Clinical outcomes of immunotherapy continued beyond radiographic disease progression in older adult patients with advanced non-small cell lung cancer

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Abstract. Immunotherapy is an effective and generally well-tolerated treatment strategy for older adult patients (aged ≥70 years) with advanced non-small cell lung cancer (NSCLC). Unfortunately, most patients who receive immunotherapy eventually exhibit disease progression during treatment. The present study reports on a subset of older adult patients with advanced NSCLC who could effectively continue immunotherapy beyond radiographic disease progression due to perceived clinical benefit. Local consolidative radiotherapy may be used in select older adult patients to prolong the duration of immunotherapy they receive, with a particular consideration of their preexisting co-morbidities, performance status and tolerance of potential toxicities associated with combined modality therapy. However, prospective research is needed to determine which patients benefit most from the addition of local consolidative radiotherapy, including whether type of disease progression (i.e., sites of progression, pattern of progression) and/or extent of consolidation offered (i.e., complete or incomplete) impact clinical outcomes. Further research is also warranted to determine which patients would most benefit from the continuation of immunotherapy beyond documented radiographic disease progression.

Introduction

Limited evidence is currently available regarding the clinical outcomes of older adult patients (≥70 years) with advanced non-small cell lung cancer (NSCLC) who receive immunotherapy, because this patient population was largely underrepresented in clinical trials (1). Our group recently reported the results of a retrospective, single-institution study of the clinical outcomes of older adult patients with advanced-stage NSCLC who received immunotherapy (2), and we found that immunotherapy is effective and well tolerated in these patients. Despite an initial response to treatment, most patients (of all ages) with advanced NSCLC develop resistance to immunotherapy (3-9). However, during our retrospective review, we identified a subset of older adult patients who continued to receive immunotherapy beyond documented radiographic disease progression (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1]) owing to perceived clinical benefit. The current case series reviews the outcomes of this subset of older adult patients who received immunotherapy beyond radiographic progression to highlight a potential treatment strategy that may be of benefit to select patients.

Materials and methods

Patients. Using The University of Texas MD Anderson Cancer Center Gemini Lung Cancer database, our group performed a retrospective review of the clinical outcomes of older adult patients (age ≥70 years) with advanced stage III/IV (per American Joint Committee on Cancer 8th Edition) NSCLC treated with anti-PD-(L)1 monotherapy from March 2015 through April 2019. Clinical therapy responses were evaluated by a clinical radiologist using RECIST v1.1 criteria, with radiographic progression of disease defined as one or more of the following: i) ≥20% increase in sum of longest diameters of target lesions; ii) progression of non-target lesions; or iii) new lesions (10). Toxicities were assessed using Common Terminology Criteria for Adverse Events version 5. Patients treated beyond disease progression were defined as individuals who received immunotherapy for a minimum of 8 weeks prior to documentation of progression and then subsequently continued immunotherapy for at least 6 weeks.

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Statistical analysis. Regarding statistical analysis, the categorical and continuous characteristics were summarized, and analyses of overall survival and duration of immunotherapy beyond progression were performed. The distributions of overall survival and duration of therapy beyond progression were estimated by the Kaplan-Meier method. Regression analysis based on the Cox proportional hazard (PH) model were conducted on overall survival and duration of therapy beyond progression. A two-sided P-value of 0.05 was considered significant. All analyses were performed in SAS 9.4 software.

Results

Patient demographics. Of the 159 patients who met the initial inclusion criteria, 33 (21%) received immunotherapy beyond radiographically indicated disease progression. Of these 33 patients, 12 (36%) were female and 21 (64%) were male, 17 (52%) were 70-74 years of age, 30 (91%) were former or current smokers, and 26 (79%) had histologically indicated adenocarcinoma. As this is a real-world patient cohort, immunotherapy was prescribed for patients per FDA label as standard of care. Thirty of the thirty-three (91%) patients received immunotherapy alone in the second-line and beyond treatment setting, as most of the patients in our retrospective study were treated prior to FDA approval in August 2018 and October 2018 of combination chemoimmunotherapy in the first-line setting of metastatic non-squamous and squamous NSCLC per KEYNOTE-189 and KEYNOTE-407, respectively (11,12). PD-L1 expression was available for 10 of 33 patients; 8 patients had PD-L1 positive disease (i.e. TPS 1% or higher), while 2 patients had PD-L1 negative disease (i.e. TPS <1%) (Table I).

Table I. Baseline patient characteristics of 33 patients who received immune checkpoint inhibitors to treat NSCLC beyond radiographic disease progression.

Characteristic	No. (%)
Sex	
Female	12 (36)
Male	21 (64)
Age, years	
70-74	17 (52)
75-79	12 (36)
80-85	4 (12)
NSCLC type	
Adenocarcinoma	26 (79)
Not otherwise specified	2 (6)
Squamous cell carcinoma	5 (15)
Immunotherapy	
Nivolumab	29 (88)
Pembrolizumab	4 (12)
Immunotherapy as first-line treatment	
No	30 (91)
Yes	3 (9)
Immunotherapy as second-line or later treatment	
Second line	18 (60)
Later than second line	12 (40)
Smoking status	
Current	2 (6)
Former	28 (85)
Never	3 (9)
PD-L1 expression level	
<1%	2 (6)
1-49%	4 (12)
≥50%	4 (12)
Unknown	23 (70)

NSCLC, non-small cell lung cancer.

Outcomes of patients who continued on immunotherapy beyond disease progression. Among the 33 patients, the median duration of immunotherapy beyond disease progression, i.e., the time from disease progression to immunotherapy end, death, or last follow-up, was 7.1 months (95% CI 3.0-8.2 months; Fig. 1). With a median follow-up period of 30.1 months, the median overall survival, defined as the time from the start of immunotherapy to death or last follow-up, was 31.5 months (95% CI 16.5 months to not reached; Table II). Eight patients (24%) received local consolidative radiotherapy, with a median duration of immunotherapy beyond disease progression of 8.2 months (95% CI 1.9-13.3 months). Twenty-five patients (76%) did not receive local consolidative therapy, and these patients had a median duration of immunotherapy beyond disease progression of 4.1 months (95% CI 2.3-7.8 months; Table II).

Outcomes of patients who received local consolidative radiotherapy and continued on immunotherapy beyond progression. A dedicated radiology review was conducted on the subset of 8 patients who received local consolidative radiotherapy and subsequently continued with immunotherapy beyond documented radiographic disease progression (Table III). Decision to pursue combined-modality therapy for these 8 patients was up to the discretion of the treating medical oncologist and radiation oncologist. Ongoing studies are evaluating a combination of stereotactic body radiotherapy with checkpoint inhibitors in oligoprogressive NSCLC to overcome acquired resistance and will help us gain insight into determining which patients would be most suitable for this combination treatment approach (13,14). At time of first radiographic progression, 3 of the 8 patients (38%) showed no response to treatment (i.e., imaging was notable for progressive metastatic lesions without any sites of tumor regression), and five patients (63%) showed a mixed response to systemic therapy (i.e., imaging was notable for simultaneous regression and progression in the metastatic lesions) (15). At time of local consolidative therapy, 5 of the 8 patients had oligometastatic disease, defined as 3 or fewer sites of progression, the other 3 patients had polymetastatic disease; 3 patients received complete consolidation and 5 patients received incomplete consolidation. After receiving local consolidative therapy and resuming immunotherapy, 7 of the 8 patients ultimately had disease progression, and the other patient did not show evidence of progression upon subsequent

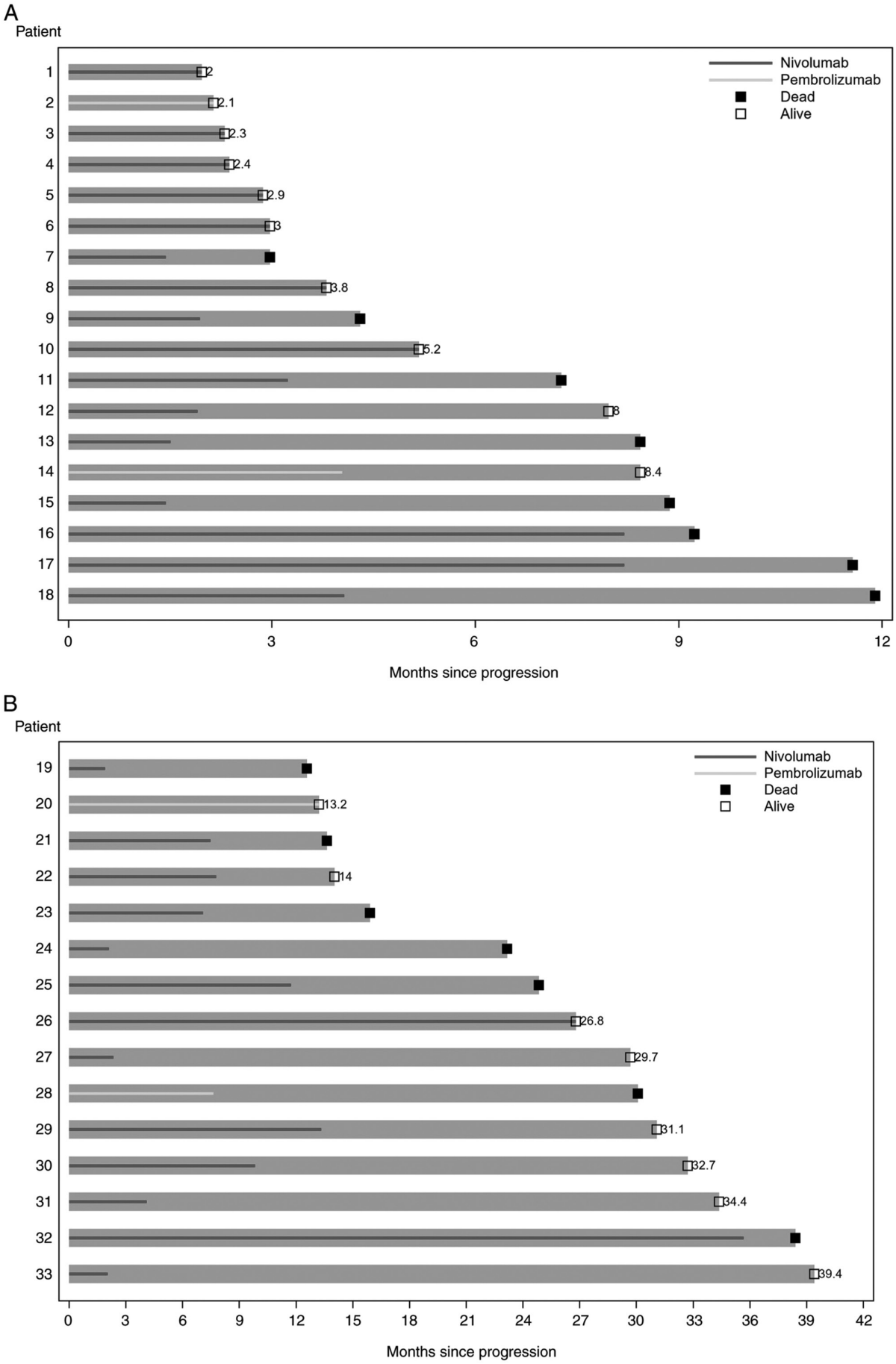

Figure 1. Duration of immune checkpoint inhibitor use (months) after radiographic disease progression for the 33 patients in our cohort. (A) Duration for patients 1-18; (B) duration for patients 19-33.

Table II. Outcomes for patients who received ICI BDP, by patient subtype.

Patient subtype	Median duration of ICI BDP, months	Median overall survival, months
Pseudo-progression, n=6	11.7 (95% CI 7.1-35.7)	26.2 (95% CI 16.5-40)
Local consolidative therapy + ICI BDP, n=8	8.2 (95% CI 1.9-13.3)	Not reached
ICI BDP alone/no local consolidative therapy, n=25	4.1 (95% CI 2.3-7.8)	31.5 (95% CI 16.5 to not reached)

The distributions of overall survival and duration of therapy beyond progression were estimated by the Kaplan-Meier method. ICI BDP, immune checkpoint inhibitors beyond radiographic disease progression.

follow-up. Of the 7 patients who had disease progression, the median time to second objective disease progression after local consolidative radiotherapy was administered was 5.8 months (95% CI 1.2-10.0 months).

Outcomes of patients who experienced pseudo-progression. Six of the 33 patients (18%) exhibited pseudo-progression, defined as a delayed response to immunotherapy with decreased tumor burden in subsequent radiologic studies (16), 4 achieved stable disease as the best response (with a return of their tumor burden to baseline), and 2 achieved a partial response. The median duration of immunotherapy continued beyond pseudo-progression was 11.7 months (95% CI 7.1-35.7 months), and the median overall survival for this group was 26.2 months (95% CI 16.5-40.0 months).

Safety. Patients who received immunotherapy beyond disease progression most commonly experienced fatigue (n=6, 18%), pneumonitis (n=4, 12%), rash (n=3, 9%), and hypothyroidism (n=3, 9%). Three patients (9%) had grade 3 or higher toxicities. One patient had grade 3 arthralgias, and 2 patients had grade 3 pneumonitis resulting in discontinuation of therapy. Four of thirty-three patients (12%) were treated with pembrolizumab; one patient on pembrolizumab experienced grade 1 rash and grade 1 diarrhea, while one patient on pembrolizumab experienced grade 1 fatigue. All other toxicities described occurred in the twenty-nine patients treated with nivolumab.

Discussion

Immunotherapy continued beyond disease progression (defined by RECIST v1.1) in older adults with advanced NSCLC may be of benefit to a select group of patients. Additionally, local consolidative therapy with radiation may allow prolonged duration of immunotherapy.

Real-world outcomes of this treatment strategy in the management of NSCLC and other tumor types, such as advanced-stage melanoma, have been retrospectively studied by previous groups, and select patients had durable progression-free survival benefit despite discordant responses to immunotherapy (17-22). For example, one retrospective study analyzed the clinical outcomes of 208 NSCLC patients treated with immunotherapy and found that oligoprogression was the major pattern of progression after acquired resistance from immunotherapy (17). The most common treatment used for management of oligoprogression was a combination of local radiotherapy and continued immunotherapy (33%, n=38 patients). This resulted in significantly longer second progression-free survival (PFS) (12.0 months vs. 10 months, P=0.006) and overall survival (26.3 months vs. 18.5 months, P=0.001) compared to other treatment strategies (17). Reinhorn *et al* previously evaluated real-life practice and outcomes related to immunotherapy beyond progression in advanced NSCLC patients treated with immunotherapy (18). Of 207 patients, 22% received immunotherapy beyond progression, and 36% achieved a clinical benefit. 27% of patients had a progression-free interval over 6 months after receiving immunotherapy beyond progression (18). A retrospective study of 125 Chinese patients with advanced NSCLC who experienced progressive disease after receiving monotherapy or combination therapy with PD-1/PD-L1 inhibitors by Ge *et al* found that patients who were treated with immunotherapy for more than 6 weeks after PD (n=39) had longer overall survival (26.6 months vs. 9.5 months; P<0.001) and PFS (PFS, 8.9 months vs. 4.1 months; P<0.001), compared to those who did not receive immunotherapy beyond progression (19). Subgroup analysis showed significant benefits for overall survival and PFS in the overall population and particularly for overall survival in males, squamous histology, no brain or liver metastases, any age, not beyond ≥ the third treatment line, with partial response to previous immunotherapy and monotherapy as previous immunotherapy (19).

Our retrospective case series is unique given the limited dedicated study of the continuation of immunotherapy beyond radiographic progression specifically in patients aged 70 years or older. Our findings are of clinical significance and potentially address an unmet need in standard clinical practice for these patients, who are likely to be more frail and potentially more vulnerable (23).

Exploratory analysis of selected population subgroups in our retrospective study revealed no statistically significant interaction between duration of immunotherapy administered beyond radiographic progression and patient sex, age, NSCLC subtype, immunotherapy agent used, smoking status, or if immunotherapy was used in the first line setting or beyond (data not shown). However, we acknowledge that

Table III. Clinical characteristics and outcomes of patients who received local consolidative therapy at the time of first radiographic progression.

Patient	Duration of immunotherapy prior to first radiographic progression	Progression pattern (progression or mixed response)	Site of progression (oligometastatic or polymetastatic)	Sites of active disease at initiation of local consolidative therapy	Complete or incomplete consolidation	Progression during subsequent follow-up	Time to second objective disease progression after local consolidative therapy
1	3.6 months	Progression	Oligometastatic	Left chest wall, right pelvic mass	Complete	Yes	10 months
2	23.7 months	Progression	Polymetastatic	Retroperitoneal lymph node, paraaortic lymph node, right iliac, acetabular and ischial bone	Incomplete	Yes	1.2 months
3	7.3 months	Mixed response	Oligometastatic	Right lower	Complete lobe	No	Not applicable
4	11.1 months	Mixed response	Polymetastatic	Multiple pulmonary nodules in mediastinal lymph nodes, retroperitoneal soft tissue	Incomplete	Yes	6.5 months
5	4.1 months	Mixed response	Oligometastatic	Axillary lymph node, brain metastases	Incomplete	Yes	3.4 months
6	21.4 months	Mixed response	Oligometastatic	Pleural metastases, left supraclavicular lymph node	Complete	Yes	6.7 months
7	11.6 months	Mixed response	Oligometastatic	Adrenal gland, supraclavicular lymph node, brain metastases	Incomplete	Yes	2.6 months
8	9.5 months	Progression	Polymetastatic	Brain, pulmonary metastases, mediastinal lymph node, paraaortic lymph nodes, liver	Incomplete	Yes	5.8 months

the relatively smaller sample sizes may not provide adequate power for subgroup analysis. A prospective study with a larger sample size is needed to draw further conclusions regarding clinical characteristics and biomarkers that would clarify which patients would benefit most from such a treatment strategy.

Due to small sample sizes, results from our retrospective study are primarily hypothesis-generating with regards to determining which patients may benefit most from a combined modality treatment approach. However, previous studies suggest that a combination of radiation therapy and immune checkpoint inhibition may act at various stages of the antitumor response to induce synergy between the two treatment modalities (24); radiotherapy may enhance the immunotherapeutic effects of PD-1/PD-L1 inhibitors, as it can prime antigen release and improve antigen processing to result in enhanced T-cell killing. Welsh *et al* in a phase I/II trial of pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer found that combined immunoradiotherapy was generally safe, with only a few high-grade adverse events observed; exploratory findings from this study suggested that RT may be more beneficial for patients with low PD-L1 expression (25).

In conclusion, our retrospective study demonstrates that treatment with immunotherapy beyond radiographic progression may be safe and feasible in a selected subset of older adult patients with metastatic NSCLC. Future studies are needed to prospectively validate the safety and efficacy of this treatment strategy in different clinical and histopathologic subsets of patients with metastatic NSCLC, including individuals of different age groups.

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Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available due to patient security but are available from the corresponding author on reasonable request.

Authors' contributions

EKS and MA confirm the authenticity of all the raw data. EKS performed conceptualization, data curation (i.e. organization and management of the raw data set), investigation, and preparation of the original draft of the manuscript. FM performed conceptualization, data curation, and review and editing of the manuscript. MW performed data curation, investigation, and review and editing of the manuscript. CHL performed formal analysis with statistical software. JJL performed formal analysis, software use, and supervision. BC performed data curation and investigation. CJP performed conceptualization and review and editing of the manuscript. JVH performed supervision, conceptualization, and review and editing of the manuscript. MA performed conceptualization, data curation, supervision, investigation, and original draft preparation of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved and conducted in accordance with the institutional review board at The University of Texas MD Anderson Cancer Center (approval no. PA13-0589). All patients provided written informed consent/authorization for participation in research.

Patient consent for publication

All identifying information of patients has been removed. All patients when consenting were made aware that study information and study analyses may be published in scientific literature and/or other public scientific resources.

Competing interests

MW is an employee of Medscape, LLC, New York, NY. JVH has served on the scientific advisory boards for AstraZeneca, EMD Serono, Boehringer-Ingelheim, Catalyst, Genentech, GlaxoSmithKline, Hengrui Therapeutics, Eli Lilly, Spectrum, Sanofi, Takeda, Mirati Therapeutics, BMS, BrightPath Biotherapeutics, Janssen Global Services, Nexus Health Systems, Pneuma Respiratory, Kairos Venture Investments, Roche, Leads Biolabs, RefleXion, and Chugai Pharmaceuticals. He receives research support from AstraZeneca, Bristol-Myers Squibb, Spectrum, and Takeda and royalties and licensing fees from Spectrum outside of the submitted work. MA received research funding (to institution) from Genentech, Nektar Therapeutics, Merck, GlaxoSmithKline, Novartis, Jounce Therapeutics, Bristol Myers Squibb, Eli Lilly, Adaptimmune, Shattuck Lab, and Gilead and receives consultant and advisor fees from GlaxoSmithKline, Shattuck Lab, Bristol Myers Squibb, and AstraZeneca. He receives speaker fees from AstraZeneca, Nektar Therapeutics, and SITC and acknowledges participation in safety review committees for Nanobiotix-MDA alliance and Hengenix outside of the submitted work. The remaining authors declare no conflict of interest.

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