One patient had one subsequent time point

### 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 lesion(s) of disease been included with the baseline target lesions. Of the remaining 16% (8 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 (example shown in Figure 3). This represents unequivocal progression of NT disease, warranting a change in the patient’s therapy.

### 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 subjective unequivocal 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.
- The increase in non-measurable tumor burden is 20% or greater and the target disease has started to increase from the nadir.

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 realized and as indicated in Figure 3.

- 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 point after the assessment of NT PD.
- One patient had one subsequent time point received which did not confirm PD.

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**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)**

Kristin Borraldie MS ¹, Robert Ford MD ¹

¹ RadPharm Imaging Core Lab (Princeton, NJ)