A Phase II Trial of Consolidation Pembrolizumab Following Concurrent Chemoradiation for Patients with Unresectable Stage III Non-Small Cell Lung Cancer (NSCLC): Hoosier Cancer Research Network (HCRN) LUN 14-179

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Abstract:

Background: The 5-year overall survival (OS) for patients with unresectable stage III NSCLC is poor. Until recently, a standard of care was concurrent chemoradiation alone. Patients with metastatic NSCLC treated with anti-PD-1 antibodies have demonstrated improved OS. This trial evaluated Pembrolizumab as consolidation therapy following concurrent chemoradiation in patients with unresectable stage III disease.

Materials and Methods: Patients with unresectable stage III NSCLC received concurrent chemoradiation with either Cisplatin/Etoposide, Cisplatin/Pemetrexed or Carboplatin/Paclitaxel and 59.4-66.6 Gy radiation. Patients with non-progression of disease were enrolled and received Pembrolizumab 200mg IV every 3 weeks for up to 12 months. The primary endpoint was time to metastatic disease or death (TMDD). Secondary endpoints included progression free survival (PFS) and OS.

Results: Median follow-up of 93 patients (92 for efficacy) was 32.2 months (range 1.2-46.6). Median TMDD was 30.7 months (95% CI, 18.7 to NR). Median PFS was 18.7 months (95% CI, 12.4 to 33.8) and median OS was 35.8 months (95% CI, 24.2 to NR). The 1, 2, and 3-year overall survival estimates are 81.2%, 62.0%, and 48.5%, respectively. Forty (43.5%) patients completed 12 months of treatment (median number of cycles 13.5). Symptomatic pneumonitis (grade ≥2) was noted in 16 (17.2%) patients which includes 4 (4.3%) grade 3, 1 (1.1%) grade 4, and 1 (1.1%) grade 5 event.

Conclusions: Consolidation Pembrolizumab following concurrent chemoradiation significantly improves TMDD, PFS, and OS compared with historical controls of chemoradiation alone. Rates of grades 3-5 pneumonitis were similar to that reported with chemoradiation alone.

Introduction:

Non-small cell lung cancer (NSCLC) makes up approximately 80% of new lung cancer cases, and about one-third of these patients have stage III (locally advanced) disease at the time of their diagnosis. Until recently, a standard of care for patients in this setting was treatment with concurrent platinum-based chemotherapy with radiation (1). Unfortunately, despite this treatment, overall survival in this population is poor with only an approximately 15% survival rate at 5 years (1, 2). Furthermore, despite numerous trials evaluating the incorporation of induction chemotherapy (3), consolidation chemotherapy (4, 5), epidermal growth factor receptor (EGFR) inhibitors (6-8), anti-angiogenic agents (9-12), and higher doses of radiation (6), none of these strategies has demonstrated improvements in overall survival over concurrent chemoradiation alone.

Pembrolizumab is a humanized monoclonal antibody targeting programmed death 1 (PD-1), a T-cell regulatory protein. The interaction of PD-1 with its ligand PD-L1 results in negative regulatory signaling that diminishes the T-cell response. Inhibition of PD-1 or its ligand results in improved T-cell activity and

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renewed immune anti-tumor response. Pembrolizumab has shown activity in NSCLC as a single agent (13, 14) and in combination with chemotherapy (15), and is currently FDA-approved in the front-line and second-line settings in patients with metastatic NSCLC.

There is a strong pre-clinical and clinical rationale for the use of PD-1 or PD-L1 inhibitors following chemoradiation for patients with unresectable stage III NSCLC. Animal models demonstrate that combining checkpoint inhibition with ionizing radiation results in improved tumor control both locally and at distant sites. These studies also suggest synergy may exist when these two strategies are combined (16, 17). Clinically, radiotherapy is thought to enhance the immune response in a number of ways including the release of neoantigens, recruitment of T cells to the tumor bed, up-regulation of PD-L1, and the neutralization of the immunosuppressive effects of the tumor microenvironment (18). Based on this rationale, we designed a trial to evaluate the role of Pembrolizumab as consolidation therapy following concurrent chemoradiation for patients with unresectable stage III NSCLC.

Methods:

Patients:

Patients with histologically or cytologically confirmed stage III, unresectable or inoperable NSCLC were eligible for enrollment. Patients must have been treated with concurrent chemoradiation with one of three chemotherapy backbones (cisplatin/etoposide, cisplatin/pemetrexed [non-squamous NSCLC only], or carboplatin/paclitaxel) and a standard dose of radiation between 59.4-66.6 Gray. Repeat imaging was done 4-8 weeks following completion of chemoradiation, and if no progressive or metastatic disease was noted at that time, the patient was enrolled on the study. Additional inclusion criteria included age $\geq$ 18, an Eastern Cooperative Oncology Group performance status of 0 or 1, and a last dose of radiation received between 28 and 56 days prior to beginning immunotherapy. Patients were permitted to receive up to two cycles of consolidation chemotherapy, at the discretion of their treating physician, prior to starting consolidation immunotherapy. In those cases, patients were required to start immunotherapy within 4 weeks of their last cycle of consolidation chemotherapy. Patients were excluded if they had a history of autoimmune disease or a condition requiring systemic corticosteroids or immunosuppressive agents, a history of primary immunodeficiency, or a history of interstitial lung disease or pneumonitis.

Trial Design and Treatment:

This is a single-arm, phase II, multi-institutional trial. Patients were enrolled 28 to 56 days after completion of chemoradiation, and they were treated with Pembrolizumab 200 mg intravenously (IV) every 3 weeks for up to one year. Pembrolizumab was continued until progression, unacceptable toxicity, withdrawal of consent, or completion of one year of treatment. Dose reductions were not permitted, and dose delays for toxicity were allowed up to a maximum duration of 12 weeks. If toxicity had not resolved to grade 0-1 within 12 weeks, study drug was discontinued permanently.

Study Endpoints and Assessments:

The primary endpoint was TMDD and secondary endpoints included PFS, OS, toxicity (as graded by CTCAE v4), and feasibility of giving Pembrolizumab following concurrent chemoradiation. The hypothesis was that Pembrolizumab would improve TMDD from a historical control of 12 months to 18

months. Time to metastatic disease was defined as any new site of disease outside of the previously radiated field. Exploratory endpoints included the assessment of PD-L1 status and its correlation with TMDD, PFS, OS, histology, and toxicity. Additional slides for PD-L1 analysis were submitted at the time of study enrollment but documentation of PD-L1 expression was not required for study entry. Patients underwent computed tomography (CT) scans every 9 weeks while on Pembrolizumab. Following completion of treatment patients were followed with imaging every 3 months for years 1 and 2 and then every 6 months in years 3-5.

PD-L1 testing was performed using modified proportion score (MPS). This scoring system includes both PD-L1 positive mononuclear inflammatory cells (MIC), including macrophages and lymphocytes, and tumor cells. It also evaluates MICs within the tumor-associated stroma, though this is not factored into the percent MPS score.

Trial Oversight:

The trial was an investigator-initiated trial written and developed by the principal investigator with input from co-investigators. The trial was conducted through the HCRN and funded by Merck and Co. The trial protocol and all amendments were approved by the appropriate regulatory committees at each participating site. All patients provided written, informed consent for participation in the trial. A data safety monitoring board performed interim safety analyses throughout the conduct of the trial.

All the authors attest that the trial was conducted in accordance with the protocol and all its amendments and with Good Clinical Practice standards. All authors were given access to the data and participated in the writing or reviewing or editing of the manuscript. The main portion of the manuscript was written by the first author. All the authors vouch for the accuracy and completeness of the data and analyses.

Statistical Analysis:

Efficacy of pembrolizumab was to be quantified and evaluated by TMDD. Under conventional chemoradiation, the median time is around 12-months. We expected pembrolizumab to improve median time by 50% (to at least 18-months). Brookmeyer and Crowley's method was to be used to test the following one-sided hypotheses: H0:median≤12-months versus Ha: median>12-months. With type I error level as 0.05, 83 subjects were required to obtain a power of 80%. The sample size was adjusted to 93 patients to account for 10% lost-to-follow-up.

Baseline demographic and disease characteristics were summarized as median (range) for continuous variables and proportions for categorical variables. The Kaplan-Meier method was used analyze time to metastatic disease or death, progression free survival and overall survival. For time till metastatic disease or death, patients who did not have distant metastasis or die were censored at their last radiological imaging. For progression free survival, patients who did not progress or die were censored at their last radiological imaging. For overall survival, patients who did not die were censored at their last known alive date. Median with 95% confidence intervals were calculated along with the 12, 18, 24

and 36-month probabilities. The median for time till metastatic disease or death was compared to the historical median of 12 month using Brookmeyer and Crowley's method. Cox proportional hazard models were used to correlate PD-L1 status and other variables of interest with TMDD, PFS and OS. Hazard ratios and 95% confidence intervals were generated. All statistical analyses were conducted using SAS version 9.4.

Results:

Patients and Treatment

Between March 2015 and November 2016, 93 patients were enrolled and received at least one dose of Pembrolizumab (Table 1). One patient was determined to be ineligible and was not included in the efficacy analysis but was included in the toxicity analysis. The median age was 66, and the majority of patients were male (64%). Sixty percent of the patients had stage IIIA and 40% had stage IIIB. Patients with squamous cell carcinoma made up 45% of the patients and 55% had non-squamous NSCLC. Nearly all patients were either former (77.2%) or current (17.4%) smokers, and only 5.4% were never smokers. Weekly carboplatin and paclitaxel was the chemotherapy regimen used in 71% of patients, while cisplatin and etoposide was given in 26% of patients, and 2% of patients received cisplatin and pemetrexed. Consolidation chemotherapy was given in only 4 patients. PD-L1 testing was available for 53 patients. Of these, 31 had a PD-L1 MPS of ≥50%, 11 had an MPS from 1-49%, and 11 patients were PD-L1 negative.

As of the data cutoff of May 7, 2019, the median follow-up time was 32.2 months (1.2-46.6). Of the 92 eligible patients enrolled on the trial, 77 (84%) were able to receive ≥ 4 cycles of Pembrolizumab while only 15 (16%) of patients received < 4 cycles. The median number of cycles received was 13.5 (range 1-19), and 40 (43.5%) patients were able to receive the entire planned year of therapy. The reasons for not completing a full year of therapy included disease progression (25%), adverse events (19.6%), patient withdrawal (7.6%), death on study (3.3%), and other complicating medical disease (1.1%).

Efficacy

Median TMDD was 30.7 months (95% CI, 18.7 to NR) [Figure 1]. The estimates of 12, 18, 24, and 36-month TMDD were 77.6%, 61.8%, 55.3%, and 49.9%, respectively. At the time of analysis, 15 patients had developed metastatic disease [sites included lung (n=5), liver (n=4), lymph nodes (n=4), brain (n=3), bone (n=3), adrenal (n=1), renal (n=1), and pleura (n=1)]. The study met its primary endpoint as the null hypothesis was a TMDD of 12 months. TMDD was similar in PD-L1 < 1% and ≥ 1% patients (hazard ratio, 0.96, 95% CI, 0.33 to 2.82; p=0.94). Median PFS was 18.7 months (95% CI, 12.4 to 33.8) [Figure 2]. Estimates of 12, 18, 24, and 36-month PFS were 61.2%, 50.3%, 46.3%, and 37.4%. PFS did not differ by PD-L1 status (hazard ratio 0.84, 95% CI 0.34 to 2.04; p=0.70). The median OS was 35.8 months (95% CI, 24.2 to NR), and the estimated 1, 2, and 3-year survival rates are 81.2% and 62.0%, and 48.5%, respectively [Figure 3]. There was no difference in OS in PD-L1 < 1% vs. ≥1% patients (hazard ratio 0.79, 95% CI, 0.27 to 2.31; p=0.66).

The association with improved outcomes was analyzed with a number of variables, including smoking status, timing of the initiation of Pembrolizumab, and chemotherapy regimen backbone (Table 3). Smoking status was not associated with differences in any efficacy measure, including TMDD, PFS, or OS. Timing of initiation of Pembrolizumab was also not associated with these endpoints. Those who initiated Pembrolizumab between 4-6 weeks did not do better than those who initiated Pembrolizumab between 6-8 weeks after chemoradiation. Lastly, while it was observed that patients receiving cisplatin/etoposide had a numerical advantage over those receiving carboplatin/paclitaxel, this was not statistically significant.

Safety

The most commonly reported adverse event (AE) was fatigue in 47% of patients, though most of these were grade 1-2. Cough (25.8%), dyspnea (21.5%), anorexia (17.2%), arthralgia (16.1%), diarrhea (16.1%), and rash (15.1%) were also reported in > 15% of patients with no grade 4 events and few grade 3 events (Table 4). Other potential immune-related adverse events included hypothyroidism (12.9%), hyperthyroidism (7.5%), elevated creatinine (5.4%), colitis (3.2%), and AST and ALT elevations (2.2% and 1.1%, respectively). All of these additional AEs were either grade 1 or 2 with the exception of a single grade 4 colitis (Table 5). Treatment related serious adverse events (SAEs) were reported in 13 (14.1%) patients.

Pneumonitis was an AE of high interest during this study. Only 16 (17.2%) patients developed symptomatic pneumonitis (grade ≥ 2). Of these 16 patients, 10 (10.8%) experienced grade 2, 4 (4.3%) experienced grade 3, and 1 (1.1%) experienced grade 4 pneumonitis. There was 1 pneumonitis-related death. Most instances of symptomatic pneumonitis (12/16, 75%) occurred during the first 12 weeks of treatment with Pembrolizumab (range 1.1-48.3 weeks). Median time to development of pneumonitis was 8.4 weeks, and only one case occurred after 18 weeks of treatment.

Discussion:

This trial of consolidation Pembrolizumab met its primary endpoint of improving TMDD over a historical control expected from concurrent chemoradiation alone. The historical estimate for TMDD after chemoradiation alone was around 12 months, and the addition of Pembrolizumab considerably improves upon this with a median TMDD of 30.7 months. For comparison in a similar patient population, the consolidation placebo arm of the PACIFIC trial (i.e. patients received chemoradiation alone) had a TMDD of 16.2 months (19). Progression free survival (PFS) and overall survival (OS) appear to be substantially improved above historical estimates as well. The median PFS of this trial was 18.7 months and the median OS was 35.8 months with 1, 2, and 3-year OS estimates of 81.2%, 62.0%, and 48.5%. These values are statistically and clinically significant in a patient population that had not seen substantial improvements in outcomes for many years. It should be noted that local progression was sometimes difficult to assess in the setting of chemoradiation followed by checkpoint inhibition secondary to changes in the radiation field that did not always represent true progression. This suggests that PFS may not be the optimal endpoint for future consolidation immunotherapy trials. Since the completion of our trial, the PACIFIC trial investigators have reported improvements in TMDD, PFS and OS with the use of consolidation Durvalumab compared with placebo in a phase III study in this same

patient population (19, 20). Our trial also demonstrates that Pembrolizumab substantially improves outcomes in this patient population and further solidifies the strategy of consolidation PD-1/PD-L1 inhibition as the new standard of care. The patient population and design of our study is very similar to the PACIFIC trial. Each study permitted various chemotherapy regimens and radiation dosages. The PACIFIC trial permitted induction chemotherapy, while our study did not. Our study permitted consolidation chemotherapy (utilized in only 4 patients), while the PACIFIC trial did not permit this. All efficacy outcomes, toxicity outcomes, and amount of therapy that was delivered is nearly identical between the reports of consolidation durvalumab and consolidation pembrolizumab.

We performed exploratory analyses to determine whether certain variables are associated with better outcomes with consolidation pembrolizumab. PD-L1 expression did not appear to be a predictor of efficacy on this trial as there was no difference in TMDD, PFS, or OS when comparing PD-L1 <1% vs. PD-L1 MPS ≥1% patients. PD-L1 data was available on only 53 patients and most patients were reported to be PD-L1 $\underline{\geq}$ 1%. This limits the conclusions that can be made from this data. Secondly, a modified proportion score (MPS) was utilized on this trial rather than the tumor proportion score (TPS), which is typically reported in other trials of checkpoint inhibitors in NSCLC. MPS may be less predictive of benefit compared with TPS in NSCLC patients. Nevertheless, there was no suggestion from our trial results that PD-L1 < 1% did worse than their PD-L1 positive counterparts (PD-L1 < 1% group actually achieved numerically better efficacy outcomes). In contrast to this, an unplanned post hoc analysis of the PACIFIC trial appears to show numerically better survival for placebo compared with durvalumab (although PFS was still better with durvalumab in this group). Based on these conflicting reports, the role of PD-L1 as a predictive biomarker in this setting remains unclear.

The optimal timing of PD-1 or PD-L1 inhibitors in the treatment of patients with stage III NSCLC remains an open question. PACIFIC allowed patients to begin consolidation therapy at any time after completion of chemoradiation. Our trial required therapy to begin 4-8 weeks following completion of chemoradiation. The PACIFIC trial demonstrated that OS was better in patients who initiated therapy within 14 days of completion of chemoradiation compared to those who started after 14 days. This may be secondary to a positive effect of chemoradiation on Durvalumab efficacy or it may be a function of this group being healthier with less chemoradiation-induced toxicity. In contrast, our trial did not demonstrate a difference in TMDD, PFS, or OS when comparing those who initiated Pembrolizumab from 4-6 weeks vs. those who started between 6-8 weeks. In fact, those who started later had numerically improved outcomes though this was not statistically significant. Perhaps initiation within the first two weeks is the optimal timeframe to initiate consolidation checkpoint inhibition; however, based on conflicting results from our trial, this hypothesis requires further validation. Our data suggest no detriment for waiting up to 8 weeks before initiating consolidation pembrolizumab, allowing for sufficient time for recovery from toxicities of chemoradiation. A number of additional questions remain unanswered in this patient population, including the optimal duration of consolidation therapy, the optimal timing (induction, concurrent, consolidation) of checkpoint therapy, and the role of consolidation checkpoint inhibitors in patients with stage III disease who have undergone surgery.

Pembrolizumab appears to be well tolerated following chemoradiation in patients with stage III NSCLC, although not all patients could complete 1 year of therapy. Forty (43.5%) patients were able to receive the entire planned year of therapy, and the median number of cycles received was 13.5 (40.5 weeks). This data is nearly identical to the median number of weeks of treatment with consolidation durvalumab reported on the PACIFIC trial. Furthermore, most AEs on this trial and the PACIFIC trial were grade 1 or 2 with very few grade 3 events. Immune-related adverse events were mainly grade 1 or 2. The rate of pneumonitis was not demonstrably more than what is expected with chemoradiation alone. In addition, the rate of grade 3 or higher pneumonitis was not much higher than what would be expected from treatment with checkpoint inhibitors alone or chemoradiation alone. Most cases of pneumonitis occurred within the first 12 weeks (75%), corresponding to the period with the highest risk for radiation pneumonitis, and only one patient developed pneumonitis after 18 weeks suggesting that the risk decreases substantially outside of this window.

In conclusion, consolidation pembrolizumab after concurrent chemoradiation in patients with stage III unresectable NSCLC resulted in improved TMDD, PFS, and OS compared with historical controls. The results reported here with pembrolizumab are similar to those reported with consolidation durvalumab on the PACIFIC trial. While this finding signifies a major advance in the treatment of stage III NSCLC, efforts are underway to build off this success. Examples of such effort include the evaluation of combination immunotherapy (NCT 03285321) and trials assessing chemoradiation concurrent with immunotherapy with (NCT 03871153) or without (NCT 02434081) resection.

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Table 1. Patient and Disease Characteristics

Characteristic	Total (N=92)
Age (year)	
Mean (Std)	64.4 (8.6)
Median (Range)	66.0 (45.0-84.0)
Gender, n (%)	
Female	33 (36%)
Male	59 (64%)
Race, n (%)	
White	84 (91.3%)
Black or African American	3 (3.3%)
Asian	4 (4.3%)
Unknown	1 (1.1%)
Disease Stage, n (%)	
IIIA	55 (60%)
IIIB	37 (40%)
Tumor Histologic Type, n (%)	
Squamous	41 (45%)
Non-Squamous	51 (55%)
Smoking Status, n (%)	
Current smoker	16 (17.4%)
Former Smoker	71 (77.2%)
Never smoker	5 (5.4%)
Prior Radiation Dose	
Mean (Std)	61.0 (6.2)
Median (Range)	60.0 (6.6-66.6)
Prior Chemo Received, n (%)	
Cisplatin/Etoposide	24 (26%)
Carboplatin/Paclitaxel	65 (71%)
Cisplatin/Pemetrexed	2 (2%)
Carboplatin/Paclitaxel & Carboplatin/Pemetrexed	1 (1%)
PD-L1, n (%), (n=53)	
Negative	11 (20.8%)
1-49%	11 (20.8 %)
≥50%	31 (58.5 %)

Table 2. Efficacy Endpoints

Endpoint	
Median Follow-Up (range)	**32.2 months (1.2-46.6)**
Time to Metastatic Disease or Death	
Median (95% CI)	30.7 months (18.7 to NR)
12-month	77.6%
18-month	61.8%
24-month	55.3%
36-month	49.9%
Progression Free Survival	
Median (95% CI)	18.7 months (12.4 to 33.8)
12-month	61.2%
18-month	50.3%
24-month	46.3%
36-month	37.4%
Overall Survival	
Median (95% CI)	35.8 months (24.2 to NR)
12-month	81.2%
18-month	65.8%
24-month	62.0%
36-month	48.5%

Table 3: Outcomes by Variable

		TMDD		PFS		OS	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Smoking status	Current vs Former	1.11 (0.51, 2.41)	0.86	1.11 (0.55, 2.23)	0.90	1.17 (0.54, 2.54)	0.79
	Current vs Never	1.53 (0.32, 7.26)		1.35 (0.37, 4.92)		1.70 (0.36, 8.06)	
	Former vs Never	1.38 (0.33, 5.80)		1.21 (0.37, 3.94)		1.46 (0.35, 6.11)	
PDL-1 status**	Negative vs Positive	0.96 (0.33, 2.82)	0.94	0.84 (0.34, 2.04)	0.70	0.79 (0.27, 2.31)	0.66
Type of chemo	Carboplatin/ Paclitaxel vs Cisplatin/Etoposide	1.23 (0.60, 2.51)	0.57	1.53 (0.78, 2.99)	0.21	1.21 (0.59, 2.46)	0.61
ECOG	0 vs 1	0.79 (0.42, 1.47)	0.46	0.79 (0.45, 1.38)	0.40	0.69 (0.37, 1.31)	0.26
Time between radiation to pembrolizumab	4-6 weeks vs 6-8 weeks	1.01 (0.45, 2.27)	0.99	0.96 (0.45, 2.05)	0.92	1.11 (0.49, 2.50)	0.81

*Reference category is the latter category

**PD-L1 [+] defined as MPS ≥1%

Table 4. Adverse Events Occurring in ≥10% of Patients

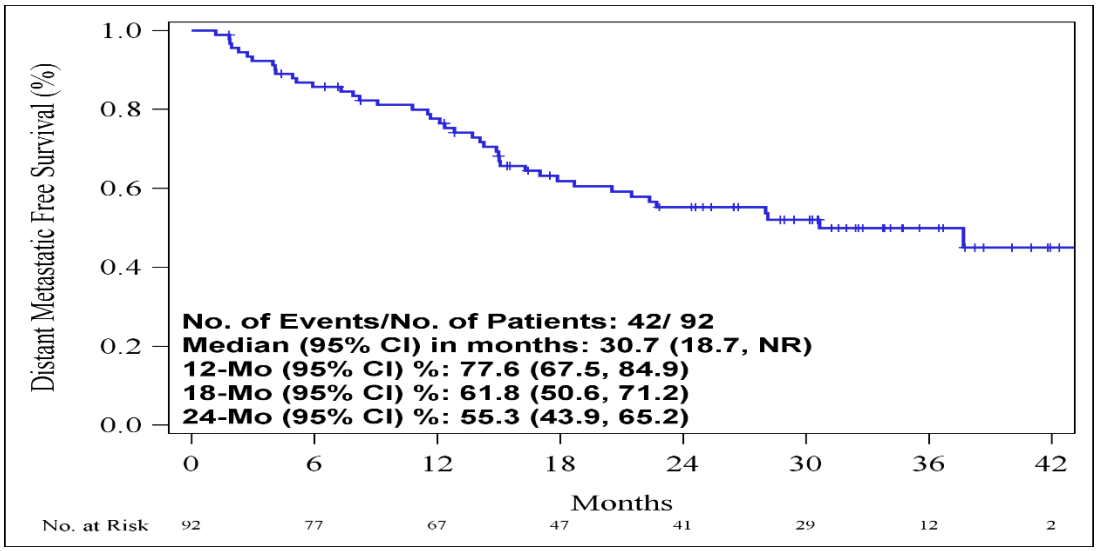
Adverse Event	Any Grade (%), N=93	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Fatigue	44 (47.3)	16 (17.2)	4 (4.3)	0 (0.0)
Cough	24 (25.8)	16 (17.2)	1 (1.1)	0 (0.0)
Dyspnea	20 (21.5)	10 (10.8)	5 (5.4)	0 (0.0)
Anorexia	16 (17.2)	3 (3.2)	1 (1.1)	0 (0.0)
Arthralgia	15 (16.1)	8 (8.6)	1 (1.1)	0 (0.0)
Diarrhea	15 (16.1)	3 (3.2)	4 (4.3)	0 (0.0)
Rash	14 (15.1)	3 (3.2)	1 (1.1)	0 (0.0)
Nausea	13 (14.0)	3 (3.2)	1 (1.1)	0 (0.0)
Hypothyroidism	12 (12.9)	10 (10.8)	0 (0.0)	0 (0.0)
Pruritus	11 (11.8)	3 (3.2)	0 (0.0)	0 (0.0)

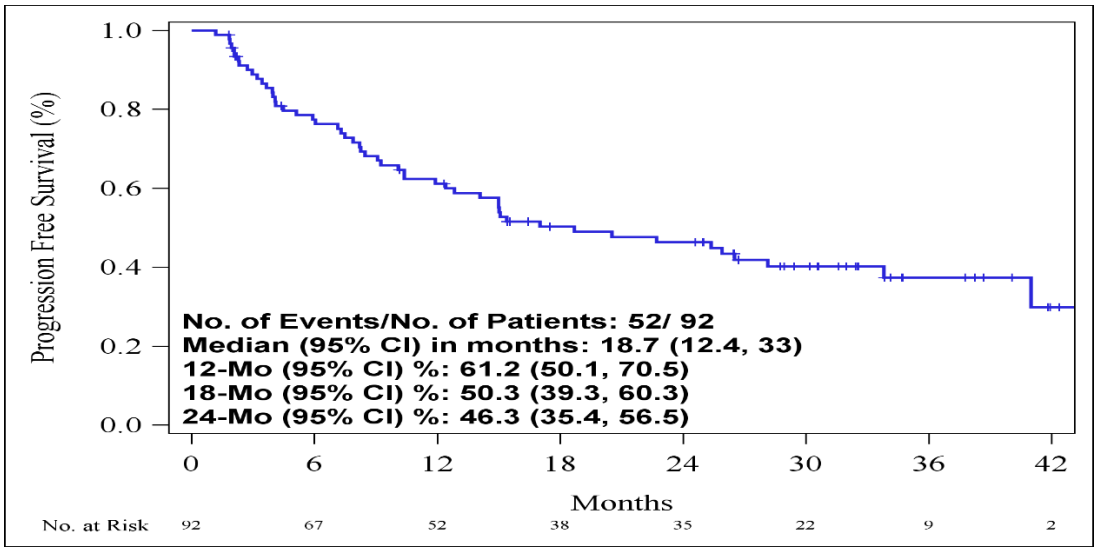
***Excluding Pneumonitis**

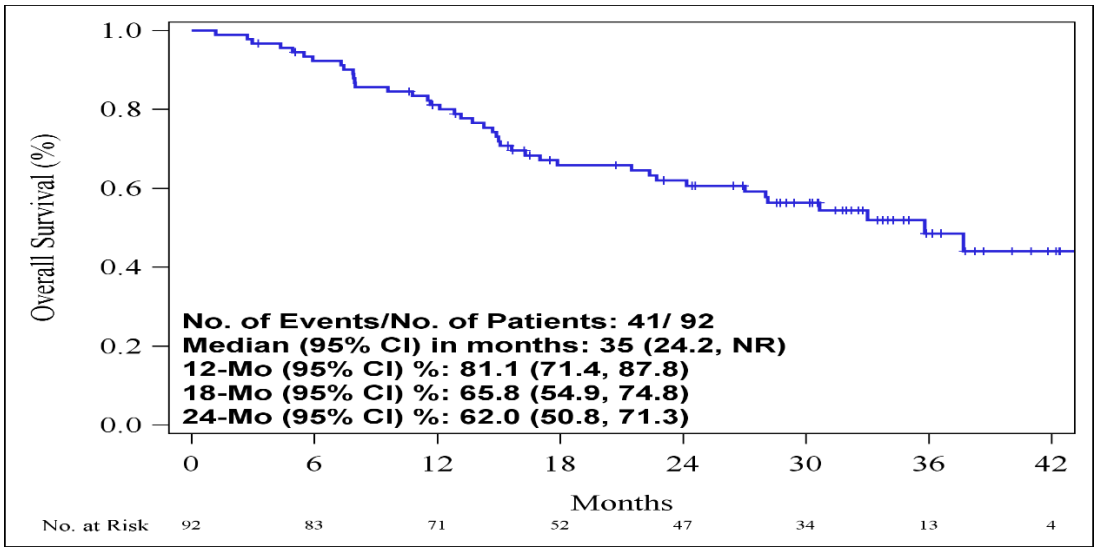
Table 5. Potential Immune-Related Toxicities

Adverse Event	Any Grade (%), N=93	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Pneumonitis*	NR	10 (10.8)	4 (4.3)	1 (1.1)
Colitis	3 (3.2)	2 (2.2)	0 (0.0)	1 (1.1)
Increased Creatinine	5 (5.4)	1 (1.1)	0 (0.0)	0 (0.0)
Elevated AST	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated ALT	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthyroidism	7 (7.5)	2 (2.2)	0 (0.0)	0 (0.0)
Hypothyroidism	12 (12.9)	10 (10.8)	0 (0.0)	0 (0.0)

*Grade 1 pneumonitis not recorded. One patient with grade 5 pneumonitis.


Distant Metastatic Free Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
No. of Events/No. of Patients: 42/ 92
Median (95% CI) in months: 30.7 (18.7, NR)
12-Mo (95% CI) %: 77.6 (67.5, 84.9)
18-Mo (95% CI) %: 61.8 (50.6, 71.2)
24-Mo (95% CI) %: 55.3 (43.9, 65.2)
0 6 12 18 24 30 36 42
Months
No. at Risk 92 77 67 47 41 29 12 2


Progression Free Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
No. of Events/No. of Patients: 52/ 92
Median (95% CI) in months: 18.7 (12.4, 33)
12-Mo (95% CI) %: 61.2 (50.1, 70.5)
18-Mo (95% CI) %: 50.3 (39.3, 60.3)
24-Mo (95% CI) %: 46.3 (35.4, 56.5)
0 6 12 18 24 30 36 42
Months
No. at Risk 92 67 52 38 35 22 9 2


Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
No. of Events/No. of Patients: 41/ 92
Median (95% CI) in months: 35 (24.2, NR)
12-Mo (95% CI) %: 81.1 (71.4, 87.8)
18-Mo (95% CI) %: 65.8 (54.9, 74.8)
24-Mo (95% CI) %: 62.0 (50.8, 71.3)
0 6 12 18 24 30 36 42
Months
No. at Risk 92 83 71 52 47 34 13 4