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Radiographic assessment and therapeutic decisions at RECIST progression in EGFR-mutant NSCLC treated with EGFR tyrosine kinase inhibitors*

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Abstract

Purpose—Advanced NSCLC harboring epidermal growth factor receptor (*EGFR*) mutations treated with EGFR tyrosine kinase inhibitors (TKIs) typically progresses after initial response due to acquired resistance. TKIs are often continued beyond progressive disease by RECIST. We investigated the practice of continuing EGFR-TKIs after RECIST-PD via CT findings.

Methods—Among 101 advanced NSCLC patients with sensitizing EGFR mutations treated with first-line EGFR-TKIs, 70 patients had baseline and at least one follow-up CT for retrospective radiographic assessments using RECIST1.1; 56 patients had experienced PD by the data closure date of June 2011.

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Conflicts of interest

Radiographic assessment and therapeutic decisions at RECIST progression in EGFR-mutant NSCLC treated with EGFR tyrosine kinase inhibitors.

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Bruce E. Johnson, M.D.: Consultant: Astra-Zeneca, Genentech, Pfizer. Stock Ownership: KEW-Group. Other: Post marketing royalties from Dana-Farber for EGFR testing.

Results—Among 56 patients experiencing PD, 82% were female, median age was 63 years, 50% were never-smokers, 57% had distant metastasis, 57% had exon 19 deletion, and 89% were treated with erlotinib. 49 patients (88%) continued TKI therapy beyond retrospectively assessed PD. 31/32 (97%) patients who progressed by an increase in their target lesions continued TKI. 13/16 (81%) patients who progressed by appearance of a new lesion remained on TKI. 5/6 (83%) patients with both increase of target lesions and new lesion at PD continued TKI. Two patients with PD in non-target lesions discontinued therapy at PD. In 49 continuing patients, the median time from retrospectively assessed RECIST-PD to termination of TKI was 10.1 months.

Conclusions—88% of EGFR-mutant NSCLC patients who progressed on first-line TKI continued therapy beyond RECIST-PD, which is not the single determining factor for terminating TKI in EGFR-mutant NSCLC patients. Additional radiographically defined progression criteria are needed for this population.

Keywords

Lung cancer; Computed tomography; Drug resistance; Epidermal growth factor receptor mutations; EGFR tyrosine kinase inhibitors; RECIST

1. Introduction

Lung cancer remains to be the most common cause of cancer deaths in the United States and worldwide, accounting for more than 160,000 deaths each year in the United States [1,2]. Recent advances in molecular characterization of lung cancer have led to the development and clinical application of effective targeted therapeutic agents, including epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) for non-small-cell lung cancer (NSCLC) with *EGFR* sensitizing mutations, and anaplastic lymphoma kinase (ALK) inhibitors for NSCLC with ALK rearrangements. These discoveries and their effective translation into clinical care have transformed the way oncologist approach and treat different patients with lung cancer.

Patients with NSCLC harboring somatic sensitizing mutations in *EGFR* treated with EGFR-TKIs, gefitinib or erlotinib, have response rates in excess of 70% and progression-free survival of 9.7–13.1 months [3–9]. However, virtually all patients with an initial response eventually relapse due to acquired resistance. The mechanism of resistance defined thus far include the development of *EGFR* T790 M mutation, MET amplification, transformation to small cell lung cancer, or PIK3CA mutation [10–14].

Oncologists typically rely on radiographic response assessment by response evaluation criteria in solid tumors (RECIST) as the major determinant in defining the tumor progression and deciding when to change therapeutic regimen [15,16]. However, increasing clinical experience indicates that RECIST, originally developed to assess response to cytotoxic agents, may not be sufficient to fully characterize response and progression in genomically-defined subsets of patients treated with targeted therapy [17–19]. Experienced thoracic oncologists continue to treat NSCLC patients harboring *EGFR* mutation with erlotinib or gefitinib for extended periods of time despite evidence of RECIST progression; their tumors tend to grow very slowly suggesting that some tumor cells remain sensitive to erlotinib [20–22]. Riely et al. reported that patients with *EGFR*-mutant tumors can display a disease flare with symptomatic and radiographic progression after stopping EGFR-TKIs, while improvement is noted after restarting EGFR-TKIs [20]. Moreover, 23% of *EGFR*-mutant lung cancer patients and acquired clinical resistance to EGFR-TKIs experienced a symptomatic disease flare, defined as hospitalization and/or death attributable to disease progression after therapy discontinuation [23]. Similar scenario is noted in NSCLC patients with ALK translocation treated with ALK-inhibitor, crizotinib. Of 116 NSCLC patients in

the phase I trial, 16 patients remained on crizotinib following RECIST-PD for 22–447 days [24]. These observations suggest that clinicians believe there is substantial clinical benefit from maintaining targeted therapy for some of the genomically-defined NSCLC patients, as noted in patients with gastrointestinal stromal tumor (GIST) patients treated with imatinib, and HER2-amplified breast cancer patients treated with trastuzumab [19,20,25,26]. Given these observations, modifications of RECIST may be helpful in guiding clinical practice in *EGFR*-mutant NSCLC patients treated with *EGFR*-TKI.

The purpose of the present study is to investigate the frequency of continuation of *EGFR*-TKI beyond RECIST-PD, assess patterns of progression via CT imaging findings, and investigate the association of baseline patient demographics and disease characteristics with discontinuation of TKI among patients who progressed while on TKI.

2. Patients and methods

2.1. Patients

The original cohort included 101 consecutive patients with stage IV NSCLC (AJCC 7th edition) or stage I-IIIa NSCLC with systemic relapse and sensitizing *EGFR* mutations who were treated with *EGFR*-TKIs, gefitinib or erlotinib, as their initial systemic therapy for advanced NSCLC at the Dana-Farber Cancer Institute between February 2002 and May 2010 [27]. Seventy-three of the 101 patients have been studied and included in the prior publication by Heon et al. on central nervous system progression in *EGFR*-mutant advanced NSCLC patients treated with *EGFR*-TKI [27]. Patients who had previously undergone definitive treatment for stage I-IIIa NSCLC that subsequently relapsed were included if they were treated with surgical resection with curative intent, with or without radiation therapy and/or chemotherapy. Neoadjuvant/adjuvant chemotherapy or chemotherapy plus chest radiotherapy was allowed if completed more than 12 months prior to the start of systemic treatment for relapsed disease [27].

Baseline chest computed tomography (CT) scan, including the chest through the adrenal glands, and at least one follow-up chest CT scan during *EGFR*-TKI therapy performed at least 4 weeks after the initiation of therapy were available in 70 patients. The remaining 31 patients (out of 101 patients) did not have baseline CT scans and/or at least one follow-up scan available for review and were excluded from the study. Therefore, the study population of the present study consisted of 70 advanced NSCLC patients with sensitizing *EGFR* mutations treated with first-line erlotinib or gefitinib.

Forty-one patients included in this study were enrolled in prospective trials of gefitinib or erlotinib [28–31,4]. Smoking history was collected from the patients using a self-reported questionnaire. The collection of clinical information on patients with somatic *EGFR* mutations was approved by the institutional review board.

2.2. Mutation analysis

Tumor specimens for each patient on this study were obtained from diagnostic or surgical procedures. Samples consisted of either frozen tumor specimens or paraffin-embedded material. *EGFR* exons 18 to 21 were amplified by PCR and analyzed bidirectionally by direct sequencing for the presence of somatic mutations [32,33]. Mutations were confirmed by multiple independent PCR amplifications, using previously reported criteria [21,27]. For the purposes of this study, the following *EGFR* mutations were considered sensitizing: deletions in exon 19, duplications in exon 19, deletion-insertions of exon 19, L858R point mutation, L861Q point mutation, and G719 missense point mutations [21].

2.3. Radiographic assessment of RECIST-PD

Baseline and follow-up CT scans were performed to determine response to EGFR-TKIs. The follow-up CT scans were performed after every 8 weeks ($n = 38$), every 6 weeks ($n = 2$), every 12 weeks ($n = 1$) of therapy in 41 patients treated in the trials, and per clinician's recommendation in 29 patients treated as standard clinical care.

Tumor measurements and response assessment were performed by a thoracic radiologist (M.N.) on the baseline and follow-up scans during EGFR-TKI therapy using RECIST 1.1 at each follow-up scan [16,34,35]. The radiologist was aware that the patients were receiving EGFR-TKI, however, was not aware whether or not they were clinically considered to have progressed. All imaging studies that included target lesions were reviewed for tumor measurements. If any other imaging study that did not include target lesions was performed, such as brain MRI or PET-CT, the radiology report was reviewed to determine the presence of new lesion or unequivocal progression of non-target lesions. Patients with bone metastasis at baseline were typically followed by CT scans, while bone scintigraphy, PET-CT, or MRI were also performed if clinically indicated. These studies were also reviewed to assess response and progression.

In patients who experienced PD while on TKI, radiographic reasons for RECIST-PD were recorded, which included (a) at least 20% and 5 mm increase of the sum of the longest diameters of the target lesions, (b) appearance of new lesion(s), or (c) unequivocal increase of non-target lesions [16].

2.4. Patient characteristics and continuation of EGFR TKI beyond RECIST-PD

Clinical records were reviewed to identify patients who remained on EGFR-TKI beyond RECIST-PD, with or without additional systemic anti-cancer agents. Patients who discontinued EGFR-TKI within a week from RECIST-PD were considered to have discontinued therapy at PD. There was no formal institutional policy on treatment beyond RECIST, and the decision was made according to individual judgment of treating providers. The demographic and clinical characteristics were compared between patients who remained on TKI beyond PD versus those who came off TKI at PD. The date of PD by the retrospectively performed RECIST in this study was compared with the date of PD in the oncology records as previously reported [27], which was based on the prospective RECIST in clinical trials for patients treated in trials. PD was defined clinically in non-trial patients on the basis of sufficient growth of tumor to make a clinician discuss alteration of therapy and/or imaging showing a new site of metastatic disease [36].

2.5. Radiographic assessment at discontinuation of TKI beyond PD

For patients who remained on TKI beyond RECIST-PD, radiographic assessment was performed until they came off TKI or the last follow-up. For those who came off TKI after RECIST-PD, the imaging findings at the time of discontinuation of TKI were categorized as follows; (a) appearance of new lesion(s) and/or increase in size of previously noted new lesion(s), (b) further size increase of target lesions, or (c) increase of non-target lesions, simulating the findings for RECIST-PD [15,16].

2.6. Statistical analysis

Differences in baseline characteristics between groups were compared using Fisher's exact tests for categorical data and Wilcoxon signed-rank tests for continuous data. The Kaplan-Meier method was used to estimate time-to-event distributions and follow-up. All tests conducted were two-sided at the 0.05 significance level, and no corrections for multiple comparisons have been made. Time to progression (TTP) is defined as the time from the date of initiation of therapy to date of RECIST-PD. No patients in the study cohort died

prior to RECIST-PD, but patients not experiencing disease progression were censored at the last follow-up.

3. Results

3.1. Patient characteristics and continuation of EGFR TKI beyond RECIST-PD

Of 70 eligible patients, 56 patients met the criteria for RECIST-PD at the time of the closure date of June 2011. Among 56 patients who progressed by RECIST1.1, 46 (82%) were female, the median age was 63 (range: 35–79), 28 (50%) were never-smokers, 32 (57%) had distant metastasis, 32 (57%) had exon 19 deletion, and 50 (89%) received erlotinib (Table 1). 49 patients (88%) continued EGFR-TKI therapy beyond RECIST-PD for at least 2 months, and 7 patients (12%) discontinued TKI at the time of RECIST-PD.

Patients who discontinued therapy at PD were significantly younger (median 48 years, range: 35–65) than those that continued TKI beyond PD (median 64 years, range: 38–79) ($p = 0.003$). Otherwise, there were no significant imbalances between two groups in terms of demographic and disease characteristics. Among these 7 patients who discontinued TKI at the time of RECIST-PD, 4 patients subsequently received platinum-based chemotherapy, 2 patients were enrolled to a trial of HKI-272 (an irreversible EGFR/HER/ErbbB inhibitor), and one patient was enrolled into a high-dose gefitinib protocol for progressing leptomeningeal disease.

Median TTP by retrospective RECIST1.1 was 10.8 months [95% CI: 9.6–12.9] in 49 patients who continued TKI versus 9.2 months [95% CI: 4.8–not reached] in 7 patients who discontinued TKI at PD. In 49 patients who continued TKI beyond progression, the median time from RECIST-PD to termination of TKI treatment was 10.1 months [95% CI: 7–12.3 months] with a range of 2.2–64.2 months.

Fifteen of 49 (31%) patients who continued TKI received additional systemic anti-cancer therapeutic agents while on TKI, while none of 7 patients who discontinued TKI at PD received additional agents while on TKI ($p = 0.17$). Among the 15 patients treated with additional agents while on TKI, 14 patients received additional agents after RECIST-PD; the additional regimen included carboplatin and pemetrexed ($n = 4$), pemetrexed ($n = 4$), XL765, a PI3K/mTOR dual kinase inhibitor, ($n = 4$), carboplatin and paclitaxel ($n = 1$), and carboplatin, pemetrexed, and bevacizumab ($n = 1$). One patient received carboplatin and pemetrexed while on erlotinib before PD by the retrospectively performed RECIST, when 17% size increase was noted.

Among 56 patients experiencing RECIST-PD, 51 patients also progressed by the clinical records, with the median delay of the retrospectively assessed RECIST-PD from the clinical PD of 1.8 months. Five patients were not considered to have progressed by the clinical record.

3.2. Radiographic assessment of RECIST-PD

Table 2 summarizes the imaging findings at the time of RECIST-PD. Among 32 patients who progressed by the increase of target lesions, 31 patients (97%) remained on EGFR-TKI beyond PD. 13 (81%) of 16 patients who progressed with new lesions patients continued EGFR-TKI therapy beyond PD. Two patients with unequivocal progression of non-target lesions discontinued EGFR-TKI at PD. Six patients had both increase of target lesions and new lesions at PD, of which 5 (83%) remained on TKI.

Three patients progressed with new brain lesions; 2 patients continued TKI after a short period of holding TKI to complete radiation therapy. One patient with new leptomeningeal disease discontinued erlotinib at PD and subsequently enrolled in high-dose gefitinib trial.

3.3. Radiographic assessment at termination of EGFR-TKI beyond RECIST-PD

Among 49 patients who continued EGFR-TKI therapy beyond RECIST-PD, the therapy was terminated in 34 patients by the closure date. The median follow-up time was 26.6 months for the 49 patients after RECIST-PD. 11 out of 34 (32%) patients were enrolled in to another trial when they came off TKI. Of 34 patients, 31 patients had imaging studies within 8 weeks before TKI discontinuation. The imaging findings at the termination of EGFR-TKI beyond RECIST-PD in these 31 patients were analyzed (Table 3). All 31 patients had at least one finding indicative of further increase of tumor burden since RECIST-PD. 13 patients (42%) had more than one finding indicative of increased tumor burden when they came off TKI. The combination of new lesions (appearance and/or further increase of previously noted new lesions) and further size increase of target lesions was most common, seen in 35% (11/31) of the patients, followed by appearance/increase of new lesions alone (32%, 10/31).

4. Discussion

The present study of 70 advanced NSCLC patients with sensitizing *EGFR* mutations treated with first-line erlotinib or gefitinib demonstrated that 88% of the patients who progressed by RECIST1.1 continued EGFR-TKI beyond RECIST-PD. While it is known that oncologists tend to continue EGFR-TKI therapy after *EGFR*-mutant patients meet the criteria for RECIST-PD, the frequency of this practice and radiographic patterns of RECIST-PD in a cohort of NSCLC patients with sensitizing *EGFR* mutations treated with first-line EGFR-TKI have not yet been reported. The high percentage of patients who remained on EGFR-TKI beyond RECIST-PD (88%) in the present study confirmed the clinically recognized tendency of continuing EGFR-TKI in *EGFR*-mutant NSCLC patients after they meet criteria for RECIST-PD. The results also indicate that RECIST-PD alone is not a determining factor to terminate EGFR-TKI in these patients in the current academic thoracic oncology practice.

The continuation of therapy beyond RECIST-PD has been performed in other tumors including GIST treated with imatinib, HER2-amplified breast cancer treated with trastuzumab, and melanoma treated with ipilimumab [17–20,25,26]. The clinical and radiographic observations of these tumors lead to the development of additional response criteria which complements RECIST. The Choi criteria for GIST incorporates tumor density in addition to size, and the immune-related response criteria for melanoma include three additional response patterns that are not captured by RECIST [17–19,37–39]. Our results indicate that a modification of the RECIST criteria may also be useful in *EGFR*-mutant NSCLC patients treated with EGFR-TKIs to establish additional criteria which may better guide therapeutic decision making. Future research assessing volumetric change with the passage of time is ongoing to help define criteria to aid in these clinical decisions.

Seven patients who discontinued TKI at PD was significantly younger compared to 49 patients who continued TKI beyond PD; however, the reason remains unclear. No other significant difference was observed in patient characteristics between 2 groups. TTP from the initiation of TKI therapy was similar in 2 groups. In 49 continuing patients, the median time on TKI after RECIST-PD was 10.1 months. When compared to the retrospective RECIST-PD, the clinically-recorded PD tends to be later, with the median lag of 1.8 months. These findings were similar to the previous report in renal cell carcinoma (RCC), in which the median lag was 2.9 months [40]. It should be noted that the use of the retrospective RECIST-PD in the present study may have resulted in slightly longer time on TKI beyond

PD compared to that when the clinical PD was used. In the present study, we used the retrospectively assessed RECIST-PD by a single radiologist strictly following the RECIST guideline, which is free from interobserver variability. In addition, the date of progression in the clinical record may be influenced by whether or not patients came off therapy, because the conventional practice is to discontinue therapy when patients meet the criteria for progression.

RECIST is widely accepted as a standard method to assess response and measure time-to-progression. Most oncology trials include RECIST-PD as one of the endpoints [16,19]. Although most trials interpret “RECIST-PD” as a uniform phenomenon, in actuality, RECIST-progression consists of heterogeneous radiographic manifestations reflecting heterogeneous biological phenomena. Radiographic assessment at RECIST-PD was performed in our study to further investigate the heterogeneity of “RECIST-PD”, assess therapeutic implications of each radiographic pattern of progression, and obtain insight for additional criteria for progression. Further investigation is warranted to radiographically define clinically-significant PD, as has been done with immune-related response criteria that incorporates the concept of “clinically-insignificant PD” to continue therapy beyond PD in melanoma patients treated with immunotherapy [17]. A similar concept has been applied in a phase I trial of crizotinib for NSCLC patients with ALK rearrangements, in which patients with RECIST-PD may remain on crizotinib if they are judged by the investigators to still be receiving clinical benefit, representing another clinical scenario requiring new criteria in genomically-defined patients [19,24]. In *EGFR*-mutant NSCLC patients treated with erlotinib, ASPIRATION study, an Asian, multicenter, phase II trial (NCT01310036) which allows continuation of erlotinib beyond RECIST-PD at investigator’s discretion, is ongoing [41]. In the study, examples of scenarios where erlotinib may be continued beyond PD include slow PD (>6 months of PR/SD), asymptomatic minimal PD, or new brain metastasis controlled locally. On the other hand, erlotinib should not be continued in patients with symptomatic extracranial PD, rapid PD and/or worsening of performance status, or life-threatening complications [41]. Detailed radiographic analyses of the results from such studies, focusing on radiographic manifestations of progression and rate of tumor progression, will help to establish more appropriate criteria for PD than RECIST in TKI-treated NSCLC patients harboring *EGFR*-mutations.

At termination of therapy, 67% of patients demonstrated an increase in tumor burden by appearance/increase of new lesions. It may be reasonable to incorporate the size and growth of new lesions in response assessment to reflect entire tumor burden, as in immune-related response criteria for melanoma treated with immunotherapy [17]. The appearance of a small lung nodule in the presence of maintained response in the dominant lesion(s) may not immediately indicate the need for therapeutic change [22], however, the growth of the nodule on follow-up scans is an important factor for treatment decisions. Further study of radiographic indicators of progression, such as the overall rate of change of tumor burden, may help to better guide therapeutic decisions.

The limitations of the present study include retrospective nature and patients treated in a single institution. Not all information of the response assessment by retrospective RECIST1.1 was available for oncologists at the time of their decision making. However, response assessment performed by a single board-certified radiologist has advantages in being objective and free from inter-observer variability, and defines progression independent from therapeutic decisions. Radiographic assessment at RECIST-PD and at therapy termination was made possible by the retrospective review of all the scans throughout *EGFR*-TKI therapy. We designed the study this way since one of our purposes was to obtain clues for additional radiographic criteria for discontinuation of *EGFR*-TKI in *EGFR*-mutant NSCLC patients.

In conclusion, our investigation of 70 NSCLC patients with *EGFR* mutations demonstrated that 88% of *EGFR*-mutant NSCLC patients treated with first-line TKI continued TKI therapy beyond RECIST-PD. It is clear that RECIST progression is not the single determining factor for terminating TKI in *EGFR*-mutant NSCLC patients. Although retrospective, the results of the present study indicate the need for additional criteria beyond RECIST, which is specifically designed for *EGFR*-mutant NSCLC patients treated with *EGFR*-TKI to better guide therapeutic decision making.

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Table 1

Demographics and disease characteristics by continuation of EGFR TKI at RECIST PD.

Characteristics	Continued TKI (n = 49)	Discontinued TKI (n = 7)	Total (n = 56)
Sex			
Female	41 (84)	5 (71)	46 (82)
Male	8 (16)	2 (29)	10 (18)
Age			
Mean (SD)	63.0 (11.1)	48.0 (9.0)	61.1 (11.9)
Median (Q1,Q3)	64 (54,73)	48 (44,50)	63 (51,71)
[Range]	[38–79]	[35–65]	[35–79]
Race			
White	44 (90)	7 (100)	51 (91)
Asian	3 (6)	0 (0)	3 (5)
Black	2 (4)	0 (0)	2 (4)
Smoking status			
Never	24 (49)	4 (57)	28 (50)
Former	24 (49)	3 (43)	27 (48)
Current	1 (2)	0 (0)	1 (2)
Histology			
Adenocarcinoma	47 (96)	5 (71)	52 (93)
NSCLC NOS ^a	2 (4)	2 (29)	4 (7)
ECOG Performance status ^b			
0	21 (43)	3 (43)	24 (43)
1	27 (55)	3 (43)	30 (54)
2	1 (2)	1 (14)	2 (4)
Distant metastasis	26 (53)	6 (86)	32 (57)
TKI			
Erlotinib	45 (92)	5 (71)	50 (89)
Gefitinib	4 (8)	2 (29)	6 (11)
EGFR mutation			
Exon 19 del	28 (57)	4 (57)	32 (57)
Exon 19 del and L861Q	1 (2)	0 (0)	1 (2)
L858R	15 (31)	3 (43)	18 (32)
L861Q	1 (2)	0 (0)	1 (2)
L861Q and G719	1 (2)	0 (0)	1 (2)
G719	3 (6)	0 (0)	3 (5)
T790M ^c	1 (2)	1 (14)	2 (4)
Other EGFR mutation	9 (18)	0 (0)	9 (16)

The values in parenthesis represent the percentage unless otherwise specified.

^aNSCLC NOS, Non-small-cell lung cancer not otherwise specified.^bECOG, Eastern Cooperative Oncology Group.

^cThe patients had been exposed to EGFR-TKI before tissue sampling, which demonstrated both T790M mutation and a sensitizing mutation of *EGFR*.

Table 2

Imaging findings at RECIST progression.

Reason for PD by RECIST 1.1	20% and 5 mm size increase	New lesion	Unequivocal progression of non-target lesions	More than one findings
Continued therapy after PD	31	13	0	5 ^a
Discontinued therapy at PD	1	3	2	1 ^a
	32	16	2	6
				56

^aAll patients had 20% increase and new lesions.

Table 3

Imaging findings at termination of TKI therapy.

Findings on last imaging	Number of patients
Appearance of new lesion(s) or increase in size of previously noted new lesion(s)	10 ^a
Further size increase of target lesions	4
Increase of non-target lesions	4
Both a and b	11 ^b
Both b and c	2
	31

^a Appearance of new lesion(s) was noted in 5 patients, increase in size of previously noted new lesion(s) was noted in 4 patients, and both appearance and further increase in size of new lesion(s) were noted in one patient.

^b Appearance of new lesion(s) was noted in 2 patients, increase in size of previously noted new lesion(s) was noted in 8 patients, and both appearance and further increase in size of new lesion(s) were noted in one patient.