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Prognostic variables associated with improved outcomes in patients with stage III NSCLC treated with chemoradiation followed by consolidation Pembrolizumab: a subset analysis of a phase II study from the Hoosier Cancer Research Network LUN 14-179

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Abstract:

Introduction

HCRN LUN 14-179 is a phase II trial of consolidation pembrolizumab following concurrent chemoradiation for the treatment of patients with stage III NSCLC. Time to metastatic disease, progression free survival and overall survival appear superior to historical controls of chemoradiation alone. Unfortunately, not all patients benefit from consolidation immunotherapy. We performed a univariate analysis evaluating variables associated with PFS, metastatic disease, and OS.

Methods

We conducted a retrospective analysis from patients enrolled on HCRN LUN14-179. Data collected included age, sex, stage, smoking status, PD-L1 status, $\geq$G2 vs $\leq$G1 adverse event, $\leq$G2 vs. $\geq$G3 pneumonitis, duration of pembrolizumab (<4 vs. $\geq$4 cycles), chemotherapy regimen, PS 0 vs 1, time to start pembrolizumab (4-6 vs. 6-8 weeks from radiation), V_{20} (<20% vs. $\geq$20%). Univariable Cox regression was performed to determine the variables associated with 3 endpoints: TMDD; PFS; and OS.

Results

From April 2015 to December 2016, 93 patients were enrolled and 92 were included in the efficacy analysis (1 patient was ineligible). For TMDD, improved outcomes may be associated ($p<0.1$) with stage IIIA, non-squamous cell, $\geq$4 cycles of pembrolizumab, and $V_{20}<$ 20%. For PFS, improved outcomes ($p<0.1$) may be seen for $\geq$4 cycles of pembrolizumab, and $V_{20}<$ 20%. For OS, improved outcomes ($p<0.1$) may be seen for non-squamous histology, $\geq$4 cycles of pembrolizumab.

Conclusion

Non-squamous NSCLC, longer duration of pembrolizumab, and $V_{20}<$ 20% may be associated with prolonged time to metastatic disease or death, PFS, and OS for patients with stage III NSCLC treated with chemoradiation followed by pembrolizumab.

Keywords:

Immunotherapy, Non-small cell lung cancer, Adjuvant therapy, Prognosis.

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Introduction:

Over the last 20 years, the 5 year survival rate for patients with stage IIIA and IIIB NSCLC has been 10-15% and 3-7%, respectively[1]. The standard of care for these patients during this period remained concurrent chemotherapy and radiation therapy[2-4]. This standard has recently changed, based upon the results from the randomized, phase III PACIFIC trial. In this study, patients with stage III NSCLC were treated with a variety of chemotherapy regimens concomitantly with radiation therapy and subsequently randomized in a 2:1 fashion to receive either durvalumab, a PD-L1 inhibitor, or placebo for up to 1 year. Median progression-free survival for those receiving durvalumab was 16.8 compared with 5.6 months for placebo. Overall survival was also improved for those receiving durvalumab with a 24-month overall survival rate of 66.3% compared with 55.6% in the placebo group[5]. A phase II study from the Hoosier Cancer Research Network (HCRN LUN 14-179) evaluated the role of consolidation pembrolizumab after chemoradiation in patients with stage III NSCLC. This study recruited patient from 14 sites in the U.S. Results from this study indicated efficacy outcomes [progression free-survival (PFS), time to metastatic disease or death (TMDD), and overall survival (OS)] similar to those achieved with durvalumab in the PACIFIC trial with median TMDD of 22.4 months and a median PFS of 17 months in a similar study population.

Prognostic variables associated with improved outcomes in patients with stage III NSCLC treated with chemoradiation are well characterized. Performance status 0-1, absence of weight loss in the 3 months preceding the diagnosis of lung cancer, stage IIIA (compared with IIIB) disease, and volume of lung receiving at least 20 Gy of radiation (V20) < 20% are associated with improved outcomes[6-8]. However, prognostic variables associated with improved efficacy from consolidation immunotherapy after chemoradiation therapy have not been defined. The anti-cancer mechanisms of checkpoint inhibitors is substantially different than conventional chemotherapy. Furthermore, checkpoint inhibitors are associated with a vastly different side effect profile compared with conventional chemotherapy. We, therefore, performed this retrospective subset analysis to evaluate potential prognostic variables associated with improvements in TMDD, PFS, and OS in patients with stage III NSCLC treated with chemoradiation followed by pembrolizumab from the HCRN LUN 14-179 clinical trial.

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Methods:

Study population

We conducted a retrospective analysis from patients enrolled on HCRN LUN 14-179. This was a single arm, phase II trial of concurrent chemoradiation followed by consolidation pembrolizumab 200 mg IV every 3 weeks until disease progression, unacceptable toxicity, or up to 1 year of therapy was completed. Patients were permitted to receive carboplatin plus paclitaxel, cisplatin plus etoposide, or cisplatin plus pemetrexed (non-squamous cell only) given concurrently with 59.4-66.6 Gy XRT. Patients were also permitted up to 2 cycles of consolidation chemotherapy. Patients with non-progression of disease were then enrolled onto the clinical trial. Eligible patients had a PS of 0-1, stage IIIA or IIIB squamous or non-squamous NSCLC. Patients with contraindications to checkpoint inhibitors were excluded, including a history of non-infectious pneumonitis or interstitial lung disease. Patients were not excluded based upon pulmonary function, V20 or weight loss. The primary objective of the overall study was to determine if consolidation pembrolizumab following concurrent chemoradiation improves time to death or metastatic disease in inoperable stage III NSCLC patients. The efficacy and safety results of the overall study population have been reported[9]. The primary objective of this subset analysis was to determine prognostic variables associated with TMDD, PFS and OS.

Prognostic variables

Prognostic variables considered for this analysis included age, sex, stage of NSCLC (IIIA vs. IIIB), histology (squamous vs. non-squamous), smoking status (current vs. former vs. never smoker), PD-L1 status ($\geq$1% vs. < 1%), any adverse event grade (($\leqq$ G2 vs. $\geqq$ G3), pneumonitis ($\leqq$ G2 vs. $\geqq$ G3), duration of treatment with pembrolizumab (< 4 vs. $\geqq$ 4 cycles), chemotherapy regimen (carboplatin/paclitaxel vs. cisplatin/etoposide), ECOG performance status (0 vs. 1), interval between completion of radiation to start of pembrolizumab (4-6 weeks vs. 6-8 weeks) and volume of lung receiving at least 20 Gy of radiation (V20) ($\leq$ 20% vs. >20%). 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.

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Statistical analysis

Data analysis was conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC). A p-value < .05 denoted statistical significance for all tests. Basic comparisons were made using Chi-Square Tests. Univariable Cox regression was performed to determine the variables associated with 3 endpoints: TMDD, PFS and OS. Variables found to have a $P < 0.1$ on univariable Cox regression analysis were included in a multivariable Cox regression model. Due to a small sample size (n=92), we chose $p < 0.1$ as the cutoff in the univariable regression for inclusion into the multivariable regression model, to allow us to still develop hypothesis-generating prognostic variables to be studied in larger trials in the future..

Results:

From April 2015 to December 2016, 93 patients were enrolled and 92 were included in the efficacy analysis (1 patient was ineligible). The median follow-up was 30.5 months with a minimum follow-up of 26 months for patients who are alive. Patient and disease characteristics are summarized in Table 1.

For time to metastatic disease or death (TMDD), improved outcomes ($p<0.1$) were associated with stage IIIA ($p=0.0922$), non-squamous cell ($p=0.0999$), $\geq$ 4 cycles of pembrolizumab ($p<0.001$), and V20 $\leq$ 20% ($p=0.0716$) according to the Univariable Cox regression model. A multivariable model was run with those variables and Stage IIIA (HR=2.9, $p=0.02$) and $\geq$4 cycles of pembrolizumab (HR=9.1, $p<0.001$) remained significant. On the other hand, smoking status was not associated with a difference in TMDD ($p=0.7204$) on univariable Cox regression model. PDL-1 status was also not associated with TMDD ($p=0.3505$) (Table 3).

For PFS, improved outcomes ($p<0.1$) may be seen for $\geq$4 cycles of pembrolizumab ($p<0.001$), and V20$\leq$ 20% ($p=0.0630$) according to the Univariable Cox regression model. A multivariable model was run with those variables and $\geq$4 cycles of pembrolizumab (HR=3.9, $p<0.001$) remained significant. Smoking status ($p=0.9679$), PDL-1 status ($p=0.3261$), and stage IIIA vs. IIIB ($p=0.1444$) were not associated with PFS. (Table 4).

For OS, improved outcomes ($p<0.1$) may be seen for non-squamous histology ($p=0.0829$), and $\geq$ 4 cycles of pembrolizumab ($p<0.001$) according to the univariable Cox regression model. A multivariable model was run with those variables and $\geq$ 4 cycles of

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pembrolizumab (HR=4.9, p<0.001) remained significant. Smoking status (p=0.6043), PDL-1 status (p=0.1901) and stage of disease (p=0.1588) were not prognostic for OS (Table 5).

Table 1: Baseline characteristics of study population (N=92)

Characteristics	Statistics
Age (years), mean (std)	64 (8.6)
Gender, n (%)	
Male	59 (64)
Female	33 (36)
Stage, n (%)	
IIIA	55 (60)
IIIB	37 (40)
Histology of NSCLC, n (%)	
Non-squamous	51 (55)
Squamous	41 (45)
Distant metastasis or death on follow-up*, n (%)	
Present	34 (37)
Not present	57 (63)

*One patient did not have an evaluable response for distant metastasis or death

Table 2: Basic comparisons of outcomes

Variable	TMDD	PFS	OS
IIIA (n=55)	69% p=0.12	56% p=0.21	75% p=0.13
IIIB (n=37)	51%	41%	59%
Non-SCCA (n=51)	69% p=0.11	55% p=0.21	75% p=0.16
SCCA (n=41)	54%	44%	61%
PD-L1 [-] (n=11)	82% p=0.13	64% p=0.19	91% p=0.07
PD-L1 [+] (n=42)	57%	40%	62%

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≥ 4 pembro (n=77)	68% p=0.01	55% p=0.04	75% p=0.001
< 4 pembro (n=15)	33%	27%	33%
V_{20} ≤ 20% (n=19)	79% p=0.07	63% p=0.08	79% p=0.15
V_{20} > 20% (n=59)	54%	39%	61%
G ≤ 2 pneumonitis (n=87)	63% p=0.28	51% p=0.61	70% p=0.16
G ≥ 3 pneumonitis (n=5)	40%	40%	40%
Female (n=33)	67% p=0.37	67% p=0.11	73% p=0.51
Male (n=59)	59%	59%	66%
<65 years old (n=43)	56% p=0.32	49% p=0.99	65% p=0.52
≥65 years old (n=49)	67%	51%	71%
Current Smoker (n=16)	50% p=0.42	50% p=0.99	56% p=0.44
Former Smoker (n=71)	66%	51%	72%
Never Smoker (n=5)	40%	40%	60%
Any AE Grade ≤2 (n=46)	70% p=0.17	56% p=0.29	76% p=0.12
Any AE Grade ≥3 (n=46)	54%	43%	61%
Carboplatin/Paclitaxel (n=66)	59% p=0.57	44% p=0.15	65% p=0.38
Cisplatin/Etoposide (n=24)	67%	63%	75%
Rad Interval 4-6 weeks (n=17)	53% p=0.56	41% p=0.71	59% p=0.34
Rad Interval 6-8 weeks (n=75)	64%	52%	71%
ECOG=0 (n=40)	68% p=0.40	55% p=0.38	73% p=0.47
ECOG=1 (n=52)	58%	46%	65%

Table 3: Univariate analysis for prognostic variables associated with time to metastatic disease or death

		Univariable Results		**Multivariable Results**	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age	<65 vs. ≥65 years old	1.00 (0.96, 1.04)	0.9678		
Gender	Female vs Male	0.97 (0.46, 2.04)	0.9401		

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		Univariable Results		Multivariable Results	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Stage	IIIB vs IIIA	1.79 (0.91, 3.52)	0.0922	2.87 (1.21, 6.81)	0.0165
Histology	non-squamous vs squamous	0.57 (0.29, 1.12)	0.0999	0.63 (0.30, 1.32)	0.2192
Smoking status	Current vs Former	1.39 (0.62, 3.10)	0.7204		
	Current vs Never	1.21 (0.25, 5.74)			
	Former vs Never	0.87 (0.20, 3.71)			
PDL-1 status	Negative vs Positive	0.50 (0.12, 2.16)	0.3505		
Any adverse event	Grade <=2 vs Grade >=3	0.65 (0.33, 1.29)	0.2194		
Pneumonitis grade	Grade <=2 vs Grade >=3	0.57 (0.17, 1.86)	0.3493		
Duration of treatment with pembrolizumab	<4 cycles vs >=4 cycles of treatment	5.98 (2.75, 13.00)	<.0001	9.14 (3.35, 24.92)	<.0001
Type of chemo	Carboplatin/Paclitaxel vs Cisplatin/Etoposide	1.36 (0.61, 3.03)	0.4462		
ECOG	0 vs 1	0.63 (0.31, 1.29)	0.2035		
Time between radiation to pembrolizumab	4-6 weeks vs 6-8 weeks	1.40 (0.61, 3.24)	0.4315		
V20	<=20% vs >20%	0.38 (0.13, 1.09)	0.0716	0.64 (0.21, 1.95)	0.4346

*reference category is the second category

Table 4: Univariate analysis for prognostic variables associated with progression-free survival

		Univariable Results		Multivariable Results	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age	<65 vs. ≥65 years old	1.00 (0.97, 1.04)	0.8557		
Gender	Female vs Male	0.80 (0.41, 1.55)	0.5065		
Stage	IIIB vs IIIA	1.56 (0.86, 2.83)	0.1444		

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		Univariable Results		Multivariable Results	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Histology	non-squamous vs squamous	0.72 (0.41, 1.31)	0.2859		
Smoking status	Current vs Former	1.04 (0.48, 2.25)	0.9679		
	Current vs Never	1.22 (0.26, 5.80)			
	Former vs Never	1.18 (0.28, 4.93)			
PDL-1 status	Negative vs Positive	0.59 (0.20, 1.70)	0.3261		
Any adverse event	Grade <=2 vs Grade >=3	0.78 (0.43, 1.41)	0.4031		
Pneumonitis grade	Grade <=2 vs Grade >=3	0.83 (0.26, 2.67)	0.7472		
Duration of treatment with pembrolizumab	<4 cycles vs >=4 cycles of treatment	4.25 (2.11, 8.59)	<.0001	3.87 (1.82, 8.25)	0.0005
Type of chemo	Carboplatin/Paclitaxel vs Cisplatin/Etoposide	1.65 (0.79, 3.44)	0.1839		
ECOG	0 vs 1	0.71 (0.38, 1.30)	0.2665		
Time between radiation to pembrolizumab	4-6 weeks vs 6-8 weeks	1.44 (0.66, 3.11)	0.3599		
V20	<=20% vs >20%	0.46 (0.20, 1.04)	0.0630	0.57 (0.25, 1.33)	0.1929

*reference category is the second category

Table 5: Univariate analysis for prognostic variables associated with overall survival

		Univariable Results		Multivariable Results	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age	<65 vs. ≥65 years old	1.01 (0.96, 1.05)	0.7975		
Gender	Female vs Male	0.84 (0.38, 1.85)	0.6634		
Stage	IIIB vs IIIA	1.69 (0.81, 3.52)	0.1588		
Histology	non-squamous vs squamous	0.52 (0.25, 1.09)	0.0829	0.64 (0.30, 1.35)	0.2390

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		Univariable Results		Multivariable Results	
Variable	**Comparison***	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Smoking status	Current vs Former	1.55 (0.66, 3.67)	0.6043		
	Current vs Never	1.48 (0.31, 7.18)			
	Former vs Never	0.95 (0.22, 4.11)			
PDL-1 status	Negative vs Positive	0.26 (0.03, 1.96)	0.1901		
Any adverse event	Grade <=2 vs Grade >=3	0.55 (0.26, 1.17)	0.1208		
Pneumonitis grade	Grade <=2 vs Grade >=3	0.37 (0.11, 1.23)	0.1034		
Duration of treatment with pembrolizumab	<4 cycles vs >=4 cycles of treatment	5.40 (2.43, 12.02)	<.0001	4.91 (2.18, 11.06)	0.0001
Type of chemo	Carboplatin/Paclitaxel vs Cisplatin/Etoposide	1.58 (0.64, 3.90)	0.3225		
ECOG	0 vs 1	0.71 (0.33, 1.54)	0.3862		
Time between radiation to pembrolizumab	4-6 weeks vs 6-8 weeks	1.54 (0.65, 3.63)	0.3225		
V20	<=20% vs >20%	0.51 (0.17, 1.48)	0.2136		

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Discussion:

Prognostic variables associated with better or worse outcomes for patients with stage III NSCLC treated with concurrent chemoradiation are well characterized[7]. However, prognostic variables associated with outcomes are not well defined in this patient population receiving consolidation PD-1 or PD-L1 inhibition. The analysis performed from HCRN LUN 14-179 reported here indicates that receiving 4 or more cycles of consolidation pembrolizumab is associated with improved PFS, TMDD, and OS compared with receiving fewer than 4 cycles. The interpretation of this, however, should be undertaken with caution. It is possible (and even likely) that this simply represents a patient population who tolerated therapy well and may have had more favorable tumor biology. It should be noted, though, that duration of pembrolizumab therapy remained prognostic when factoring in other variables, including stage, PD-L1 score, histology, V20, and PS, which can influence efficacy outcomes. The optimal duration of consolidation PD-1 or PD-L1 inhibition after chemoradiation is not defined. The PACIFIC trial and the HCRN LUN 14-179 trials each permitted up to 1 year of consolidation checkpoint inhibition. Approximately 40% of patients on each study were able to receive 1 year of therapy, and the median duration of consolidation therapy received in both studies was approximately 9 months[5].

Other known prognostic variables for patients with stage III NSCLC were evaluated in the current study. V20 < 20% is associated with less toxicity and better outcomes for patients treated with chemoradiation for stage III NSCLC[10]. Based upon the current analysis, it appears that V20 < 20% is also associated with improved PFS and TMDD with consolidation pembrolizumab. Lower V20 may simply be a surrogate for lower volume of disease, selecting out patients who may be more curable. Furthermore, non-squamous NSCLC was also associated with improved survival with consolidation pembrolizumab.

Subset analyses from the PACIFIC trial suggested that patients with PD-L1 expression of < 1% may not have improved survival with consolidation durvalumab compared with placebo, although PFS was improved with durvalumab in that analysis[5]. The HCRN LUN 14-179 trial utilized a PD-L1 testing platform that assessed PD-L1 expression in tumor cells along with other cells in the microenvironment. Utilizing this assay, PD-L1 expression of < 1% was not associated with inferior survival with consolidation pembrolizumab. It is possible that the

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utilization of different assays resulted in disparate results between HCRN LUN 14-179 and the PACIFIC trial. The optimal therapy for patients with PD-L1 scores of 1% remains undefined.

In addition, a subset analysis from the PACIFIC trial suggested that initiating consolidation durvalumab within 2 weeks of completing chemoradiation was associated with improved outcomes[5]. In contrast, patients enrolled onto HCRN LUN 14-179 were required to wait a minimum of 4 weeks and a maximum of 8 weeks after completing chemoradiation prior to initiating pembrolizumab. The current study evaluated the differences in outcomes of patients initiating pembrolizumab 4-6 weeks after chemoradiation versus those initiating pembrolizumab 6-8 weeks after chemoradiation. No difference was detected in efficacy outcomes (PFS, TMDD, OS) between these subgroups. It is possible that patients receiving durvalumab within 2 weeks of chemoradiation on the PACIFIC trial represented patients with fewer medical problems, improved tolerance to therapy, and better performance status. Furthermore, smoking status, age, gender, chemotherapy regimen, and development of pneumonitis during consolidation immunotherapy do not appear to be associated with outcomes in this patient population.

While this was the first attempt to evaluate prognostic variables utilizing immunotherapy after chemoradiation for patients with stage III NSCLC, it is important to recognize the limitations of this analysis. This analysis was retrospective and unplanned. Secondly, a p value of <1% was utilized as a cut-off for utilization in the multivariate model. Third, the sample size of this study is relatively small. Fourth, the PD-L1 assay utilized is not standard. Fifth, PFS can be challenging to define in a patient population treated with radiation due to the difficulty of interpreting local progression. Nevertheless, despite these significant limitations, this study serves as hypothesis generating to test variables in larger studies of this patient population..

In conclusion, this is the first dedicated report assessing prognostic variables associated with outcomes in patients with stage III NSCLC treated with chemoradiation followed by consolidation pembrolizumab. Efforts are underway to build off the success of the PACIFIC and HCRN LUN 14-179 trials. Given the increased risks and costs associated with consolidation immunotherapy in this setting, it is essential to define the optimal duration of immunotherapy and to identify prognostic markers associated with benefit (or detriment) with this strategy. One such effort is underway through the BIG10 Cancer Research Consortium (NCT03285321) which

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will evaluate multiple clinical factors, radiation treatment variables, and molecular biomarkers associated with outcomes in patients treated with consolidation immunotherapy strategies.

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