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Post-Progression Therapy after Chemoradiation and Consolidation Pembrolizumab: An Analysis from the Hoosier Cancer Research Network LUN 14-179 Phase 2 Clinical Trial

Meagan Miller[1]*, Nasser Hanna[2], Shadia Jalal[3], Salma K Jabbour[4], Robin Zon[5], Goetz Kloecker[6], Michael Williamson[7], Karen Reckamp[8], Ebenezer Kio[9], Robert Langdon[10], Bamidele Adesunloye[11], Ryan Gentzler[12], Wael Harb[13], Radhika Walling[14], Christina Yeon[8], Marianna Koczywas[8] and Greg Durm[1]*

[1]*Indiana University Simon Cancer Center, Indianapolis, USA*

[2]*Department of Biostatistics, Indiana University, Indianapolis, USA*

[3]*Fort Wayne Medical Oncology and Hematology, Fort Wayne, USA*

[4]*Rutgers Cancer Institute of New Jersey, New Brunswick, USA*

[5]*Michiana Hematology Oncology, South Bend, USA*

[6]*University of Louisville, Louisville, USA*

[7]*IU Health Ball Cancer Center, Muncie, USA*

[8]*City of Hope Comprehensive Cancer Center, Duarte, USA*

[9]*Goshen Center for Cancer Care, Goshen, USA*

[10]*Nebraska Methodist Hospital, Omaha, USA*

[11]*IU Health Arnett Cancer Center, Lafayette, USA*

[12]*University of Virginia Cancer Center, Charlottesville, USA*

[13]*Horizon Oncology Research, Lafayette, USA*

[14]*Community Regional Cancer Care, Indianapolis, USA*

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Correspondence:
Meagan Miller, Indiana University Simon Cancer Center, Indianapolis, USA, Tel: (316) 207-7335; E-mail: meaemill@iu.edu

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Abstract

Despite the improved survival rates with consolidation PD-1/PD-L1 inhibitors after CRT, patients still experience disease recurrence. To date, there is no reported data about the efficacy of subsequent treatments, including re-treatment with checkpoint inhibitors, at the time of progression in this patient population. HCRN LUN 14-179 was a phase II, single-arm, multi-center trial which enrolled patients with stage III NSCLC who had received CRT (cisplatin/pemetrexed, carboplatin/paclitaxel, or cisplatin/etoposide + range 59.4 Gy to 66.6 Gy) of 92 total patients. A total of 37 (40%) participants developed progressive disease. Of those, 24 went on to receive subsequent therapy. 19/24 received chemotherapy only with response rates similar to those reported in a similar population of patients with stage IV disease. 6/24 were re-trialed with immunotherapy at some point [1]. Of those receiving subsequent immunotherapy, 5/6 had progressive disease as their best response; however, a patient receiving 2nd line Pembrolizumab achieved a partial response. Re-challenging patients with a PD-1 inhibitor may be reasonable to consider if the patient had disease progression after completing 1 year of consolidation immunotherapy.

Keywords: Stage III NSCLC; Consolidation immunotherapy; Salvage therapy

Introduction

Based upon the results of the PACIFIC trial, the standard of care treatment for most patients with inoperable or unresectable stage III Non-Small Cell Lung Cancer (NSCLC) is Chemoradiation (CRT) followed by consolidation Durvalumab. Patients randomized after CRT to receive Durvalumab experienced longer Progression-Free Survival (PFS), time To Metastatic Disease or Death (TMDD), and Overall Survival (OS) compared to those receiving placebo. We previously reported similar efficacy outcomes on 92 patients with stage III NSCLC treated with CRT followed

by consolidation Pembrolizumab. Despite the improved survival results with consolidation PD-1/PD-L1 inhibitors after CRT, many patients still experience a disease recurrence. To date, there is no reported data about the efficacy of subsequent treatments, including re-treatment with checkpoint inhibitors, at the time of progression in this patient population. We report the outcomes of patients who received subsequent systemic treatment at the time of progressive disease after receiving initial CRT and consolidation Pembrolizumab.

Material and Methods

Patients who experienced disease progression after CRT and consolidation Pembrolizumab on the HCRN LUN 14-179 were evaluated for subsequent treatment received and efficacy of those treatments. HCRN LUN 14-179 was a phase II, single-arm, multi-center trial which enrolled patients with Stage III NSCLC who had received CRT (cisplatin/pemetrexed, carboplatin/paclitaxel, or cisplatin/etoposide + RT range 59.4 Gy to 66.6 Gy). Four patients also received consolidation chemotherapy for 2 cycles prior to Pembrolizumab. Those without progressive disease 4 to 8 weeks following CRT were treated with consolidation Pembrolizumab 200 mg IV every 3 weeks for up to 1 year. Patient demographics, disease characteristics, treatment received, and efficacy of treatment were evaluated for patients who experienced progression of disease after consolidation Pembrolizumab.

Results

Of the 92 eligible patients treated on protocol HCRN LUN 14-179, 37 (40%) experienced disease progression at the time of this report. Two patients experienced disease progression were lost to follow-up. Of the remaining 35 patients with known disease progression, 24 (68.6%) received subsequent systemic therapy. Patient and disease characteristics of these 24 patients is summarized in Table 1. The majority of patients were male and received Carboplatin/Paclitaxel/XRT as their chemoradiation regimen. The median number of cycles of consolidation pembrolizumab received was 9 (range 3 to 18). Six of 24 patients (25%) received at least 15 cycles of consolidation pembrolizumab.

Of the 24 patients who received subsequent salvage systemic therapy on this protocol, 80% (n=19) received chemotherapy only. While 2 (8.3%) patients received a subsequent PD-1 or PD-L1 inhibitor only, a total of 25% (n=6) patients received a PD-1 or PD-L1 inhibitor at some point (i.e. after initial salvage chemotherapy). Twelve (50%) received 2 lines of subsequent therapy, 2 received 3 lines, and 1 received 4 (16.7%) subsequent lines of therapy.

Salvage treatment received and efficacy outcomes are summarized in Table 2. Nine patients received single agent chemotherapy, 4 of whom achieved brief stable disease while the other had progression as their best response. Only 1 out of 9 patients who received combination chemotherapy achieved a partial response. Of those receiving subsequent PD-1 or PD-L1 inhibitors, Pembrolizumab was received by 1 patient as 2nd line, Atezolizumab in 1 patient as 2nd line, 3 patients received Nivolumab as 3rd line and 1 as 4th line. Five of these 6 patients had progressive disease as their best response; however, the patient receiving 2nd line Pembrolizumab achieved a partial response. This patient had completed 18 cycles of consolidation Pembrolizumab and was off therapy for 14 months prior to disease progression. His metastatic sites included a growing lung mass, hilar adenopathy, pleural disease and bone metastasis. A biopsy confirming recurrence demonstrated a PD-L1 score of 90%.

Table 1: Patient demographics and Disease Characteristics (n=24).

Characteristic	Patients, No.
Median Age	62.75 (45-78)
Sex	-
Male	17
Female	7
Histology	-
Adenocarcinoma	14
Squamous Cell Carcinoma	8
Large Cell Neuroendocrine	1
Adenosquamous	1
Stage	-
IIIA	12
IIIB	12
PDL1 MPS Score	-
NA	9
0-10	5
11-50	1
51-80	1
81-100	8
Initial Chemoradiation Regimen	-
Platinum + Etoposide + Radiation	7
Carboplatin + Paclitaxel + Radiation	17
Cycles of Consolidation Pembrolizumab Received	-
0-5	9
6-10	5
11-15	5
16-20	5
Median (range)	9.33 (3-18)

Discussion

To our knowledge, this is the first report of the efficacy of subsequent therapy in patients with Stage III NSCLC previously treated with CRT and consolidation immunotherapy. Our data suggest that response rates to subsequent therapy are modest with some patients achieving stable disease, but most patients experiencing progressive disease as their best response. This efficacy with salvage therapy is similar to that observed with salvage chemotherapy in patients with metastatic disease treated with initial chemotherapy. This is also the first study to report the efficacy of subsequent treatment with PD-1 or PD-L1 inhibitors after progression on consolidation immunotherapy. Unfortunately, 5 of the 6 patients re-challenged with a PD-1 or PD-L1 inhibitor had continued progressive disease. It is noteworthy; however, that 1 patient re-challenged with pembrolizumab has achieved an ongoing partial response [2]. This patient had favorable disease characteristics; namely, they completed the 1 year of consolidation therapy, relapsed >1 year off therapy, and had a PD-L1 score of 90%. Based on this experience, it is reasonable to re-challenge select patients with immunotherapy in this setting. This report underscores the poor prognosis most patients face when experiencing disease progression after initial chemoradiation and consolidation immunotherapy for stage III NSCLC. Prior reports of re-challenging patients with immunotherapy after prior immunotherapy have been

Table 2: Response to initial salvage systemic therapy (n=24).

Characteristic	Patients, No.	Treatment Response
PD during Pembrolizumab Consolidation	12	-
PD after Pembrolizumab Consolidation	12	-
Salvage regimens	-	-
Single Agent Chemotherapy	8	-
Pemetrexed	5	1 SD, 4 PD
Docetaxel	3	1 SD, 2 PD
Combination Chemotherapy	9	-
Carboplatin + Gemcitabine	1	1 PD
Carboplatin + Paclitaxel	2	1 PR, 1 SD
Carboplatin + Pemetrexed	4	4 PD
Carboplatin + Paclitaxel + Bevacizumab	1	1 SD
Docetaxel + Ramucirumab	1	1 SD
Targeted Therapy	1	
Erlotinib	1	1 SD
Immunotherapy	6	-
Atezolizumab	1	1 PD
Nivolumab	4	4 PD
Pembrolizumab	1	1 PR

described in patients with stage IV NSCLC. One study analyzed 14 of 434 patients with advanced NSCLC receiving checkpoint inhibitors as initial therapy who were re-challenged with immunotherapy at disease progression. Unfortunately, the median PFS for those re-challenged with checkpoint inhibitors was only 46 days [3]. Another retrospective analysis performed at MD Anderson evaluated the response to single agent chemotherapy in 28 patients who progressed after initial chemotherapy and immunotherapy reported a median PFS of 4.7 months, despite 11 confirmed or unconfirmed partial responses [4]. A third retrospective analysis evaluating the efficacy of next line therapy after treatment with Nivolumab in 191 patients with advanced NSCLC reported a median PFS of only 2.8 months for those receiving gemcitabine and 2.7 months for those receiving docetaxel [5].

Conclusion

In conclusion, we report the efficacy of subsequent systemic therapy at the time of disease progression in patients with Stage III NSCLC treated with CRT followed by consolidation immunotherapy [6]. Response rates with standard chemotherapy in this second line setting were 9.5%, comparable to those reported in a similar population of patients with stage IV disease [7,8]. Re-challenging patients with a PD-1 inhibitor may be reasonable to consider if the patient had disease progression after completing 1 year of consolidation immunotherapy. Ongoing studies will further define the optimal treatment in this patient population.

References

1. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Lancet. 2016;387(10027):1540-50.
2. Martin R, Rodríguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. "Pembrolizumab *versus* chemotherapy for PD-L1–positive non-small-cell lung cancer." New Eng J Med. 2016;375(19):1823-33.
3. Hiromi W, Kubo T, Ninomiya K, Kudo K, Minami D, Murakami E, et al. "The effect and safety of immune checkpoint inhibitor rechallenge in non-small cell lung cancer." J Clin Oncol. 2018;36(15 suppl):e21147.
4. Gustavo S, Peng AS, Bis G, Lee JJ, Benveniste MFK, Zhang J, et al. "Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer." Lung Cancer. 2017;112:90-5.
5. Costantini A, Corny J, Fallet V, Renet S, Friard S, Chouaid C, et al. Efficacy of next treatment received after nivolumab progression in patients with advanced non-small cell lung cancer. ERJ Open Res. 2018;4:00120-2017.
6. Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. "Increased response rates to salvage chemotherapy administered after pd-1/pd-l1 inhibitors in patients with non-small cell lung cancer." J Thorac Oncol. 2018;13(1):106-11.
7. Grigg C, Reuland BD, Sacher AG, Yeh R, Rizvi NA, Shu CA. "Clinical outcomes of patients with Non-Small Cell Lung Cancer (NSCLC) receiving chemotherapy after immune checkpoint blockade." J Clin Oncol. 2017;35(15 suppl):9082.
8. Stinchcombe TE, Socinski MA. "Considerations for second-line therapy of non-small cell lung cancer". Oncologist. 2008;13(Suppl 1):28-36.