Journal for ImmunoTherapy of Cancer

Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer

Joshua E Reuss ,[1,2] Valsamo Anagnostou,[1,2] Tricia R Cottrell,[1] Kellie N Smith,[2] Franco Verde,[3] Marianna Zahurak,[1] Mara Lanis,[1] Joseph C Murray,[1,2] Hok Yee Chan,[2] Caroline McCarthy,[4] Daphne Wang,[1,5] James R White,[1] Stephen Yang,[1,6] Richard Battafarano,[1,6] Stephen Broderick,[1,6] Errol Bush,[1,6] Malcolm Brock,[1,6] Jinny Ha,[1,6] David Jones,[7,8] Taha Merghoub,[9,10] Janis Taube,[1,5] Victor E Velculescu,[1,2] Gary Rosner,[1] Peter Illei,[1,5] Drew M Pardoll,[1,2] Suzanne Topalian,[1,2] Jarushka Naidoo ,[1,2] Ben Levy,[1,2] Matthew D Hellmann,[4,10] Julie R Brahmer,[1,2] Jamie E Chaft,[4,10] Patrick M Forde[1,2]

To cite: Reuss JE, Anagnostou V, Cottrell TR, *et al*. Neoadjuvant nivolumab plus ipilimumab in resectable non-small cell lung cancer. *Journal for ImmunoTherapy of Cancer* 2020;**8**:e001282. doi:10.1136/jitc-2020-001282

JEC and PMF contributed equally.

Accepted 05 August 2020

For numbered affiliations see end of article.

Correspondence to
Dr Patrick M Forde;
Pforde1@jhmi.edu

ABSTRACT

Background We conducted the first trial of neoadjuvant PD-1 blockade in resectable non-small cell lung cancer (NSCLC), finding nivolumab monotherapy to be safe and feasible with an encouraging rate of pathologic response. Building on these results, and promising data for nivolumab plus ipilimumab (anti-CTLA-4) in advanced NSCLC, we expanded our study to include an arm investigating neoadjuvant nivolumab plus ipilimumab.

Methods Patients with resectable stage IB (≥4 cm)–IIIA (American Joint Committee on Cancer Tumor Node Metastases seventh edition), histologically confirmed, treatment-naïve NSCLC received nivolumab 3 mg/kg intravenously plus ipilimumab 1 mg/kg intravenously 6 weeks prior to planned resection. Nivolumab 3 mg/kg was given again approximately 4 and 2 weeks preoperatively. Primary endpoints were safety and feasibility with a planned enrollment of 15 patients. Pathologic response was a key secondary endpoint.

Results While the treatment regimen was feasible per protocol, due to toxicity, the study arm was terminated early by investigator consensus after 9 of 15 patients were enrolled. All patients received every scheduled dose of therapy and were fit for planned surgery; however, 6 of 9 (67%) experienced treatment-related adverse events (TRAEs) and 3 (33%) experienced grade ≥3 TRAEs. Three of 9 patients (33%) had biopsy-confirmed tumor progression precluding definitive surgery. Of the 6 patients who underwent resection, 3 are alive and disease-free, 2 experienced recurrence and are actively receiving systemic treatment, and one died postoperatively due to acute respiratory distress syndrome. Two patients who underwent resection had tumor pathologic complete responses (pCRs) and continue to remain disease-free over 24 months since surgery. Pathologic response correlated with pre-treatment tumor PD-L1 expression, but not tumor mutation burden. Tumor *KRAS/STK11* co-mutations were identified in 5 of 9 patients (59%), of whom two with disease progression precluding surgery had tumor *KRAS/STK11/KEAP1* co-mutations.

Conclusions Though treatment was feasible, due to toxicity the study arm was terminated early by investigator consensus. In light of this, and while the long-term disease-free status of patients who achieved pCR is encouraging, further investigation of neoadjuvant nivolumab plus ipilimumab in patients with resectable NSCLC requires the identification of predictive biomarkers that enrich for response.

INTRODUCTION

Despite curative-intent surgery, the majority of patients with resectable non-small cell lung cancer (NSCLC) relapse and die from their disease,[1 2] highlighting a critical need for therapeutic innovation in this patient population. PD-1 pathway blockade has revolutionized the treatment of advanced NSCLC and is now the backbone of all FDA-approved first-line therapies for locally advanced or metastatic NSCLC lacking a targetable driver mutation.[3]

We reported the first trial of neoadjuvant PD-1 blockade in resectable NSCLC, finding nivolumab (anti-PD-1) to be safe and feasible with major pathologic response (≤10% residual viable tumor in resected specimen) observed in 9 of 20 cases (45%).[4] Building on these results, and coupled with encouraging data for nivolumab plus ipilimumab (anti-CTLA-4) in advanced NSCLC,[5 6] our study was amended to include an arm investigating neoadjuvant nivolumab plus ipilimumab (NCT02259621). Here, we report clinical safety and pathologic response data with genomic and molecular correlates from this study arm, which was terminated early by the consensus of the investigators due to unacceptable toxicity.

METHODS

Patient and public involvement

Patient advocates from the Stand Up To Cancer and LUNGevity foundations worked together with study investigators to inform the design and execution of this trial.

Patient selection and study design

In this multicenter, open-label single-arm phase Ib/II study (NCT02259621) conducted at Johns Hopkins University (JHU) and Memorial Sloan Kettering Cancer Center (MSKCC), adults ≥18 years of age with resectable stage IB (≥4 cm)–IIIA (American Joint Committee on Cancer Tumor Node Metastases seventh edition) treatment-naïve histologically confirmed NSCLC were eligible for enrollment. Other inclusion criteria included Eastern Cooperative Oncology Group performance status 0–1, normal organ function and adequate pulmonary function for resection. Key exclusion criteria included active autoimmune disease, ongoing systemic steroids (>10 mg daily prednisone equivalents) or other immunosuppressive therapy, active concurrent malignancy, history of symptomatic interstitial lung disease, preoperative chemotherapy, and any prior treatment with PD-1 or CTLA-4 pathway blockade.

Enrolled patients received nivolumab 3 mg/kg intravenously together with ipilimumab 1 mg/kg intravenously 6 weeks prior to planned resection. Two additional doses of nivolumab 3 mg/kg were given at approximately 4 and 2 weeks preoperatively (online supplementary figure 1). All patients were offered standard postoperative adjuvant chemotherapy±radiation as indicated. Primary endpoints were feasibility and safety, with feasibility defined as a delay in surgery of ≤24 days from the preplanned surgery date and safety defined by adverse events according to common terminology criteria for adverse events (CTCAE) V.4.0. A six-patient run-in was performed to preliminarily assess safety. Assessment of pathologic response was a key exploratory efficacy endpoint. Planned enrollment was 15 patients.

Study assessments

All eligible patients underwent appropriate cancer staging prior to study enrollment including pathologic assessment of mediastinal lymph nodes (if indicated), in addition to baseline PET-CT and contrast-enhanced CT or MRI of the brain and chest. Mandatory pre-treatment primary tumor core biopsy was performed. Repeat imaging was obtained within 7 days before surgery to assess radiographic response to neoadjuvant therapy and reaffirm resectability. Post-neoadjuvant treatment radiographic response was determined using response evaluation criteria in solid tumors (RECIST) V.1.1.[7] Of note, all RECIST-assessed response determinations were unconfirmed, as only one post-neoadjuvant treatment imaging assessment was made prior to surgical resection.

Resected primary tumors were assessed for residual viable tumor on routine H&E-stained slides by attending pathologists at JHU and MSKCC, as previously described.[4 8] Multiplex immunofluorescence (mIF) was performed for select patients to compare the tumor microenvironment of pre-treatment biopsy samples with post-treatment resected tumor tissue as described in online supplementary methods. Immunohistochemistry and mIF were performed for pre-treatment tumor PD-L1 evaluation.

Identification of somatic tumor genomic alterations for JHU patients was made using whole exome sequencing of tumor and matched normal samples as previously described[4 9] and outlined in online supplementary methods. For MSKCC patients, genomic alterations were identified by targeted next-generation sequencing (NGS) using the MSK-IMPACT assay as described previously.[10] Tumor mutation burden (TMB) from exome and targeted-NGS analyses was normalized as described in online supplementary methods, with normalized TMB estimates used for statistical analyses.

Statistical analysis

Protocol-defined Bayesian stopping rules were originally employed to determine feasibility and safety as previously described[4] and outlined in online supplementary methods. Treatment-related adverse events (TRAEs) were defined as adverse events (AEs) with possible or likely attribution to study drugs. Demographics and safety, as well as clinical, radiographic, pathologic and molecular response data were tabulated using descriptive statistics. Spearman's correlation was used to assess association of pathologic response with pre-treatment tumor PD-L1 expression and TMB, respectively. Reported p values are two-sided with significance level set at 0.05. Statistical analyses were performed using R V.3.4.4.

RESULTS

Safety and clinical data

Between July 2017 and March 2018, nine patients were enrolled to the study arm. Baseline demographics of enrolled patients are outlined in table 1. All nine patients received every scheduled immune-checkpoint blockade (ICB) dose and were fit for planned surgery without treatment-related delays, meeting criteria for feasibility. No patient discontinued study treatment due to AEs; however six of nine patients (67%) experienced TRAEs, and three (33%) experienced grade (G) ≥3 TRAEs including acute respiratory distress syndrome (ARDS; grade 5), as well as pneumonitis, rash, pruritus and headache (all grade 3) (table 2, online supplementary figure 2). ARDS and possible pneumonitis were attributed as possibly related TRAEs; although given the timing of events, and in the setting of complicated surgery, it was felt these were more likely postoperative complications unrelated to study treatment. One patient (11%) had a RECIST-assessed unconfirmed partial response, while four (44%) had stable disease and four (44%) had progressive disease on imaging assessment (figure 1, table 3, online supplementary figure 2). Of the four patients with RECIST-assessed progressive disease,

Table 1 Baseline demographics

Patient number	Age (years)	Gender	Ethnicity	Smoking status (pack years)	Histology	Pre-treatment stage*
1	56	Female	White	Former (3)	ADC	IB
2	50	Male	White	Active (9)	ADC	IIA
3	78	Male	White	Former (56)	ADC	IIB
4	69	Male	White	Former (35)	ADC	IIIA
5	53	Male	White	Former (80)	ADC	IIIA
6	70	Male	White	Former (11)	ADC	IIIA
7	67	Male	White	Former (45)	ADC	IIIA
8	48	Female	White	Former (37)	ADC	IIIA
9	64	Male	White	Former (80)	SCC	IIIA

*Staged according to AJCC TNM 7th edition.
ADC, adenocarcinoma; SCC, squamous cell carcinoma; AJCC TNM, American Joint Committee on Cancer Tumor Node Metastases.

one underwent resection and continues to be disease-free while three had biopsy-proven tumor progression with distant metastases during neoadjuvant therapy that precluded definitive surgery or chemoradiation (figure 1, table 3). In total, six of nine patients (67%) underwent definitive resection. As of data cut-off on December 15, 2019, among the six patients who underwent resection, three are alive and disease-free, two experienced recurrence and are actively receiving systemic treatment, and one died postoperatively due to ARDS (figure 1, online supplementary figure 2). While no protocol-defined dose-limiting TRAEs met the pre-determined stopping boundary for safety, due to substantial clinical toxicity, further study accrual was halted early by consensus of the investigators.

Table 2 Treatment-related adverse events (TRAEs) of possible or likely attribution to study therapies for enrolled population (n=9)

Toxicity	Grade 1–2 n (%)	Grade 3–5 n (%)
Rash	3 (33)	1 (11)
Pruritus	1 (11)	1 (11)
Fatigue	2 (22)	0
ARDS	0	1 (11)*†
Headache	0	1 (11)
Pneumonitis	0	1 (11)*
Abdominal pain	1 (11)	0
Arthralgia	1 (11)	0
Diarrhea	1 (11)	0
Fever	1 (11)	0
Hypothyroidism	1 (11)	0
Infusion reaction	1 (11)	0
Nausea	1 (11)	0
Psoriasis	1 (11)	0

*Suspected to be more likely related to post-surgical complications but coded as "possibly related" TRAEs to be conservative.
†Grade 5 TRAE; all other grade 3–5 TRAEs were grade 3.
ARDS, acute respiratory distress syndrome; TRAE, treatment-related adverse event.

Pathologic assessment and genomic analyses

Pathologic, genomic and molecular data are summarized in figure 1, table 3 and online supplementary data. Pathologic complete response (pCR) was observed in two of six (33%) resected tumors, both from patients with pre-treatment stage IIIA disease. Pathologic response was significantly associated with pre-treatment tumor PD-L1 expression (Spearman rho=−0.88; p=0.02) but not TMB (figure 1). Both patients with pCR had pre-treatment tumor PD-L1 expression ≥50% and continue to be disease-free over 24 months since resection (figure 1, table 3). In patient 5, who had partial radiographic response and pCR to neoadjuvant ICB, dense inflammatory infiltrates with abundant $CD8^+$ cytotoxic T cells fully replaced tumor in the post-treatment resection tissue (figure 2A). In patient 4, who had primary disease progression precluding resection, post-ICB treatment tumor biopsy revealed fully intact tumor with stromal macrophage-predominant infiltrates (figure 2B).

Co-occurring tumor mutations in *KRAS/STK11* were identified in five of nine patients (56%) including two (patients 2 and 4) with co-mutations in *KRAS/STK11/KEAP1* who experienced primary tumor progression precluding definitive resection (figure 1, table 3). A third patient (patient 8) with primary tumor progression precluding surgery had co-occurring mutations in *BRAF/STK11/TP53*. All four patients with RECIST-assessed primary progression were TMB-low with low (≤1%) pre-treatment tumor PD-L1 expression (figure 1, table 3). Patient 1 with co-occurring *KRAS/STK11* mutations and absent PD-L1 expression had progressive disease on pre-surgical imaging but underwent definitive surgery and had 100% residual tumor in the resected specimen. Interestingly, patient 5, who achieved a pCR with neoadjuvant

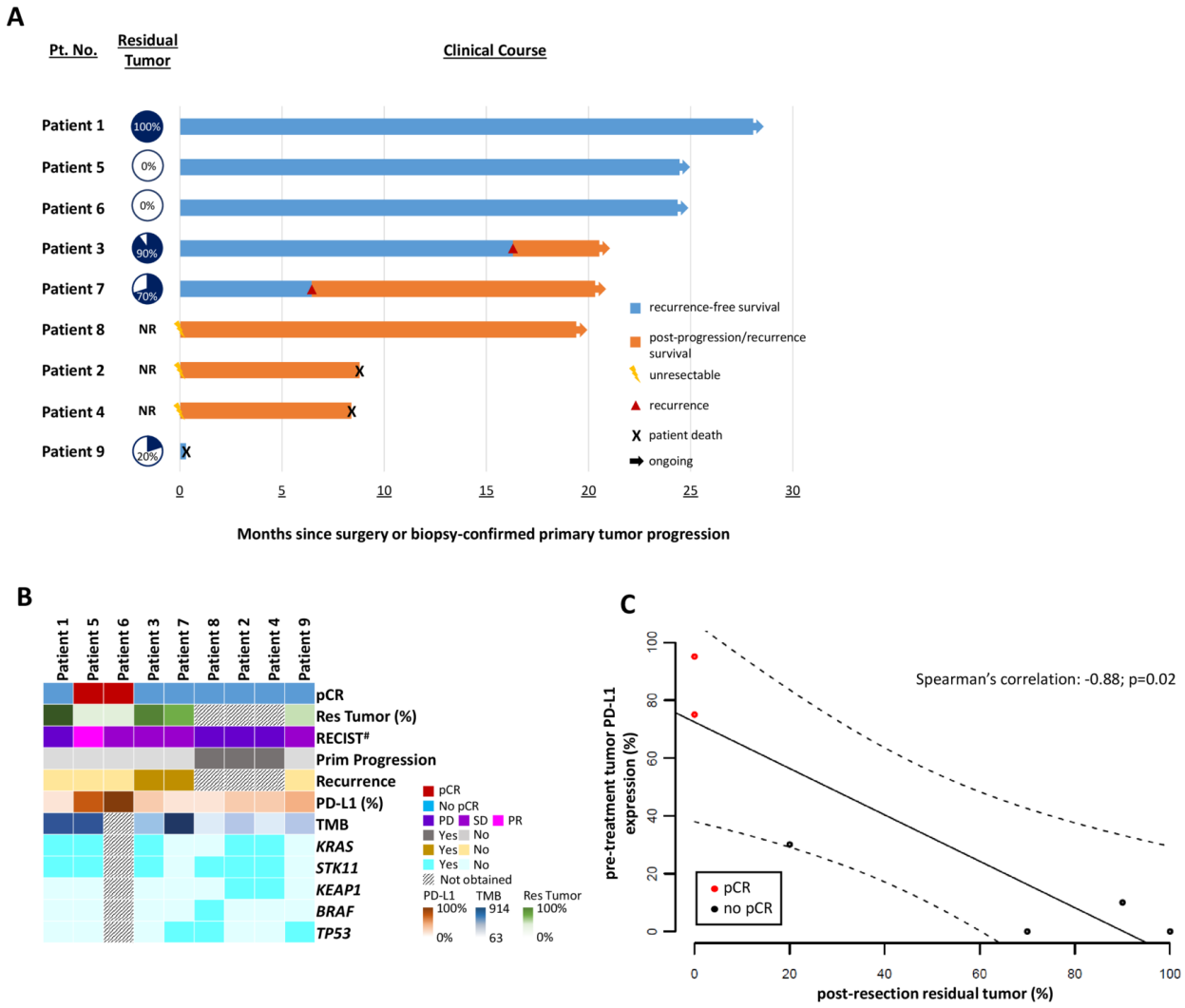


Figure 1 Clinical follow-up with radiographic and pathologic response characteristics plus molecular correlates. (A) Swimmer-style clinical follow-up plot detailing clinical course of all enrolled patients. Residual viable tumor at resection is noted in the column to the right of patient number and to the left of outlined clinical course for that patient. NR indicates a tumor that was "not resected" due to primary disease progression precluding definitive surgery. Clinical course outlines time following surgery or biopsy-confirmed primary disease progression. (B) Genomic data for study patients including pathologic and radiographic response data, in addition to pre-treatment tumor PD-L1 expression. (C) Correlation between pre-treatment tumor PD-L1 expression and post-resection residual tumor. The solid dark line indicates the linear regression line, and the dashed lines indicate the upper and lower boundaries of the 95% CI. #All radiographic RECIST assessments were unconfirmed, as only one post-neoadjuvant treatment imaging assessment was made prior to surgical resection. Patient 2 demonstrated clear progressive disease on PET imaging despite stable disease on RECIST response assessment of chest CT and was thus categorized as having "PD". NR, not resected; pCR, pathologic complete response; PD, progressive disease; PR, partial response; Prim. Progression, primary progression; RECIST, response evaluation criteria in solid tumors; Res. Tumor, residual tumor; SD, stable disease; TMB, tumor mutation burden.

ICB, had a tumor with co-occurring *KRAS/STK11* mutations with high TMB and 75% pre-treatment tumor PD-L1 expression.

DISCUSSION

After demonstrating the safety and feasibility of neoadjuvant anti-PD-1 monotherapy in resectable NSCLC,[4] we amended our study to include an arm investigating neoadjuvant nivolumab plus ipilimumab, a decision supported by promising data in metastatic NSCLC.[5 6] While technically feasible without dose-limiting TRAEs meeting the pre-defined safety stopping rule, this regimen was associated with toxicity. Furthermore, when examining key metrics for perioperative clinical trials, in this study one-third of patients experienced primary disease progression precluding potentially curative surgery and a fourth patient died postoperatively. Given these factors, the study arm was closed to further accrual.

Grade 3 or higher TRAEs were observed in 33% of enrolled patients in our study, a numerically higher rate than that reported in an interim presentation of the NEOSTAR study, an ongoing phase II single-center study

Table 3 Radiographic, pathologic and molecular response characteristics

Patient number	Radiographic response*	Residual tumor (%)	Pre-treatment PD-L1 (%)	Normalized tumor mutation burden	Driver genes with sequence alterations
1	PD	100	0	344	*KRAS, STK11*
2	PD†	N/A	1	109	*KRAS, KEAP1, STK11*
3	SD	90	10	147	*KRAS, STK11, TP53*
4	PD	N/A	1	63	*KRAS, KEAP1, STK11*
5	PR	0 (pCR)	75	554	*KRAS, STK11*
6	SD	0 (pCR)	95	Undeterminable‡	Undeterminable‡
7	SD	70	0	914	*TP53*
8	PD	N/A	0	78	*BRAF, STK11, TP53*
9	SD	20	30	99	*TP53*

*All radiographic RECIST assessments were unconfirmed, as only one post-neoadjuvant treatment imaging assessment was made prior to surgical resection.
†Clear metastatic disease on PET imaging despite stable disease on RECIST response assessment of chest CT and thus coded as having "PD".
‡Pre-treatment tumor tissue for patient 6 was insufficient for whole exome sequencing and thus genomic assessments could not be performed.
N/A, not applicable; pCR, pathologic complete response; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

which randomized 44 patients with resectable NSCLC to neoadjuvant nivolumab or nivolumab plus ipilimumab.[11] Differences in toxicity rates are likely attributable to sample size and overall the observed rate of ≥G3 TRAEs in our study was similar to that seen with nivolumab plus ipilimumab in advanced NSCLC[6] and in neoadjuvant studies of resectable melanoma.[12] Nevertheless, the toxicity in our study arm exceeded that reported in neoadjuvant studies of anti-PD1 monotherapy[4 11 13 14] and combination ICB plus chemotherapy,[15 16] which was a major determinant in our decision to terminate this study arm early.

All patients with imaging-assessed progressive disease in our study appeared to have true progression (vs pseudoprogression), as progressive disease was biopsy-confirmed in the three patients who were no longer surgical candidates, and 100% residual tumor was present in the resection specimen from the patient who underwent definitive surgery. Biopsy confirmation of progressive disease is important as, while not seen in this small study, cases of pseudoprogression have been observed in other studies of neoadjuvant checkpoint blockade,[11] and it is vital that such patients are not excluded from potentially curative surgery. With the caveat of sample size, the rate of disease progression precluding surgery (33%) observed in this study was greater than that seen in our prior neoadjuvant nivolumab monotherapy study (5%).[4] While neoadjuvant treatment was delivered over a greater length of time in our study of nivolumab plus ipilimumab (6 vs 4 weeks), time alone was unlikely the sole factor contributing to the higher observed rate of disease progression, as only 5% of patients randomized to the nivolumab plus ipilimumab arm of NEOSTAR (identical treatment duration) experienced progressive disease precluding surgery.[11] However, early progression as a potential limitation of neoadjuvant ICB does have a corollary in advanced lung cancer; progressive disease as best response was observed in 23% of patients with treatment-naïve advanced NSCLC randomized to the nivolumab plus ipilimumab arm (n=583) of the phase III CheckMate 227 trial.[6] Furthermore, the median time to response to nivolumab plus ipilimumab in this trial was 2.7 months, suggesting the unconfirmed response rate of 11% observed in our study may underestimate the true response rate with this regimen, though speculation on this is severely limited by sample size. For comparison, neoadjuvant chemotherapy has demonstrated a radiographic response rate of ~50% in phase III trials in resectable NSCLC with only 9% of patients unable to undergo surgery.[17 18] Taken together, this highlights the magnified importance of response rate, disease control and maintaining resectability in assessing the clinical utility of neoadjuvant ICB in resectable NSCLC, where surgery remains paramount to the goal of cure.

One possible explanation for the poor clinical outcomes observed in our study was the high incidence (56%) of genomic alterations reported to be associated with ICB resistance. Co-mutations in *KRAS/STK11* and *KRAS/KEAP1* have both been associated with ICB resistance and poor survival in advanced NSCLC,[19 20] as have concurrent *STK11/KEAP1* mutations, which frequently co-occur with *KRAS* mutations.[21 22] Furthermore, *STK11/KEAP1* co-mutations have been observed to occur twice as frequently in metastatic versus resectable lung adenocarcinoma, suggesting this molecular profile may be an indicator of aggressiveness.[22] While limited by sample size, our finding of tumor progression precluding resection in patients with *KRAS/STK11/KEAP1* co-mutations

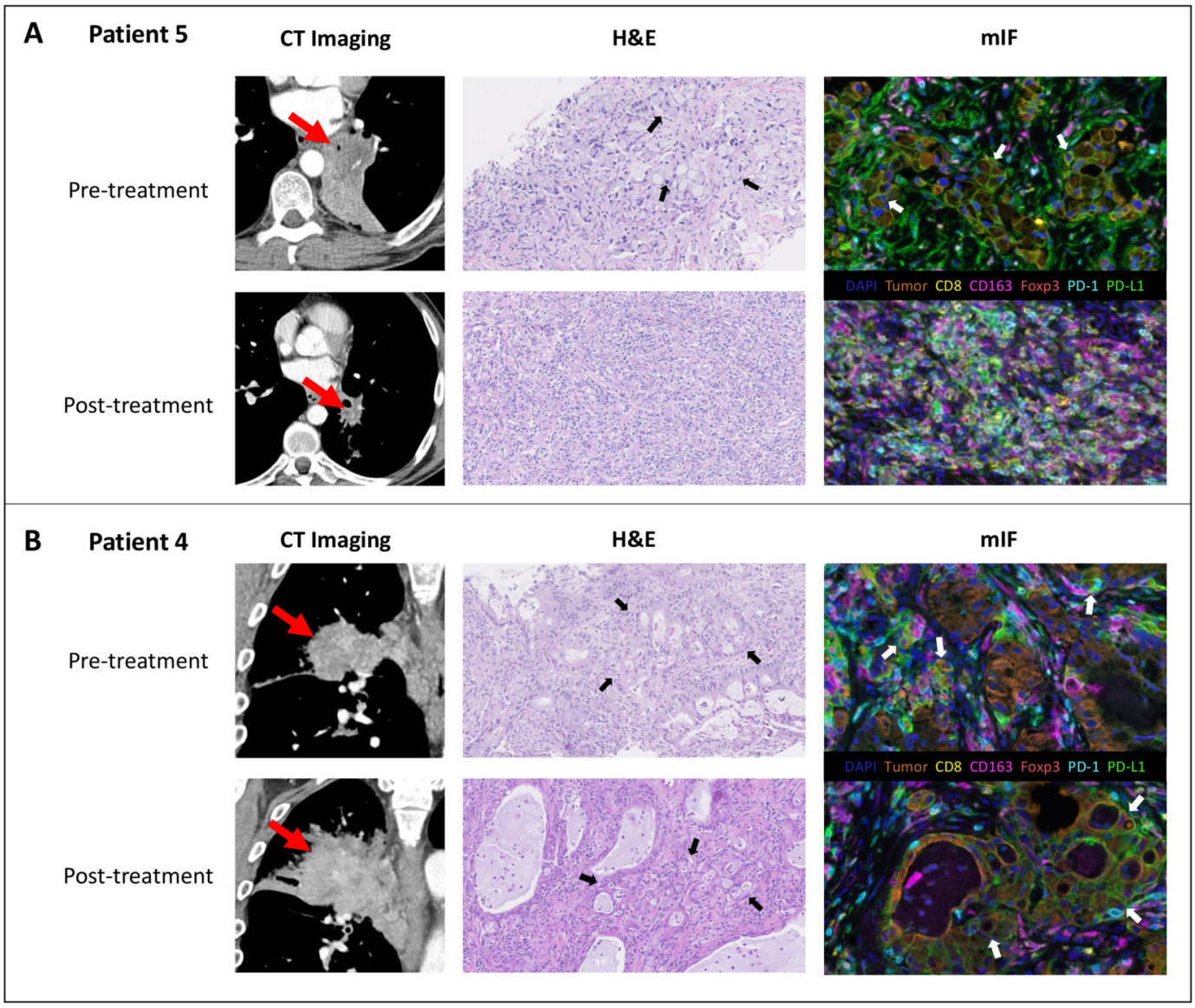


Figure 2 Radiographic and pathologic response to neoadjuvant nivolumab plus ipilimumab for (A) patient with pathologic complete response (pCR) and (B) no pathologic response to treatment. (A) Radiographic and pathologic response for patient 5 with pCR to neoadjuvant nivolumab plus ipilimumab. Pre-treatment contrast-enhanced CT imaging demonstrates a 4.4×4.2 cm left lower infrahilar mass (red arrow) encasing adjacent bronchi with posterior post-obstruction atelectasis. Pre-treatment biopsy demonstrates abundant infiltrating malignant signet ring cells distinguished by atypical eccentric nuclei surrounding a large mucinous vacuole (black arrows). The pre-treatment tumor shows abundant PD-L1 positive tumor and stromal cells (PD-L1 in green, cytokeratin expression in orange highlights tumor cells (white arrows)). Post-treatment pre-resection imaging demonstrates decreased size of mass now measuring 2.2×2.7 cm (red arrow) with re-expansion of previously collapsed lung. Post-treatment resection tissue shows abundant inflammatory cells, cellular fibrosis and neovascularization; features typical of immune-mediated tumor regression. Multiplex immunofluorescence (mIF) highlights abundant cytotoxic T cells (CD8, yellow) and macrophages (CD163, magenta), as well as scattered regulatory T cells (Foxp3, red). No residual tumor cells are identified (note the absence of orange tumor cells on mIF), consistent with pCR. (B) Radiographic and histologic findings for patient 4 with primary tumor progression preventing definitive surgery. Pre-treatment contrast-enhanced CT imaging demonstrates a 6.8×6.5 cm posterior right upper lobe mass (red arrow) encasing the right upper lobe bronchus. Post-treatment imaging demonstrates enlargement of mass to 8.3×6.9 cm (red arrow) with worsening encasement and enlarging paratracheal adenopathy. On assessment of pre-treatment and post-treatment biopsies, atypical glandular structures (black arrows), including confluent (cribriform) glands, are present with no histologic evidence of tumor regression in post-treatment specimen. PD-L1 expression (green) is seen on tumor cells (orange, white arrows) both pre-treatment and post-treatment. Scant pre-treatment and post-treatment inflammatory infiltrates are composed largely of macrophages (CD163, magenta), which are predominantly localized to the intra-tumoral stroma. H&E photomicrographs taken at ×200 original magnification. mIF images taken at ×400 original magnification. mIF, multiplex immunofluorescence.

further supports this. That said, the predicted functional consequence of mutational profiles alone is likely insufficient to predict ICB response. In our study, patient 5 with tumor *KRAS/STK11* co-mutations had a pCR to neoadjuvant ICB and continues to be disease-free. This tumor was TMB-high with high PD-L1 expression. Furthermore, in a retrospective analysis of the KEYNOTE-042 study, both *STK11* and *KEAP1* mutational status were not associated with survival or response to anti-PD1 therapy in advanced NSCLC.[23]

One additional consideration is whether patients with primary disease progression in our study had an aggressive disease phenotype resistant to ICB or hyperprogression induced by ICB. Hyperprogressive disease (HPD) is a putative response pattern to ICB that has yet to be fully elucidated or uniformly defined. Given this, speculation as to the occurrence of HPD in this small study is difficult. As all patients in our study with distant progression on ICB had pre-treatment node-positive disease, the presence of occult metastases in the setting of an underlying molecular predisposition for ICB resistance may have contributed to widespread progressive disease. Together, this suggests multiple intrinsic and extrinsic variables factor into ICB response, and underscores the need for further research to define reproducible predictive biomarkers.

Pre-treatment tumor PD-L1 expression, but not TMB, correlated with pathologic response in our study, the reverse of what was observed in our neoadjuvant PD-1 monotherapy study.[4] Small sample size likely contributed to this difference, though pre-treatment PD-L1 expression was also found to correlate with pathologic response in the NEOSTAR study.[11] With the caveat of sample size, both NEOSTAR and our study report a pCR rate of ~30% with neoadjuvant nivolumab plus ipilimumab.[11] In addition, neoadjuvant PD-1 blockade plus chemotherapy has demonstrated an encouraging pCR rate of 33%–59% with tolerable safety profile in both published and ongoing phase II trials in resectable NSCLC.[16 24] This is substantially higher than the median pCR rate observed with neoadjuvant chemotherapy, which has been reported at ~4% in resectable NSCLC.[25] With additional long-term follow-up and the pending completion of several phase III trials of neoadjuvant chemoimmunotherapy in resectable NSCLC, data will soon be available to evaluate the utility of pCR as a surrogate biomarker for survival in neoadjuvant ICB NSCLC trials, which will be vital in determining the clinical utility of this approach in resectable NSCLC.

In summary, though the treatment regimen was feasible, toxicity together with several cases of primary tumor progression precluding definitive resection led to early termination of our study. In light of this, and while the long-term disease-free status of patients who achieved pCR is encouraging, further investigation of neoadjuvant nivolumab plus ipilimumab in patients with resectable NSCLC requires the identification of predictive biomarkers that enrich for response.

Author affiliations
[1]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, Maryland, USA
[2]The Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University, Baltimore, Maryland, USA
[3]Department of Radiology, Johns Hopkins, Baltimore, Maryland, USA
[4]Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[5]Department of Pathology, Johns Hopkins, Baltimore, Maryland, USA
[6]Department of Surgery, Johns Hopkins, Baltimore, Maryland, USA
[7]Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[8]Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[9]Parker Institute for Cancer Immunotherapy, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[10]Weill Cornell Medical College, New York, New York, USA

Correction notice This article has been corrected since it was published online. The author name 'Matthew Hellmann' was updated to 'Matthew D Hellmann'.

Twitter Joshua E Reuss @Joshua_Reuss and Patrick M Forde @FordePatrick

Acknowledgments We would like to thank the patients and families who participated in this study, as well as the research teams at Johns Hopkins University and Memorial Sloan-Kettering Cancer Center.

Contributors Conceptualization and study design: VA, KNS, MZ, GR, JEC, PMF. Data acquisition and analysis: all authors. Data interpretation: all authors. Original drafting of manuscript and figures: JER. Manuscript revision and editing: all authors. All authors read and approved the final manuscript, and have agreed to be accountable for all aspects of the work.

Funding This work was funded in part by grants from the National Institutes of Health (CA121113, CA006973, CA180950, CA233259, T32 CA193145, T32 CA009071-38, R01 CA142779), Stand Up To Cancer – CRI Immunology Dream Team (SU2C-AACR-DT1012), Stand Up To Cancer – American Cancer Society Lung Cancer Dream Team, Bristol-Myers Squibb International Immuno-Oncology Network, Conquer Cancer: The ASCO Foundation – Young Investigator Award (90083528), LUNGevity Foundation, the V Foundation, Lung Cancer Foundation of America, MacMillan Foundation, Eastern Cooperative Oncology Group–American College of Radiology Imaging Network, Swim Across America, The Allegheny Health Network – Johns Hopkins Research Fund and the Maryland Department of Health and Mental Hygiene Cigarette Restitution Fund Program, the Commonwealth Foundation, the Bloomberg–Kimmel Institute for Cancer Immunotherapy, Memorial Sloan Kettering Cancer Center (P30 CA008748), Johns Hopkins University Cancer Center (P30 CA006973).

Disclaimer Funding sources had no role in the study design, data collection/analysis/interpretation, report writing or decision to submit the article for publication.

Competing interests JER has received grants from Conquer Cancer: The ASCO Foundation. VA has received grants from the National Institutes of Health, The LUNGevity Foundation, The V Foundation, Swim Across America, The Allegheny Health Network – Johns Hopkins Research Fund and the Maryland Department of Health and Mental Hygiene Cigarette Restitution Fund Program, Bristol-Myers Squibb, and Personal Genomic Diagnostics. KS has received personal fees from Illumina. JRW is the founder and owner of Resphera Biosciences LLC. SB has received personal fees from Bristol-Myers Squibb. DJ has been on the advisory boards of Diffusion Pharmaceuticals, Merck, and AstraZeneca. TM has received grants from Bristol-Myers Squibb, Surface Oncology, Kyn Therapeutics, Infinity Pharmaceuticals, Peregrine Pharmaceuticals, Adaptive BioTechnologies, Leap Therapeutics, and Aprea; has received personal fees from Leap Therapeutics, Immunos Therapeutics, and Pfizer; is co-founder and holds equity in Imvaq Therapeutics; and has filed patents for work related to PD-1 and CTLA-4. JT has received grants from Akoya Biosciences and Bristol-Myers Squibb, has received non-financial support from Akoya Biosciences, and has been on the advisory boards of Bristol-Myers Squibb, Merck, AstraZeneca, Compugen, and Regeneron. VEV has received grants from the National Institutes of Health, The Commonwealth Foundation, and Bloomberg–Kimmel Institute for Cancer Immunotherapy; has been on the advisory boards of Bristol-Myers Squibb, Genentech, Merck, and Takeda Pharmaceuticals; and is the founder, serves on board of directors and owns stock in Delfi Diagnostics and Personal Genome Diagnostics. GR has received personal fees from Medicago and owns stock in Johnson & Johnson.

PI has received grants from Bristol-Myers Squibb and Biomarker Strategies, LLC; has received personal fees from AbbVie, AstraZeneca, Bayer, Veran Medical Technologies Inc., and Roche Diagnostics; and has been on the advisory boards of AstraZeneca and Guardant Health. DMP and ST have received research grants from Bristol-Myers Squibb and Compugen; have received personal fees from Aduro Biotech, Five Prime Therapeutics, Tizona Therapeutics, DNAtrix, RAPT, WindMIL, Dragonfly Therapeutics, Ervaxx, Amgen, MedImmune, Merck, Compugen, Dynavax, Immunomic Therapeutics, Janssen Oncology, Immunocore, Bristol-Myers Squibb, Arbor Pharmaceuticals, and NexImmune; and own equity in Aduro Biotech, Potenza Therapeutics, Five Prime Therapeutics, Tizona Therapeutics, DNAtrix, RAPT, WindMIL, Dragonfly Therapeutics, Ervaxx, and Trieza Therapeutics. JN has received grants from AstraZeneca and Merck; has been on the advisory boards of AstraZeneca, Bristol Myers-Squibb, and Genentech/Roche; and has received personal fees from AstraZeneca, Bristol-Myers Squibb, and Merck. BL has received grants from Eli Lilly, Genentech, Bristol-Myers Squibb, AstraZeneca, Turning Point Therapeutics, and Amgen; and has received personal fees from Eli Lilly, Genentech, AstraZeneca, Celgene, Pfizer, Merck, Novartis, and Takeda. MH has received grants from Bristol-Myers Squibb; has received personal fees from Bristol-Myers Squibb, Merck, AstraZeneca, Genentech/Roche, Nektar, Syndax, Mirati, Shattuck Labs, Immunai, Blueprint Medicines, Achilles, Arcus, and Eli Lilly; owns equity in Shattuck Labs, Immunai, and Arcus; and has filed patents related to the use of tumor mutation burden to predict response to immunotherapy. JRB has received grants from AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, Merck, RAPT Therapeutics, Inc., and Revolution Medicines; has received personal fees from Genentech/Roche; has been on the advisory boards of Amgen, Bristol-Myers Squibb, Genentech/Roche, Eli Lilly, GlaxoSmithKline, Merck, and Sanofi; and has been on the Data and Safety Monitory boards of GlaxoSmithKline and Sanofi. JEC has received grants from the National Institutes of Health; and has also received grants and personal fees from Merck, Bristol-Myers Squibb, Genentech, and AstraZeneca. PMF has received grants from the LUNGevity Foundation, Stand Up To Cancer, AstraZeneca, Bristol-Myers Squibb, Kyowa, Novartis, and Corvus; and has been on the advisory boards of Abbvie, AstraZeneca, and Bristol-Myers Squibb. The remaining authors declare no conflicts of interest.

Patient consent for publication Not required.

Ethics approval Patients provided written informed consent for inclusion. The study protocol was approved by the institutional review boards of JHU and MSKCC.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Patient and correlative datasets beyond those published in supplementary data are available from the corresponding author on reasonable request.

ORCID iDs
Joshua E Reuss http://orcid.org/0000-0002-6401-9080
Jarushka Naidoo http://orcid.org/0000-0002-3470-8686

REFERENCES

1 Goldstraw P, Chansky K, Crowley J, *et al*. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016;11:39–51.
2 Higgins KA, Chino JP, Berry M, *et al*. Local failure in resected N1 lung cancer: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 2012;83:727–33.
3 Remon J, Passiglia F, Ahn MJ, *et al*. Immune checkpoint inhibitors in thoracic malignancies: review of the existing evidence by an IASLC expert panel and recommendations. *J Thorac Oncol* 2020.
4 Forde PM, Chaft JE, Smith KN, *et al*. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018;378:1976–86.
5 Hellmann MD, Ciuleanu T-E, Pluzanski A, *et al*. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018;378:2093–104.
6 Hellmann MD, Paz-Ares L, Bernabe Caro R, *et al*. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019;381:2020–31.
7 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
8 Cottrell TR, Thompson ED, Forde PM, *et al*. Pathologic features of response to neoadjuvant anti-PD-1 in resected non-small-cell lung carcinoma: a proposal for quantitative immune-related pathologic response criteria (irPRC). *Ann Onc* 2018;29:1853–60.
9 Anagnostou V, Niknafs N, Marrone K, *et al*. Multimodal genomic features predict outcome of immune checkpoint blockade in non-small-cell lung cancer. *Nature Cancer* 2020;1:99–111.
10 Cheng DT, Mitchell TN, Zehir A, *et al*. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *J Mol Diagn* 2015;17:251–64.
11 Cascone T, William WN, Weissferdt A, *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. *JCO* 2019;37:8504.
12 Rozeman EA, Menzies AM, van Akkooi ACJ, *et al*. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. *Lancet Oncol* 2019;20:948–60.
13 Kwiatkowski DJ, Rusch VW, Chaft JE, *et al*. Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): interim analysis and biomarker data from a multicenter study (LCMC3). *JCO* 2019;37:8503.
14 Gao S, Li N, Gao S, *et al*. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. *J Thorac Oncol* 2020;15:816–26.
15 Provencio M, Nadal E, Insa A, *et al*. Neoadjuvant chemo-immunotherapy for the treatment of stage IIIA resectable non-small-cell lung cancer (NSCLC): a phase II multicenter exploratory study—final data of patients who underwent surgical assessment. *JCO* 2019;37:8509.
16 Shu CA, Gainor JF, Awad MM, *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;21:786–95.
17 Gilligan D, Nicolson M, Smith I, *et al*. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007;369:1929–37.
18 Felip E, Rosell R, Maestre JA, *et al*. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol* 2010;28:3138–45.
19 Arbour KC, Jordan E, Kim HR, *et al*. Effects of co-occurring genomic alterations on outcomes in patients with *KRAS*-mutant non-small cell lung cancer. *Clin Cancer Res* 2018;24:334–40.
20 Skoulidis F, Goldberg ME, Greenawalt DM, *et al*. *STK11/LKB1* mutations and PD-1 inhibitor resistance in *KRAS*-mutant lung adenocarcinoma. *Cancer Discov* 2018;8:822–35.
21 Skoulidis F, Byers LA, Diao L, *et al*. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov* 2015;5:860–77.
22 Shen R, Martin A, Ni A, *et al*. Harnessing clinical sequencing data for survival stratification of patients with metastatic lung adenocarcinomas. *JCO Precis Oncol* 2019;3:9.
23 Cho BC LG, Kowalski DM, Kasahara K, *et al*. CT084—Relationship between *STK11* and *KEAP1* mutational status and efficacy in KEYNOTE-042: pembrolizumab monotherapy versus platinum-based chemotherapy as first-line therapy for PD-L1-positive advanced NSCLC. 2020 AACR Virtual Annual Meeting I 2020.
24 Provencio M, Nadal E, Insa A, *et al*. OA13.05 NADIM study: updated clinical research and outcomes. *J Thorac Oncol* 2019;14:S241.
25 Hellmann MD, Chaft JE, William WN, *et al*. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. *Lancet Oncol* 2014;15:e42–50.

SUPPLEMENTARY METHODS

Multiplex Immunofluorescence

Select specimens were assessed with multispectral immunofluorescence as previously described [1] with minor modifications as follows. Tumors were stained for simultaneous detection and quantitation of cytokeratin (tumor cells), CD8 (cytotoxic T cells), FoxP3 (regulatory T cells), CD163 (macrophages), PD-1, and PD-L1 as outlined in table below. Nuclei were visualized by DAPI staining (Perkin Elmer Opal 7-color kit). Multiplexed slides were scanned using the PerkinElmer Vectra3.0 (Perkin Elmer, Hopkington, MA) multispectral microscope. PD-L1 expression on tumor cells for Johns Hopkins University (JHU) patients was manually interpreted on whole slide scans consistent with interpretation guidelines for PD-L1 immunohistochemistry using the SP142 clone. Immunohistochemistry using the E1L3N clone was utilized to quantify PD-L1 expression on pre-treatment tumor cells for Memorial Sloan Kettering Cancer Center (MSKCC) patients.

Position	Antibody	Clone (host)/Company	Final Concentration	Incubation	TSA dyes
1	FoxP3	236A/E7 (mouse)/Affymetrix	5.00 µg/mL	30 min	570
2	CD8	4B11 (mouse)/AbD Ser	1:800	30 min	540
3	AE1/AE3	M3515 (mouse) DAKO	1:500	30 min	620
4	PD-1	EPR4877 (rabbit)/AbCam	0.5 µg/mL	30 min	650
5	PD-L1	SP142 (rabbit)/Spring Bio.	0.19 µg/mL	60 min	520
6	CD163	10D6 (mouse)/Leica Bio.	0.49 µg/mL	120 min	520
7	DAPI*	Perkin Elmer Opal 7-color kit	2 drops/ml	5 min	

*Technically non-antibody fluorescent dye that binds minor groove of DNA and allows nuclei visualization.

Whole exome sequencing and bioinformatics analysis

Whole exome sequencing was performed on pre-treatment tumor and matched normal samples for the 5 Johns Hopkins University (JHU) cases with sufficient tissue (Supplemental Table 2). Formalin-fixed paraffin-embedded (FFPE) tumor samples underwent pathological review for confirmation of diagnosis and assessment of tumor purity. Tissue sections from each FFPE block were macrodissected to remove normal tissue. Matched normal samples were provided as peripheral blood. DNA was extracted from

patients' tumors and matched peripheral blood using the Qiagen DNA FFPE and Qiagen DNA blood mini kit, respectively (Qiagen, CA). Fragmented genomic DNA from tumor and normal samples was used for library construction and exonic regions were captured in solution using the Agilent SureSelect v.4 kit (Agilent, Santa Clara, CA) according to the manufacturers' instructions as previously described [2]. Paired-end sequencing, resulting in 100 bases from each end of the fragments for the exome libraries was performed using Illumina HiSeq 2500 instrumentation (Illumina, San Diego, CA). The mean depth of total coverage for the JHU tumor samples was 217x (Supplementary Table 2). Somatic mutations, consisting of point mutations, insertions, and deletions across the whole exome were identified using the VariantDx custom software for identifying mutations in matched tumor and normal samples as previously described [2]. Somatic sequence alteration calls are listed in Supplementary Table 3.

For the 3 MSKCC cases, the MSK-IMPACT targeted next-generation sequencing (NGS) assay was utilized to identify tumor-derived mutation in 468 genes [3]. Sequencing metrics and variants identified are summarized in Supplementary Tables 1-3.

Normalized tumor mutation burden conversion

Tumor mutation burden (TMB) values from whole exome sequencing and targeted NGS were normalized to provide comparability of samples across platforms as follows: the regions of interest (ROI) from each panel were applied to an *in silico* evaluation of exome-based mutation burden and panel-specific mutation burden. Exome-based somatic mutations identified by the TCGA PanCancer Atlas MC3 project [4] from 9,041 patients were collected, requiring a minimum of 4 supporting reads and 5% mutant allele frequency. Mutations present within each panel's ROI were aggregated to compute *in silico* panel tumor mutation loads for each patient. For each ROI, we computed moving quantile values (5^{th}, 10^{th}, 25^{th} and 50^{th} percentiles) of total mutational load across a sliding window of log-transformed

panel loads. We employed the moving median values (50th percentile) to generate an estimate for expected total mutational burden given a specific panel load (Supplementary Tables 1-2).

Feasibility & Safety Stopping Rules

Feasibility

The feasibility of neoadjuvant nivolumab plus ipilimumab was based on patients proceeding to surgery without extended treatment-related delay, defined as greater than 24 days following the initially planned surgery date. A probability-based decision rule was used to decide if the probability of successfully proceeding to surgery as planned was convincingly less than .90.

Previously we expected*, a priori*, the feasibility of neoadjuvant nivolumab to be high and that 90% of patients would not have surgery delayed. Based on results of our study of neoadjuvant nivolumab in resectable NSCLC,[5] where all 19 patients proceeded to surgery without delay, we expected this would be true for the nivolumab plus ipilimumab arm as well. The monitoring rule for the nivolumab plus ipilimumab arm therefore used an *a priori* optimistic Beta(9,1) prior distribution. This distribution corresponds to an assumption that 9 out of 10 patients will proceed to surgery as planned and 90% certainty that feasibility is between .715 and .994. The stopping rule would hold enrollment if, given the data, there is at least 90% probability that fewer than 90% of patients could continue to surgery without treatment related delays (see table below).

Stopping Rule for Feasibility

No. patients for whom the regimen is feasible	0	1	2	3	4	5	6	7
No. of patients	2	4	5	6	8	10	12	14

Safety

Neoadjuvant nivolumab, 3 mg/kg IV, on days -28 and -14 prior to surgery had been tested for safety and feasibility in 19 patients in our previous study of neoadjuvant nivolumab in resectable NSCLC.[5] Eighteen of 19 patients received all doses of neoadjuvant therapy.

The primary dose-limiting toxicities (DLTs) of concern for safety monitoring in this study arm of neoadjuvant nivolumab plus ipilimumab included grade 3-4 toxicities of liver, GI, renal, lung parenchyma and any other grade 3-4 toxicity, defined according to CTCAE v4.0, that in the opinion of the investigator significantly interfered with the subjects' optimal perioperative management. They were monitored continuously through day 100 following the last dose of study treatment (or day 30 post surgery, whichever was longer).

For our study of neoadjuvant nivolumab in resectable NSCLC, we assumed that the risk of grade 3-4 toxicities in advanced NSCLC and other solid tumors was 25% and used a Beta prior distribution with parameters 1 and 3.[5] With this prior, there is 90% probability that the proportion of these toxicities is between 1.7% and 53.6%. The safety stopping rule for our study arm of nivolumab plus ipilimumab applied this prior distribution to the observed number of patients experiencing DLTs with computation of the resulting probability of DLT. If the posterior probability of risk >.25, based on Bayes rule and the assumption implied by the prior, was 70% or higher, the study would stop (see table below).

In the first six patients enrolled, there were two modifications to the above stopping rule:

1. If the first patient on study experienced a DLT, we would not stop, but treat one additional patient before making a decision.

2. In the first six patients, if there had been one DLT and a second DLT was seen in the fifth or sixth patient, the study would be paused for an additional safety review and may or may not continue.

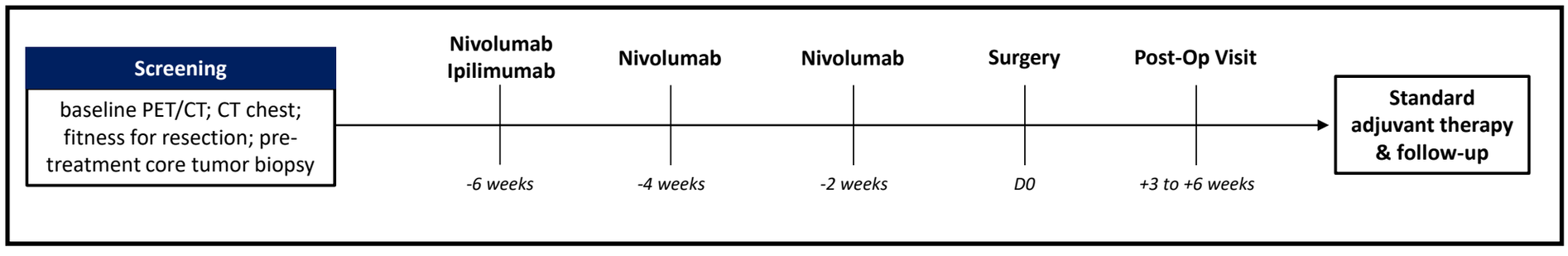
Stopping rule for safety

Stop if DLTs in	2	3	4	5
And N total patients	2-4	5-8	9-11	12-15

SUPPLEMENTAL METHODS REFERENCES

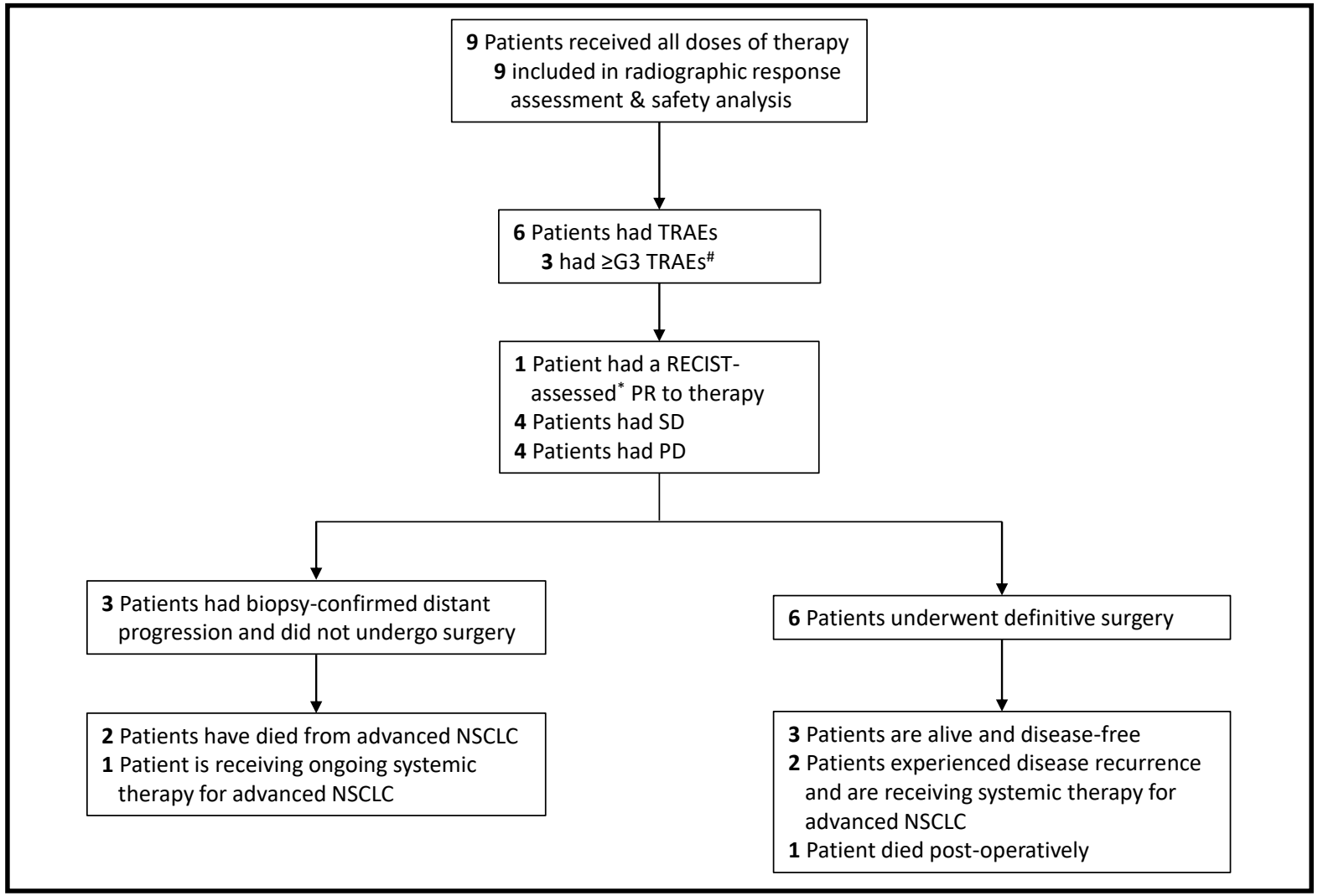
1. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med*. 2016;374(26):2542-52.
2. Anagnostou V, Niknafs N, Marrone K, et al. Multimodal genomic features predict outcome of immune checkpoint blockade in non-small-cell lung cancer. *Nature Cancer*. 2020;1(1):99-111.
3. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology. *J Mol Diagn*. 2015;17(3):251-64.
4. Ellrott K, Bailey MH, Saksena G, et al. Scalable Open Science Approach for Mutation Calling of Tumor Exomes Using Multiple Genomic Pipelines. *Cell Syst*. 2018;6(3):271-81.e7.
5. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *N Engl J Med*. 2018;378(21):1976-86.

Supplemental Figure 1



Supplemental Figure 1: Study schema for neoadjuvant nivolumab plus ipilimumab in resectable NSCLC (NCT02259621). Patients with surgically resectable AJCC TNM 7th edition stage IB (≥4cm) – IIIA histologically confirmed non-small cell lung cancer (NSCLC) were eligible for inclusion. Nivolumab 3mg/kg IV was given together with ipilimumab 1 mg/kg IV 6 weeks prior to planned resection (D0). Nivolumab 3 mg/kg was given again at approximately 4 and 2 weeks prior to resection. Blood for correlative analyses was drawn pre-treatment, with each dose of neoadjuvant therapy, prior to surgery, and post-operatively.
AJCC TNM: American Joint Committee on Cancer Tumor Node Metastases; D0: day 0 (day of surgery); NSCLC: non-small cell lung cancer IV: intravenous.

Supplemental Figure 2



Supplemental Figure 2: Patient flow chart of clinical outcomes

#One G5 TRAE (ARDS) coded as "possibly-related" TRAE but suspected to be more likely related to post-surgical complication. All other TRAEs were G3. *all radiographic RECIST assessments were unconfirmed, as only one post-neoadjuvant treatment imaging assessment was made prior to surgical resection. ARDS: acute respiratory distress syndrome; G: grade; NSCLC: non-small cell lung cancer; PD: progressive disease; PR: partial response; RECIST: response evaluation criteria in solid tumors; SD: stable disease.