



Immunotherapy and Mixed Radiographic Response in Non-Small Cell Lung Cancer

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Introduction

Since ipilimumab was first approved for the treatment of metastatic melanoma in 2010, an increasing number of immunotherapeutic agents have been developed and approved for a multitude of tumor types. The era of immunotherapy has ushered new challenges of assessing disease response. Traditionally, radiographic response as determined by Response Evaluation Criteria in Solid Tumors (RECIST) has guided cancer treatment based on the assumption that an early increase in tumor size or appearance of new lesions signaled progressive disease that warrants discontinuation of treatment [1]. However, in early trials of melanoma patients treated with ipilimumab, distinct immune related radiographic patterns were observed. A portion of patients with radiographic progression preceding response, or with expanding or new lesions in the presence of other responsive lesions derived a meaningful clinical benefit. These findings could be explained by anticancer immune activation leading to an inflammatory response apparent on imaging [2]. Clearly these patients would have been deemed to have disease progression based on RECIST criteria, and with strict implementation of RECIST, would be denied an efficacious therapeutic option. On the other hand, many patients with initial radiographic progression or a mixed response were found to have true disease progression and would not benefit from continued treatment with an ineffective drug.

Since these initial observations were made, investigators have worked towards identifying an effective way to capture and measure disease response with immune therapy. Several criteria have been proposed, including Immune-Related Response Criteria (irRC), Immune-Related RECIST (irRECIST), modified RECIST 1.1 of Immune-based Therapeutics (iRECIST), and Immune-Modified RECIST (imRECIST). Studies are ongoing to determine the validity of these tools. Based on the observation that tumor pseudo-progression was seen more frequently in melanoma as compared with non-small cell lung cancer [3,4] in clinical trials, it is unlikely that one set of criteria will be applicable to all immune therapies and all tumor types for which immune therapy has been approved.

In our institution we noted radiographic mixed response, which we define as reduction in some lesions concomitant with expansion in others or appearance of new lesions, among the early lung cancer patients treated with immunotherapy. We present five cases of patients treated with immunotherapy for advanced non-small cell lung cancer with mixed radiographic responses per RECIST criteria and divergent clinical outcomes. We anticipate that approach to management of such patients will continue to be a challenge until a standardized tool to assess true disease response is available.

Cases Presentation

Case 1

NS was a 76 year old male with stage IV poorly differentiated non-small cell lung cancer with disease consisting of a right upper lobe lung mass, small right pleural effusion, mediastinal adenopathy, bilateral adrenal masses and lytic metastases to thoracic and lumbar spine and left femur. After palliative radiotherapy to L4 and the left proximal femur, a complete baseline assessment of disease was performed (Figure 1A), he was enrolled in a clinical trial and randomized to treatment with the PDL-1 inhibitor, durvalumab. CT imaging after 8 weeks of treatment demonstrated improvement in the size and metabolic activity of lung mass, right paratracheal, right subcarinal, hilar adenopathy and left adrenal metastasis, but an increase in size of the right adrenal mass and increase in a soft tissue component of a cervical spine lesion (Figure 1B). He was continued on treatment and at 12 weeks he underwent brain and C-spine films for evaluation of ataxia and mental status changes.

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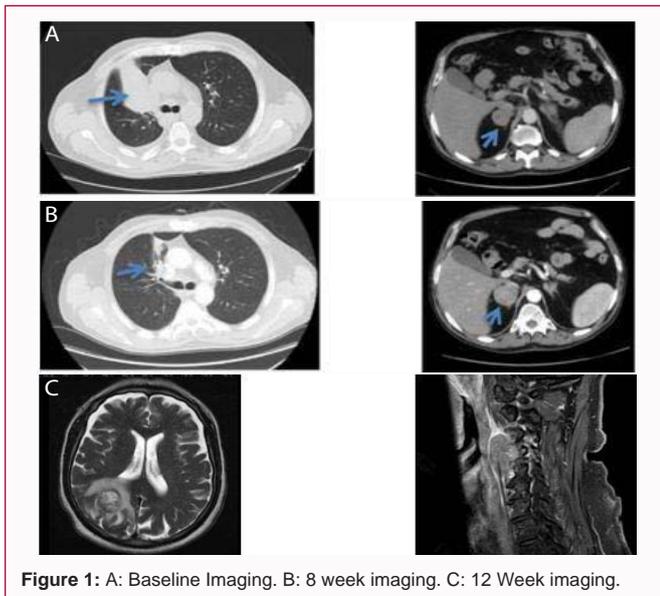


Figure 1: A: Baseline Imaging. B: 8 week imaging. C: 12 Week imaging.

He was found to have multiple new brain lesions and an increasing cervical spine metastasis with a large soft tissue component (Figure 1C). He was taken off study due to disease progression and was treated with radiation therapy to the whole brain and cervical spine.

Case 2

PD was a 74 year-old male who was found to have a 7.5 × 4.4 cm mass in the left anterior chest eroding into the ribs as well as a left supra-hilar mass, left basilar nodule and new small left pleural effusion (Figure 2A) 10 months after a VATS right upper lobectomy for a pT2apN0 (stage IB). Biopsy of the chest wall mass confirmed metastatic squamous cell carcinoma of the lung. He was treated on a clinical trial with durvalumab and after 2 cycles of treatment there was a significant decrease in disease at all measurable sites except for the chest wall mass that increased in size despite a significant decrease in pain and narcotic needs (Figure 2B). Treatment was continued for

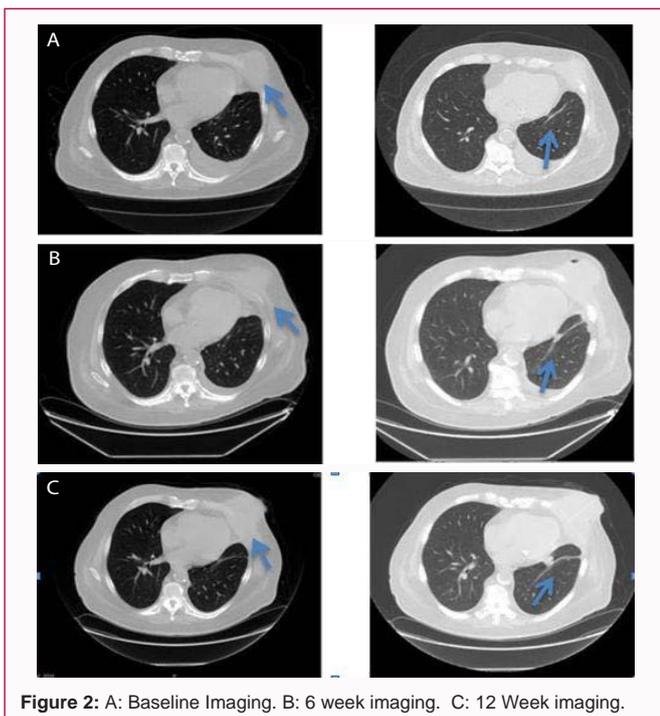


Figure 2: A: Baseline Imaging. B: 6 week imaging. C: 12 Week imaging.

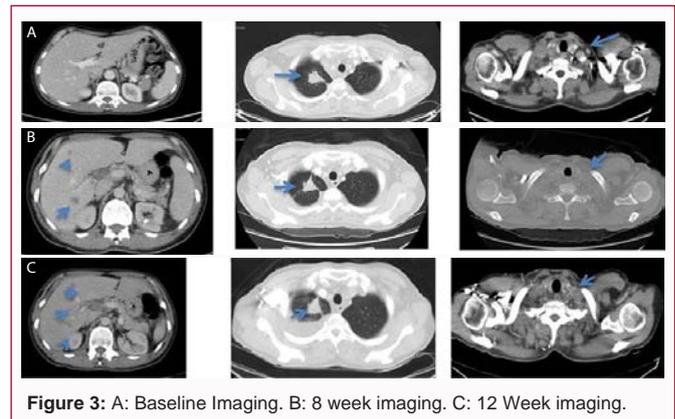


Figure 3: A: Baseline Imaging. B: 8 week imaging. C: 12 Week imaging.

3 additional cycles but CT scans documented an increase in all disease sites (Figure 2C). Clinical trial treatment was discontinued in favor of standard chemotherapy.

Case 3

LMD was a 52 year-old female with stage IV lung adenocarcinoma with a dominant right upper lobe lung mass, right hilar, paratracheal and subcarinal lymphadenopathy (Figure 3A), as well as multiple metastatic brain lesions. She was treated with SBRT to four separate brain lesions. After brain MRI documentation of response, she enrolled in a clinical trial with the PDL-1 inhibitor durvalumab (20mg/kg IV every 4 weeks) combined with the CTLA-4 antagonist tremelimumab (1 mg/kg IV every 4 weeks). She developed grade II soft tissue swelling successfully treated with diphenhydramine alone and a right pleural effusion for which she underwent thoracentesis. CT imaging performed at 8 weeks after initiation of therapy (2 cycles) showed no change in the RUL lung mass, a significant reduction in size of all lymph nodes and at least 6 new small, subcentimeter lesions throughout the liver and in the central portion of the spleen, consistent with a “mixed response” per immune response criteria (Figure 3B). Because of her generally improved clinical status, treatment was continued and another CT scan 8 weeks later (2 more cycles) demonstrated an increase in all lesions (Figure 3C). She was taken off study due to disease progression and treated with standard chemotherapy.

Case 4

AG was a 57 year-old male who presented with dyspnea and a large right lower lobe lung mass, mediastinal adenopathy and an adrenal mass (Figure 4A). A biopsy of the adrenal mass confirmed poorly differentiated adenosquamous cell carcinoma of the lung. He initiated treatment with the PDL1 inhibitor durvalumab. After cycle 2 he developed symptomatic pleural effusion and underwent thoracentesis. After 3 cycles of treatment, restaging CT scans demonstrated stability of the primary lung mass, with shrinkage of some mediastinal lymph nodes and increase in others, and slight increase in the size of the adrenal mass (Figure 4B). Durvalumab treatment was continued for another 2 cycles and a repeat CT demonstrated stability of most lesions but continued growth of the adrenal lesion (Figure 4C). With a decrease in ECOG PS, the patient was taken off study for disease progression and standard chemotherapy was initiated.

Case 5

FY was a 63 year-old male diagnosed with stage IV squamous cell carcinoma of the lung with disease progression following an initial

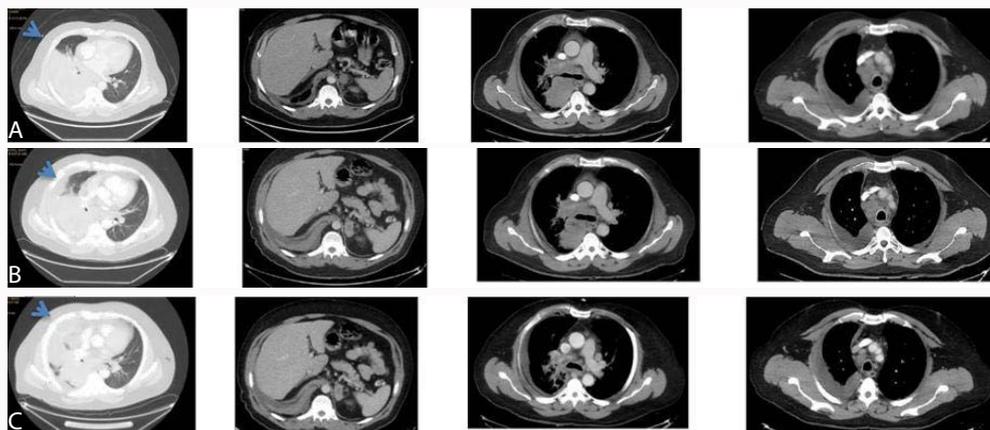


Figure 4: A: Baseline Imaging. B: 6 week imaging. C: 12 Week imaging.

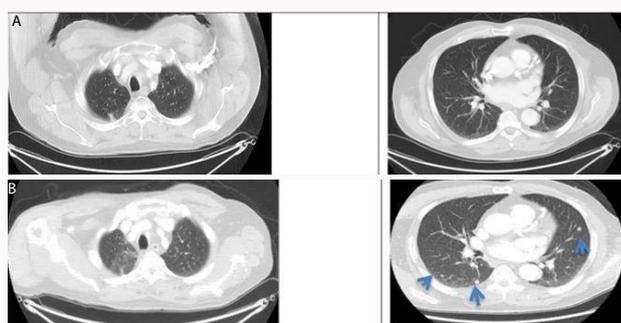


Figure 4: A: Baseline Imaging. B: 8 week imaging.

response to first line treatment with carboplatin + gemcitabine. CT scans demonstrated multiple bilateral pulmonary nodules (Figure 5A). The patient was treated with nivolumab as second line treatment. CT imaging at 8 weeks (after 5 cycles) demonstrated a major reduction in all pulmonary nodules except for two new pulmonary nodules (Figure 5B). Nivolumab was continued and he remained clinically stable after an additional three cycles.

Discussion

The cases in this report illustrate distinct radiographic patterns encountered among the first forty lung cancer patients treated with immunotherapy at our institution. Each of the patients described had a “mixed response” to PD1 or PDL-1 inhibition with or without concurrent use of CTLA-4 inhibition, which per RECIST criteria would have been defined as disease progression. In all but one of these cases, the mixed response was found to be a true indicator of disease response. Though novel immune criteria do recognize mixed response patterns, whether they accurately are able to measure them in a way that correlates to true response is unclear. An ideal tool would be able to distinguish a mixed response with true progression from mixed response with clinical benefit.

The need for an immunotherapy based response criteria became clear after it was noted from immunotherapy trials that overall survival benefit did not appear to correlate to progression free survival or response rate as measured by RECIST v1.1 [5]. The earliest iteration of immune response criteria was developed by The Cancer Vaccine Clinical Trial Working Group in 2004 [6]. These novel criteria were then examined and enhanced across phase II trials of patients evaluated with ipilimumab in metastatic melanoma after it

was noted that some patients who met criteria for disease progression based on RECIST 1.1 were later noted to have durable response [7]. Based on the data gathered, Wolchok, et al. developed immune-related response criteria (irRC) in 2009 to systematically characterize additional patterns of response. With irRC, index and measurable new lesions are included in the total tumor burden (in comparison to RECIST criteria in which presence of new lesions signified disease progression) and disease progression is defined by increase in tumor burden $\geq 25\%$ relative to the nadir. Increase in tumor burden of less than 25%, even in the presence of new lesion or progression of non-indexed lesions denotes stable disease, which permits Continuation of therapy. In order to avoid premature cessation with potential benefit, even if aggregate tumor burden grows, irRC does not define disease progression until findings are confirmed on repeat scans.

The relationship between outcome data with response per RECIST v1.1 and irRC was evaluated in patients with advanced melanoma treated with pembrolizumab as part of the phase 1b KEYNOTE-001 study, and it was determined that conventional RECIST might underestimate the benefit of pembrolizumab in approximately 15% of patients [3]. The FDA now allows for use of irRC as a secondary endpoint in many immunotherapy trials but given that it has not yet been fully validated, the agency still favors results measured by RECIST v1.1. The generalizability of irRC to other tumor types is also uncertain and since 2009 several other response criteria have emerged. Immune-related RECIST (irRECIST) combined elements of irRC and RECIST [8]. The immune modified RECIST (imRECIST) criteria were developed for implementation in atezolizumab studies [5]. Immune RECIST (iRECIST) was developed by the RECIST working group in an attempt to standardize and validate immune response criteria [9]. Though there are subtle differences between each of these criteria, they all account for delayed response and flare effect by repeat imaging up to 12 weeks after treatment, and unlike RECIST v1.1, none define progression as presence of new lesions. Details regarding radiographic mixed responses is limited in immunotherapy trials in non-small cell lung cancer but were reported in trials with the PD-1 inhibitor nivolumab. In the phase I clinical trial conducted by Brahmer, et al. Evaluating nivolumab in various refractory solid tumors, 4 of 39 patients experienced a mixed response, and 2 of those 4 later went on to have a partial response. Of note, one of the patients had a diagnosis of melanoma while the other patient had renal cell carcinoma [10]. In a large dose escalation trial, of 296 patients with refractory solid tumors, 8 patients with melanoma, lung cancer or renal cell carcinoma were noted to have a mixed response, follow up

Table 1: Mixed Responses in lung cancer immunotherapy clinical trials.

Trial	Immunotherapy	Design	Mixed Response	Clinical Benefit
Brahmer et al. [10]	Nivolumab	Phase I	4/39	2/4
Topalian et al. [11]	Nivolumab	Phase I	8/296	NR
Rizvi et al. [12]	Nivolumab	Phase II	22/117	4/22
Brahmer et al. [13]	Nivolumab	Phase III	28/272	9/28
Borghaei et al. [4]	Nivolumab	Phase III	71/292	16/71
Garon et al. [15]	Pembrolizumab	Phase I	NR	NR
Herbst et al.	Pembrolizumab	Phase II/III	NR	NR
Reck et al. [16]	Pembrolizumab	Phase III	NR	NR
Fehrenbacher et al. [18]	Atezolizumab	Phase II	Nr but 57/144 treated past progression	NR but longer median survival in those treated past progression
Barlesi et al. [19]	Atezolizumab	Phase III	NR	NR
Antonia et al. [21]	Durvalumab/tremelimumab	Phase I	NR	NR
Gulley et al. [20]	Avelumab	Phase I	NR	NR

* NR: not reported

data was not reported [11].

In studies of nivolumab in the treatment of advanced non-small cell lung cancer specifically, there has also been documentation of mixed response preceding clinical benefit. In the phase II trial CheckMate 063 evaluating nivolumab for patients with metastatic squamous non-small cell lung cancer, 4 of 22 (18%) patient's treated past RECIST defined progression went on to experience tumor burden reduction or stable disease [12]. In the follow up phase III trial CheckMate 017 comparing docetaxel to nivolumab in metastatic squamous non-small cell lung cancer, 9 of 28 (32%) patients treated past RECIST defined progression had later evidence of tumor reduction or stable disease for at least two tumor assessments [13]. Finally, in CheckMate 057, a phase III trial comparing nivolumab versus docetaxel in non-squamous non-small cell lung cancer, 16 of 71 (22%) patients treated past RECIST went onto have a clinical benefit [4] (Table 1).

A comparison of response rates using RECIST 1.1, iRECIST and irRC in 27 patients in a single center treated with nivolumab for lung, renal and head and neck cancer via retrospective chart review. Of the 17 lung cancer patients, disease control rate was 70% with RECIST compared to 77% with iRECIST and irRC [14] and it was concluded that RECIST likely underestimates response.

In studies of PD1 inhibitor pembrolizumab in patients with advanced non-small cell lung cancer, irRC were implemented, but details regarding number of patients with mixed response were not specified [15,16]. Pembrolizumab now has first line indications based on Keynote-024 which showed improved overall survival pembrolizumab versus platinum based chemotherapy in patients with PDL1 expression over 50% [17], and based on Keynote-189 which demonstrated improved PFS and OS in combination with chemotherapy compared to chemotherapy alone, regardless of PDL1 status [18]. In both of these trials, progression was defined by traditional RECIST 1.1 criteria. In Keynote-024 patients were permitted to stay on treatment after radiographic progression if the investigator determined there was a clinical benefit. Mixed responses were not separately reported.

PDL-1 inhibitor atezolizumab has been compared to docetaxel in the second line setting in the randomized phase II POPLAR trial. Objective response rates were measured by both immune-modified

RECIST criteria and RECIST v1.1 criteria, with similar response rates between the two criteria. Per imRECIST, 24/144 patients responded and per RECIST v1.1, 21/144 responded. In total, three additional patients who would have been deemed to have progressive disease were reclassified as having disease response [19]. Progression free survival was also longer with use of imRECIST, and of 57 patients on atezolizumab who received treatment post progression, 15% had at least a 30% decrease in target lesions relative to baseline. Of these 57 patients who continued atezolizumab post progression, median OS was 11.1 months, compared to 8.3 months for atezolizumab patients who were switched to another anti-cancer therapy [5]. Presumably, the patients who switched to another line therapy had clinical signs of progression, and those who continued therapy had clinical benefit. In the follow up phase III OAK trial examining atezolizumab versus docetaxel, details regarding incidence or outcome of patients with mixed responses were not reported [20].

Finally, avelumab monotherapy was studied in patients with previously treated advanced non-small cell lung cancer in the phase I JAVELIN study. Tumor response was assessed using RECIST v1.1, however modified Immune-Related Response Criteria (iRC) were also used to assess response patterns that may not have been captured by RECIST. Per RECIST, objective response rate was 14% and median progression free survival was 11.6 weeks; per iRC response rate was 12% and median progression free survival was 17.6 weeks [21].

The immunotherapeutic agents used in most patients reported above, durvalumab and tremelimumab were studied in combination in a multicenter phase 1b study [22]. Response rates were based on RECIST v1.1, mixed response not reported.

Radiographic mixed response preceding a true response is likely due to T cell infiltration and immune-mediated inflammation in pre-existing radiographically occult micro-metastasis, while mixed response as an indicator of true disease progression reflects the development of new and possibly antigenically distinct tumor [2]. Unfortunately, current imaging modalities are insufficient for distinction between pseudo-progression and true progression, and biopsy of expanding lesions may not always be feasible. As immunotherapeutics are being increasingly investigated in combination therapy with chemotherapy, targeted agents and radiotherapy, response patterns may become even more difficult to interpret.

Across ipilimumab trials for melanoma, approximately 10% of patients with disease progression per traditional RECIST criteria went on to derive clinical benefit, and in nivolumab trials approximately 20%-30% of patients had radiographic progression preceding response. Of note, the majority of patients with mixed response do not derive benefit (Table 1). Though the numbers of patients with mixed responses may be too small to draw definitive

Conclusion

It is fair to say that use of RECIST criteria in immunotherapy may lead to early discontinuation of therapy in a segment of patients, whereas use of immune response criteria may lead to continued treatment in the majority of patients for whom a mixed response signifies true disease progression. In our small sample of patients, all had mixed responses, and only one patient went on to have clinical benefit. In the case of metastatic melanoma or second line lung cancer where response rates to subsequent lines of therapy have historically been low and there is a lack of good alternative options, monitoring on treatment could be a reasonable approach. However as approval for immunotherapeutics have moved into the first line setting a timely assessment of response becomes more crucial, as delay of chemotherapy could significantly impact patient outcomes.

However, the challenges described are not unique to immunotherapy. Similar obstacles have been encountered with targeted therapies, which can cause tumor necrosis or decrease vascularity without inducing a significant decrease in tumor size [23]. As a result, RECIST underestimates tumor response to imatinib in patients with metastatic GIST [24]. In 2007 Choi et al developed new response criteria which included tumor attenuation as an additional measure of response to imatinib therapy [25]. In treatment of hepatocellular carcinoma, decrease in arterial enhancement of lesions has been recognized as a marker of response, and modified RECIST were developed with incorporation of arterial enhancement as indicative of response [26].

Emerging imaging technologies may more accurately assess response to immunotherapy. Radiolabeled caspase-3 inhibitors have been developed as Positron Emission Tomography (PET) tracers for imaging caspase-3 activation and have been used successfully to image apoptotic treatment response in mouse models of cancer [27]. Annexin A5 is a cellular protein that binds with high avidity to Phosphatidylserine (PS), a membrane associated intracellular phospholipid expressed on the cell surface early in apoptosis. Fluorescein-labeled recombinant-Annexin V has also been noted to be an early predictor of chemotherapy response in patients with advanced cancer [28]. To date, these techniques have not been applied to patients on immunotherapy. As we learn more about the complexities of immunotherapy, undoubtedly criterion for determining response to therapy will also evolve. Until then, determination of clinical benefit will be in key in deciding when to discontinue immune therapy.

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