

## How to combine radiographical and serum marker response into one endpoint?

Burkholder I, Edler L, Wunder C

*Abt. Biostatistik, Deutsches Krebsforschungszentrum Heidelberg, Deutschland  
i.burkholder@dkfz.de*

Tumor response is still the most widely used primary endpoint in Phase II trials. In 2000, new guidelines based on unidimensional measurements of tumor lesions are published to assure uniformity in determination of response for patients with different types of cancer [1]. According to these so-called RECIST criteria, all lesions are distinguished as target and as non-target lesions at baseline, assessed in subsequent evaluations and then combined for assessment of overall tumor response of the patient.

Due to the low number of measurable lesions appearing in prostate cancer clinical trials, eligible criteria and outcome measure according to RECIST are not adequate to detect important treatment effects [2]. Instead, prostate-specific antigen (PSA) has been used as an indicator of response and is now the most studied biomarker in prostate cancer. However, the use of PSA as marker of response is complicated by the fact that PSA is also produced in normal tissue and poorly differentiated tumors may produce proportionally less PSA for the level of tumor burden compared with better differentiated tumors. Furthermore, high inter-laboratory variability has been observed. Therefore, PSA can not serve as reliable single surrogate endpoint in clinical trials.

It has been shown that both single endpoints (either tumor response based on measurable lesions or PSA response) serious deficiencies. Hence, a more complex tumor response definition for prostate cancer clinical trials will be proposed combining the information on measurable lesions with time courses of PSA levels under therapy. According to this approach radiographical and serum marker response are in a first step determined separately. Measurable lesions and new lesions under therapy are assessed according to RECIST criteria and PSA response is essentially evaluated following [3]. In a second step, tumor and PSA response are combined into one response outcome whereas tumor response is the dominant outcome. Further, we will focus on the important question how to define the set of evaluable patients for combined response outcome. Data from a recent Phase II trial on a new compound will be used to illustrate both, the intrinsic problems of PSA level determination as well as the proposed approach.

### Literature

- [1] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. JNCI 2000; 92:205-16.
- [2] Scher HI, Morris MJ, Kelly WK, Schwartz LH, Heller G. Prostate cancer clinical trial end points: "RECIST"ing a step backwards. Clin Cancer Res. 2005; 11:5223-32.
- [3] Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, Figg WD, Freidlin B, Halabi S, Hudes G, Hussain M, Kaplan R, Myers C, Oh W, Petrylak DP, Redd E, Roth B, Sartor O, Scher H, Simons J, Sinibaldi V, Small EJ, Smith MR, Trump DL, Vollmer R, Wilding G. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the prostate-specific antigen working group. JCO 1999; 17:3461-7.