MIS-SELECTION OF NON-MALIGNANT LESIONS AS TARGET LESIONS:
Misclassification of RECIST 1.1 and Early Termination of Promising Drugs?

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BACKGROUND

For tumor response assessment in oncology trials with radiology, the baseline (BL) evaluation is critical as the selection of target lesions (TL) determines the quality of follow-up. The RECIST workgroup [1] provided a method and recommendations for: 1) selecting TL and non-target lesions (NTL) for reporting disease evolution, 2) choosing up to 5 targets, with a maximum of two per organs.
In the practice (Figure 1), the selection of TL is subjective; non-malignant (NM) lesions might be mistaken as TLs.

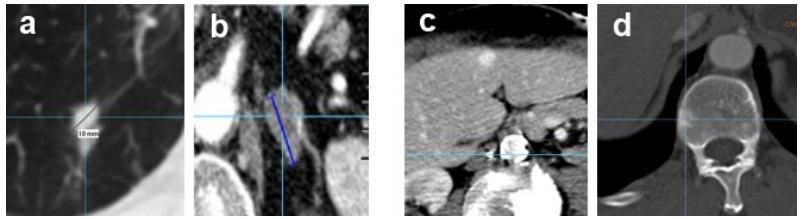

Figure 1: Clinical trial examples of equivocal lesions measurable (a & b) or not measurable (c & d) occurring at the baseline assessment. (a & d were malignant lesions).

OBJECTIVES

- TO ANALYZE THE IMPACT OF NM LESIONS MISTAKEN AS TL AT BL
- TO PROVIDE RECOMMENDATIONS TO MITIGATE RISKS IN CLINICAL TRIALS

METHODS

We assumed that:

1) Per patients, malignant lesions changed homogeneously
2) For all patients, NM lesions remain stable over time.

We simulated:

The change of tumor burden when a proportion of NM lesions were miss-selected as TL or NTL.

As a function of the proportion of NM lesions in the tumor burden, we computed the proportional increase of malignant TL required to detect a progressive disease (PD) or a partial response (PR). We also simulated the proportional increase of malignant TL required to detect a PD after a PR.

We analyzed:

The impact of NM on clinical trials endpoints as Best Overall Response (BOR) and Progression Free Survival (PFS).

RESULTS

IMPACT OF NON-MALIGNANT TARGET LESIONS

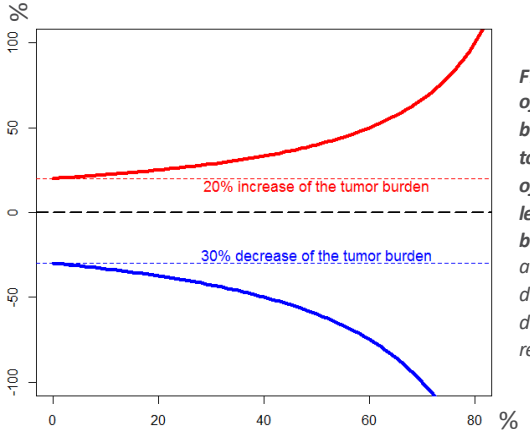

Figure 2: Change of the tumor burden according to the proportion of non-malignant lesions selected at baseline. To detect a progressive disease (Red), to detect a partial response (Blue).

Case study: One NM out of 5 targets is selected at baseline.

This situation comes to select 20% of the tumor burden as NM; the remaining pool of target tumors must increase of **24.7%** or decrease of **37.04%** to respectively detect PD or PR.

While **figure 2** displays the relative RECIST robustness when selecting less than 20% of NM in the tumor burden, even with the smallest NM fraction, no complete response can be expected.

Figure 3: In clinical trial with double read with the response as primary endpoint. Unlike the malignant (Blue) the NM (Red) lesions cannot completely disappear: Adjudications are more likely to happen.

CHANGE FROM BASELINE VS NADIR

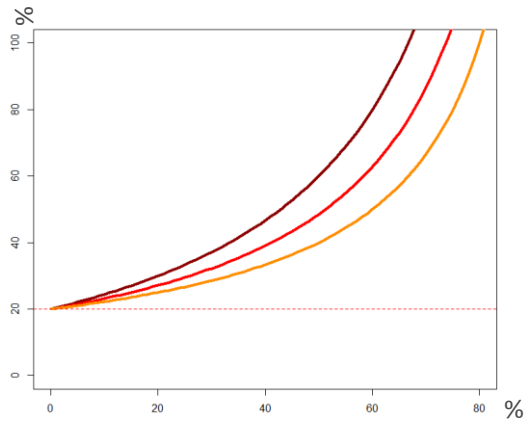

Figure 4: Increase of the tumor burden after a Nadir according to the proportion of non-malignant lesions selected at baseline. Nadir as Baseline (orange), nadir30 (after 30% of PR (Red)), nadir50 (50% of PR (dark red)).

When NMs are selected at baseline, the curves of figure 4 show the increasing bias in detecting progressive disease after a partial response occurred.

According to the example above, if 20% of the tumor burden was NM at baseline, this percentage becomes 26.7% and 29.4% after a first PR of, respectively, 30% and 50%.

For clinical trials: These data show the risk of delayed date of progression when selecting equivocal lesions as TL especially if they are larger than non equivocal targets. Including these lesions in the NTL pool will have no impact on the date of progression.

CONCLUSIONS

- RECIST guidelines are "relatively" robust when NMs are small
- **Recommendation for Phase II trials:** no record of equivocal lesion.
- **Recommendation for Phase III trials is** to record equivocal lesion as NTL to maximize the chance to capture the progression without bias

REFERENCES

[1]. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

Antoine Iannessi, Hubert Beaumont and Yan Liu declare conflict of interest as employees at Median Technologies. Anne-sophie Bertrand declares no conflict of interest.

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