chemo</th>
<th>Ipi+Nivo+Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68.2%</td>
<td>35%</td>
</tr>
<tr>
<td>1</td>
<td>9.1%</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>4.55%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>13.6%</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>4.55%</td>
<td>1</td>
</tr>
</tbody>
</table>
23 Patients assessed for eligibility
Arm C: Nivo+CT

22 Received Treatment

22 Underwent Surgery

25 Patients assessed for eligibility
Arm D: Ipi+Nivo+CT

22 Received Treatment

20 Underwent Surgery

Did Not Undergo Surgery (n=2)
- Death due to SARS-CoV-2 complications, unrelated to treatment (n=1)
- Deemed no longer surgical candidate, per surgeon discretion (n=1)
Nivo+CT

- 17 (77.3%)
- 2 (9.1%)
- 1 (4.5%)

Total=22

Ipi+Nivo+CT

- 18 (90%)
- 1 (5%)
- 1 (5%)

Total=20
Figure 3
Surgical Outcomes After Chemotherapy plus Nivolumab and Chemotherapy plus Nivolumab and Ipilimumab in Patients with Non-Small Cell Lung Cancer

**ARM C: Nivo+CT**
- 90% R0
- 95% via thoracotomy
- 59% rated as more challenging than standard lobectomy

**ARM D: Ipi+ Nivo+CT**
- 95% R0
- 80% via thoracotomy
- 45% considered challenging

**Clavien-Dindo Complications**

<table>
<thead>
<tr>
<th>Score</th>
<th>Nivo+Chemo</th>
<th>Ipi+Nivo+Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>58.2%</td>
<td>9.1%</td>
</tr>
<tr>
<td>1</td>
<td>9.1%</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
<td>4.55%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>13.6%</td>
</tr>
<tr>
<td>4</td>
<td>20%</td>
<td>4.55%</td>
</tr>
</tbody>
</table>

**Surgical resection after Nivo+CT +/- Ipi**
- Is safe ✓
- Is feasible ✓
- Demonstrates high R0 rates ✓
- But may be more challenging than standard lobectomy
Procedures

Nivo+CT

Total=22

Ipi+Nivo+CT

Total=20

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