

# Analysis of the Rate of Non-target Disease Progression in Patients with Stable or Responding Target Disease by the Response Evaluation Criteria in Solid Tumors (RECIST)

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## Background Information

The Response Evaluation Criteria in Solid Tumors (RECIST) suggests progression of non-target disease is rare in patients with stable or responding target disease. We reviewed outcomes by RECIST to determine this rate. Based on our findings, we propose rules to validate the identification of non-target progression.

## Methods

Outcomes of RECIST-based blinded independent central review (BICR) of 962 breast and colon cancer patients were used to identify 514 patients that had a progression event in order to determine the incidence of progressive disease based solely on non-target disease (NT PD). The radiographs of the 55 patients that had NT PD were further reviewed by the authors (KB, RF) to confirm the NT PD was “unequivocal”. To be considered unequivocal, there had to be a definite, substantial increase in the size of one or more metastatic NT lesions that was clearly not related to differences in imaging technique. To confirm the subjective nature of the “unequivocal progression”, the lesion(s) upon which PD was assessed was measured and a 20% increase in the longest diameter (LD) since nadir was required.

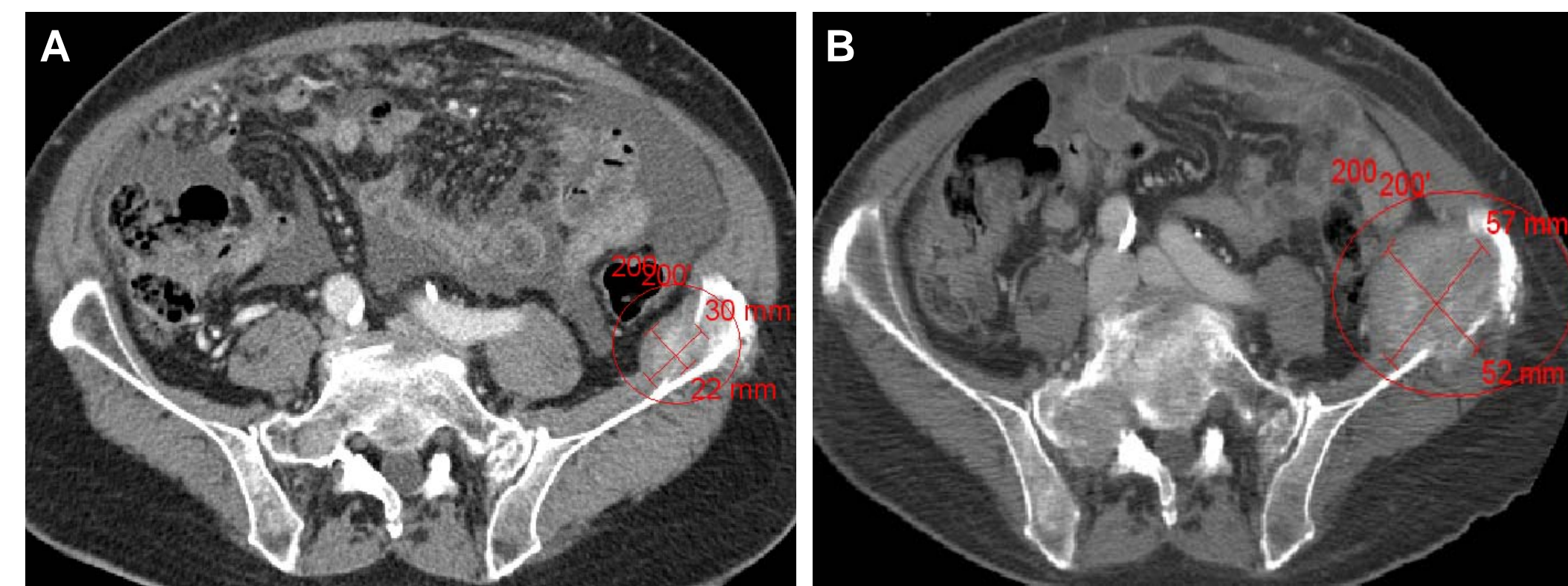
## Results

Of the 514 patients with a progression event, 55 patients (11%) progressed only on the basis of worsening NT disease. In 84% (46 of 55) of patients, two additional rules were applicable, either (1) the target disease was increasing but had not met the threshold for target progression or (2) the increase in NT disease would have resulted in target progression had the NT site(s) of disease been included with the baseline target lesions. Of the remaining 16% (9 of 55) of patients where the 2 rules did not apply:

- One patient had stable target disease but unequivocal PD of NT disease that was truly non-measurable was assessed (based on substantial worsening of lung disease which was poorly defined and infiltrating).

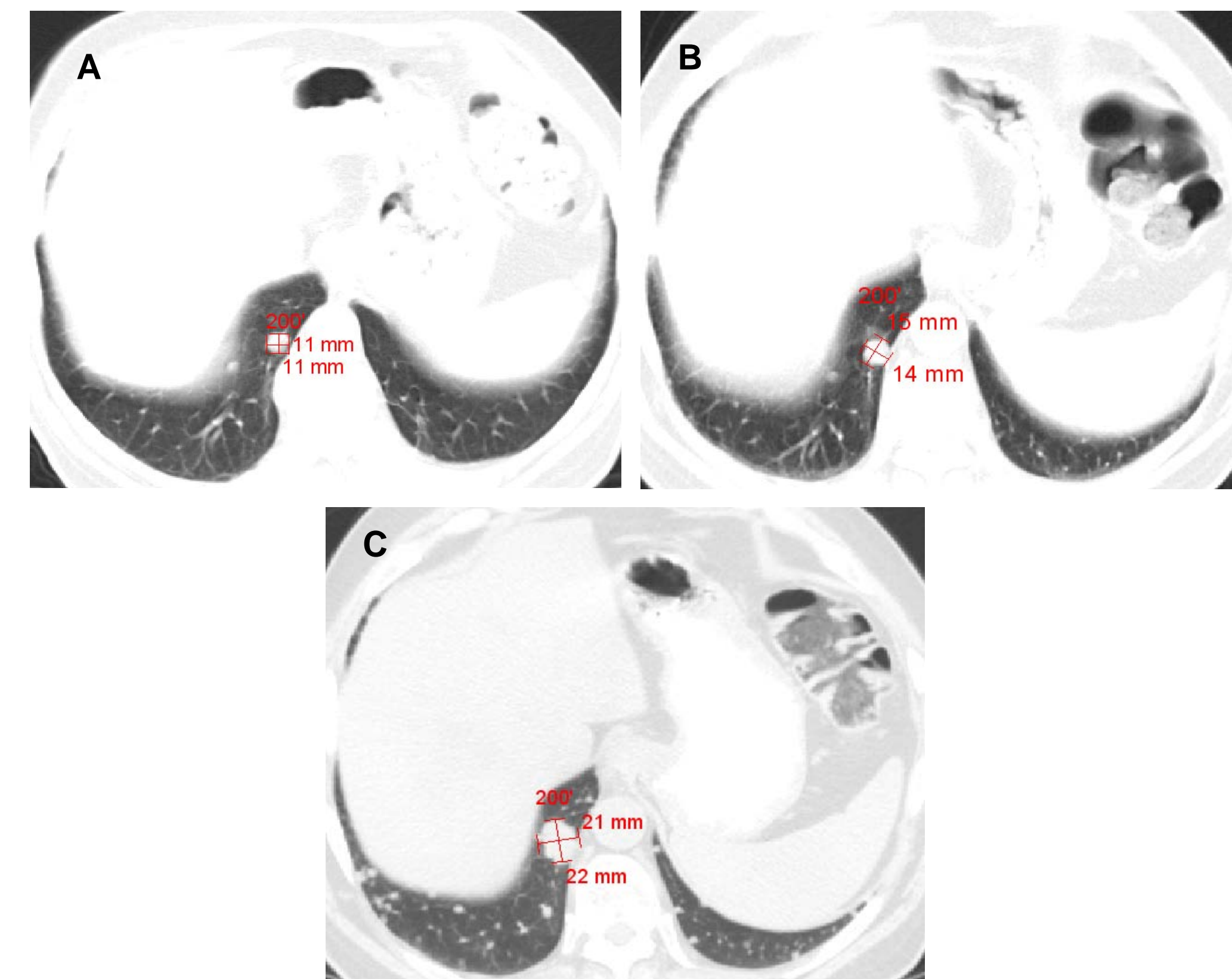
## Representative Examples of Unequivocal Progression of Non-target Disease

Figure 1



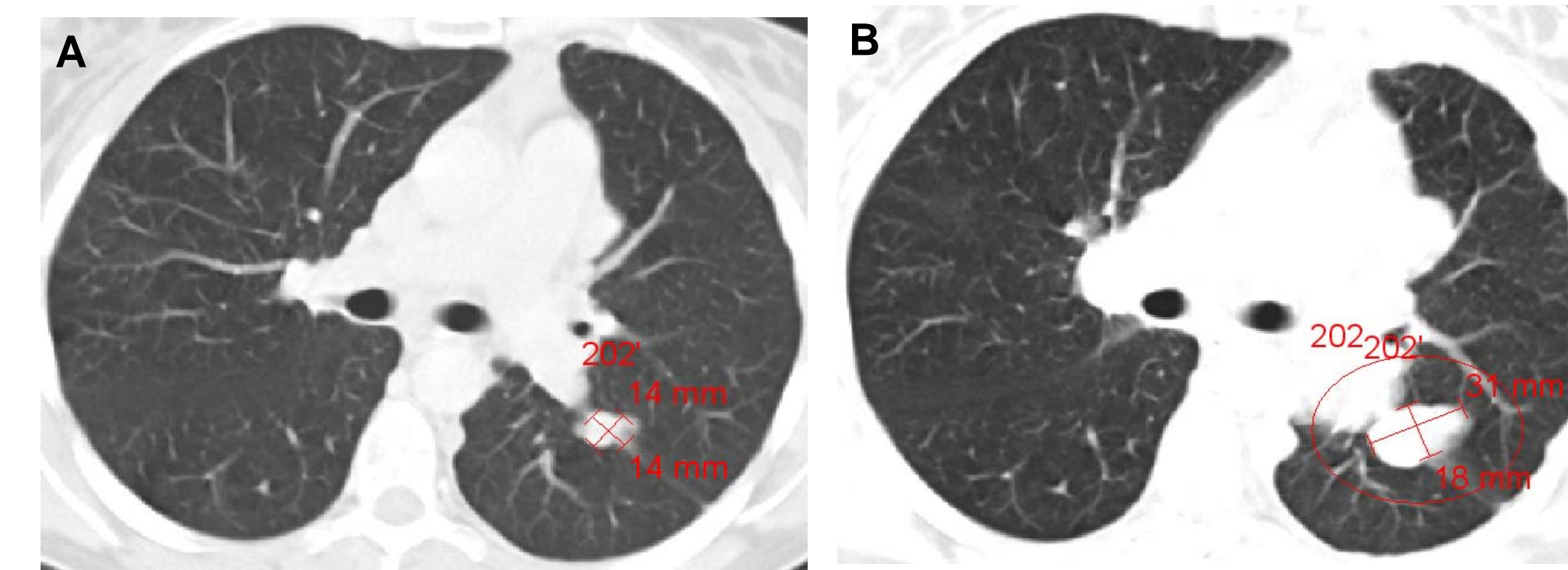
In this example, the patient's target disease has decreased by 10% at Cycle 2, however by Cycle 4, the target disease has started to increase by 5% from the nadir. At Cycle 4, NT PD is assessed on the basis of a bone mass (crosshairs) which increased from 30 mm x 22 mm at baseline (a) to 57 mm x 52 mm at Cycle 4 (b), which is a 90% increase in the LD of the NT site of disease. In this example, NT PD can be reliably assessed at Cycle 4 because the target disease has started to increase from nadir (rule 1).

Figure 2



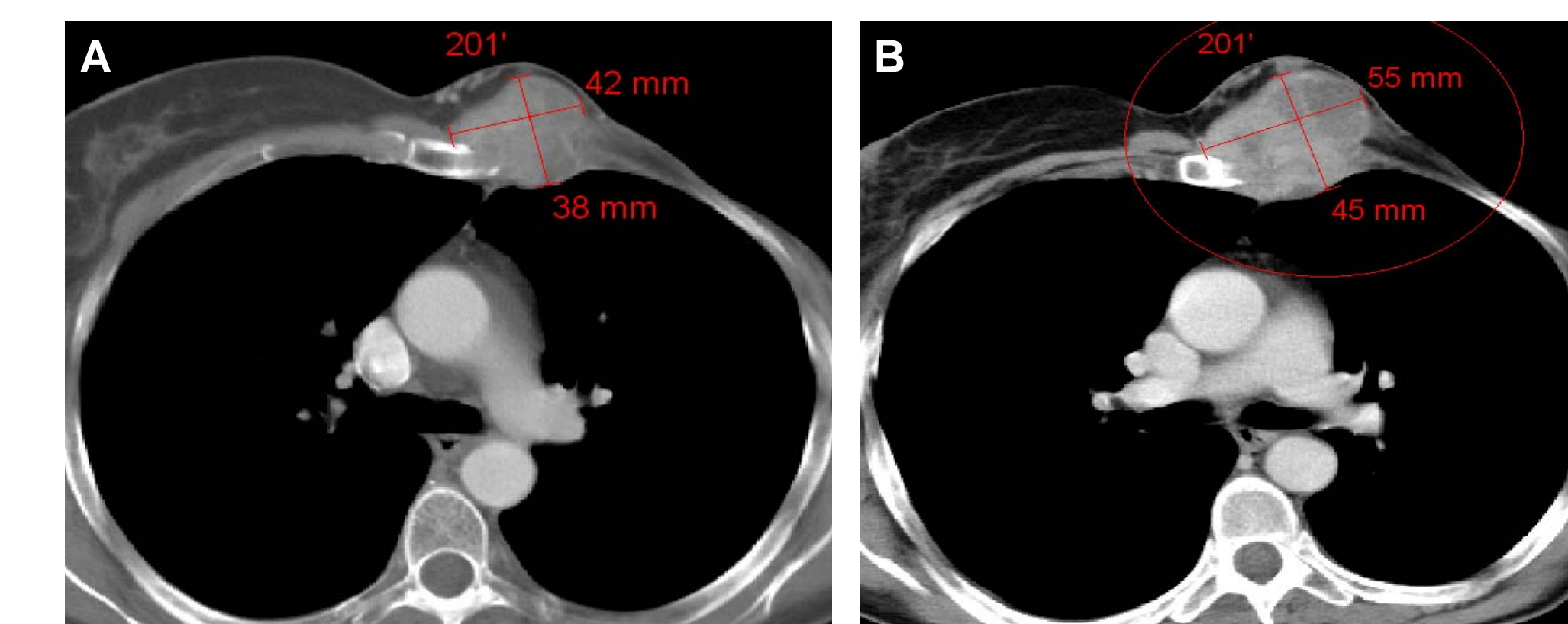
In this example, NT PD may be suspected on the basis of a lung mass which increased from 11 mm x 11 mm at baseline (a) to 15 mm x 14 mm at Cycle 2 (b). While the LD of this NT lesion has increased by 36%, the patient's target disease has decreased by 7% through 2 cycles of therapy and the NT lesion would not have resulted in target PD had the lesion been classified as target at baseline. As such, neither rule 1 nor rule 2 can be applied and the patient remains on-study until Cycle 4 (c) where PD is confirmed based on the NT lesion further increasing to 22 mm x 21 mm in addition to the identification of multiple new lung metastases.

Figure 3



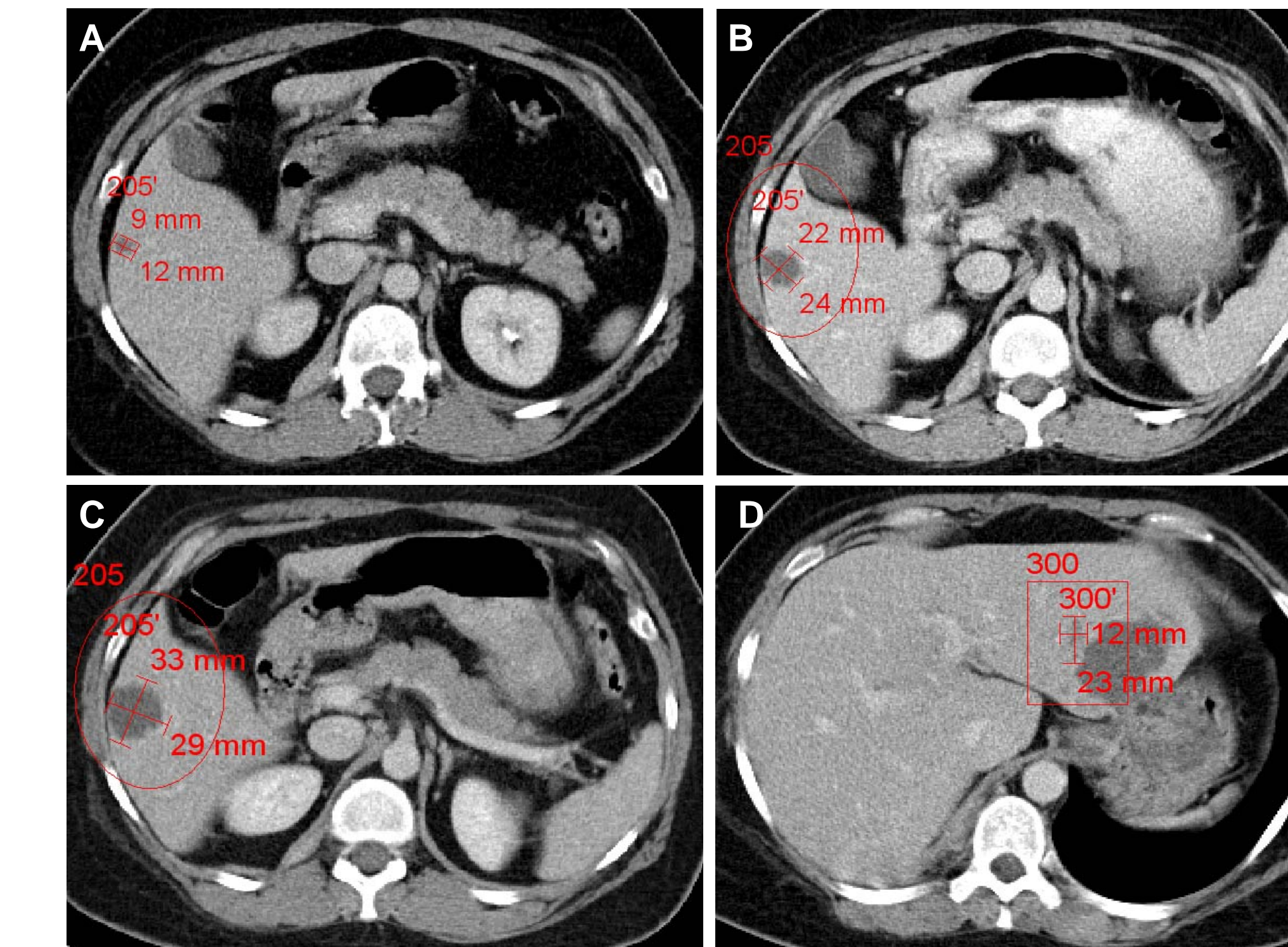
In this example, the patient's target disease has responded through 22 cycles of therapy. The target disease shows a 35% decrease in the sum of the longest diameters (SLD) from baseline but has started to increase from nadir by 17%. There is no new disease identified. At Cycle 22, unequivocal PD of NT disease has been assessed on the basis of a lung lesion which increased from 14 mm x 14 mm at Cycle 18 (a) to 31 mm x 18 mm at Cycle 22 (b). If this lesion had been classified as a target lesion at baseline, the percent change in SLD from nadir would have been +25% resulting in target disease progression. Because the NT site of disease has increased by 121% in LD, the target disease has started to increase from nadir (rule 1), and since the NT lesion would have resulted in target PD had the NT site of disease been included with the baseline target lesions (rule 2), NT PD can be reliably assessed at Cycle 22.

Figure 4



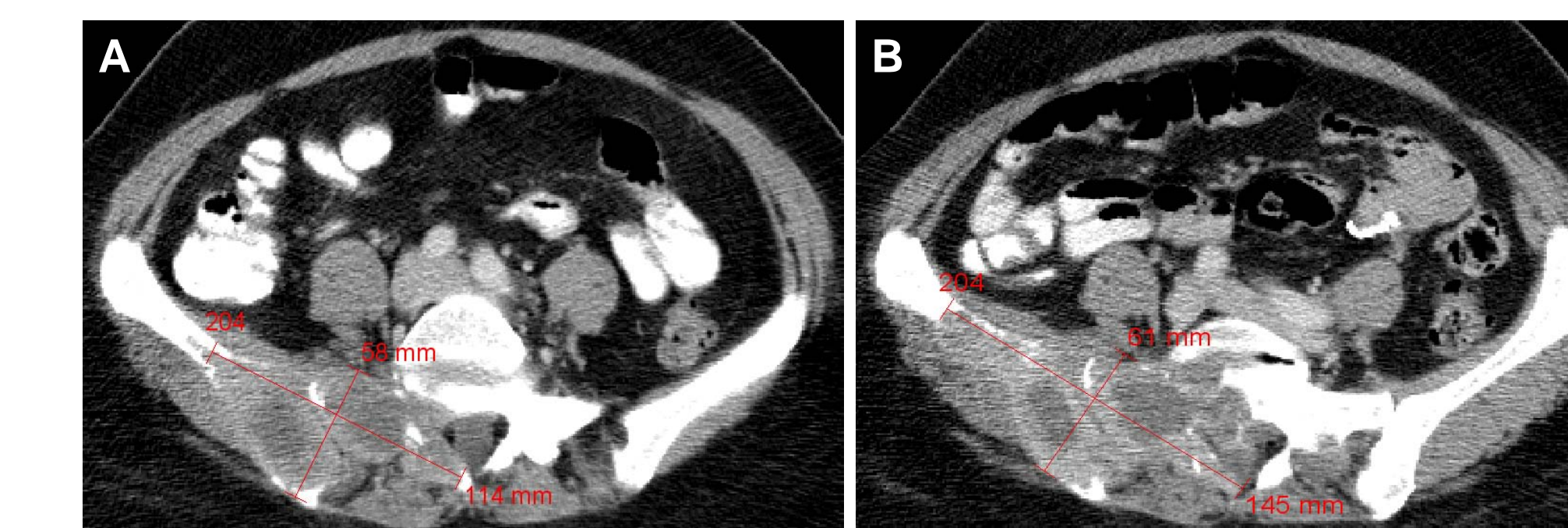
In this example, the patient is considered not to have target disease at baseline as the large chest wall mass which measured 42 mm x 38 mm at baseline (a) is classified as NT disease since it is located in a prior irradiated field that does not show evidence of post-therapy progression. By Cycle 4 (b), the chest wall mass has increased to 55 mm x 45 mm. The NT site of disease has increase by 31% from nadir and there is no measurable disease identified (rule 2 is applicable); therefore NT PD can be reliably assessed at Cycle 4.

Figure 5



In this example, the patient's target disease has decreased by 18% through 6 cycles of therapy. NT PD is suspected on the basis of a liver lesion which increased from 12 mm x 9 mm at Cycle 2 (a) to 24 mm x 22 mm at Cycle 6 (b). While the LD of this NT lesion increased by 100%, the target disease is decreasing and the NT lesion would not have resulted in target PD had the lesion been classified as target at baseline (neither rule 1 nor rule 2 are applicable). As such, this patient remained on-study until Cycle 8 where PD was confirmed based on the NT lesion increasing further to 33 mm x 29 mm (c) in addition to the identification of a new liver lesion (d).

Figure 6



In this example, the patient's target disease has decreased by 28% through 4 cycles of therapy. As compared to baseline (a), there is increasing lytic destruction of the right ilium at Cycle 4 (b) due to substantial enlargement of a soft tissue mass. The soft tissue mass has increased from 114 mm x 58 mm at baseline (a) to 145 mm x 61 mm at Cycle 4 (b). If this site of disease had been classified as a target lesion at baseline, the percent change in SLD from nadir would have been +3% which would not have resulted in target disease progression. The LD of the NT site of disease has increased by 27%. This represents unequivocal progression of NT disease, warranting a change in the patient's therapy (despite the fact that rule 1 and rule 2 are not applicable).

## Results (continued)

- One patient had target disease which was unable to be evaluated at the particular time point when NT PD was assessed (based on a 200% increase in the LD of the NT lesion).
- Three patients had PD confirmed at the next time point.
- Three patients had no subsequent time points received after the assessment of NT PD.
- One patient had one subsequent time point received which did not confirm PD.

## Conclusion

According to the updated RECIST 1.1 guidelines, in order to assess unequivocal PD of NT disease in patients with stable or responding target disease, the worsening of NT disease must have significantly increased the overall tumor burden, such that it merits discontinuation of therapy. Based on our review of subjects in 2 indications, progression on the basis of NT disease is seen in approximately 11% of patients. We suspect this percentage will vary based on the indication. In addition, we propose that PD on the basis of NT disease can be reliably assessed if the following rules apply:

- The increase in non-measurable tumor burden is 20% or greater and the target disease has started to increase from the nadir, or
- The increase in non-measurable tumor burden is 20% or greater and philosophically, if classified as a target lesion at baseline, the NT site of disease would have resulted in progression of the target disease (this includes patients without measurable disease).

If one of the above criteria is not met, it is recommended that treatment continue until progression can be confirmed at the next evaluation. We recognize these rules will not cover all circumstances in which unequivocal progression is assessed as indicated in Figure 6.

