Mouse clinical trial (MCT) - A new preclinical study concept using patient-derived xenografts

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Abstract

Patient tumor explants passed in immunocompromised mice (patient-derived xenografts, PDXs) represent the most commonly used system for preclinical efficacy testing of anti-cancer agents. The standard format for efficacy tests typically uses preselected PDXs and group sizes of 6 to 12 PDX-bearing mice to test the efficacy of a treatment relative to a vehicle control group. The strength of this approach is the high reliability of the efficacy data obtained. However, in the face of limitations of available resources this test format restricts the number of PDX models that can be tested. In many studies less than 10 PDX models are used which, in view of the genetic diversity of cancer, is often not satisfactory. The need for in vivo efficacy tests in broader PDX panels is addressed by the emerging mouse clinical trial (MCT) format. Ideally, this format relies on only one mouse per PDX model and treatment arm (referred to as xenopatient), thus enabling the investigation of efficacy in substantially larger panels of PDX models (typically 40 or 50 models which are not preselected) which collectively better mirror interpatient responses heterogeneity observed in the clinic. However, given that all PDX models display some growth heterogeneity, results obtained for individual models are less reliable. To compare results obtained for individual PDXs in the standard and in the MCT format, in the present work, five Sox drugs were tested in colorectal (cetuximab, paclitaxel, irinotecan, S-FU) and non-small cell lung cancer (cisplatin, paclitaxel) PDXs. Dosing and schedules were adapted to clinical standards. Preliminary results for 10 PDX models suggest that in approximately 80% of cases the results obtained in the MCT format (single mouse trial) are in line with the results of the standard efficacy tests. Furthermore, in about 10% of cases the results obtained with both formats were similar. The proportion of false positive or false negative results obtained with tests in the MCT format was below 5%. Our findings indicate that for the drugs tested here the risk of misjudging the sensitivity of a given PDX model based on MCT efficacy data is relatively low. For the identification of biomarkers are particularly dependent on accurate efficacy data, group sizes of three or more mice may be advantageous.

Materials and methods

Colorectal cancer and non-small cell lung cancer PDX models were established by directly implanting excised human tumor samples in male NMRI nude mice, followed by serial passages of tumors until they displayed stable growth patterns. Tumor volumes were determined by caliper measurement. Mice qualified for efficacy tests if they bore a tumor in a specific size range and were assigned to groups based on tumor volume and body weight guided randomisation. For the conventional format, the allowed tumor size range was 50-250 mm3 and mice for one treatment (4 to 12 per group) were randomised on the same day. For the MCT format (a single mouse per arm), the start size differences between individual tumors of one experiment was <100 mm3 and mice were assigned to groups by roll emollement. Drug dosing schedules and routes of administration were adapted to clinical standards. Vehicle controls were included and experiments only evaluated if tumors in vehicle control mice grew as expected. Relative tumor volumes (RTV) on day x were calculated according to the following equation: $\text{RTV} = \frac{V_x}{V_0} = \frac{\text{Tumor size on day } x}{\text{Tumor size on day } 0}$, with $V_x$ being the absolute tumor volume in mm3 on exp. days $x$ and 0, respectively. Tumor responses were evaluated as complete response (CR), partial response (PR), stable disease (SD), and disease progression (PD) according to the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines.

Discussion & Conclusions

Using large panels of PDX models, the MCT format allows the efficient and reliable identification of treatments displaying broad anti-tumor activity (Fig. 1).

Tumor response data obtained with the MCT format and with the conventional format of efficacy tests agree to a high extent (77% overall, Fig. 2). Preliminary analysis suggests that results match particularly well for very active (response: stable disease or stronger) and for inactive treatments (Fig. 2).

The MCT format allows cost-effective and rapid tests of large numbers of anti-cancer agents in large numbers of tumor models (in vivo screen).

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Table 1: Volumes of single tumors can be evaluated using relative tumor volume (RTV) calculation. The evaluation of tumor size differences between start (day 0) and end of treatment (day 21) is expressed as change of relative tumor volume (ΔRTV) and RTV decrease between days 0 and 21 (ΔRTV). The results of two independent experiments with cetuximab in colon and lung cancer PDX models are shown. The results agree to a high extent (77% overall).

Figure 1: Efficacy testing in MCT format facilitates the identification of the most broadly active treatments across tumor model panels. Sensitivity profiles of SoC drugs as evaluated in the MCT format (single mouse per arm) and the conventional format (4 to 12 per group) are shown. Results are sorted by increasing sensitivity towards the respective treatments.

Figure 2: Comparison of efficacy data obtained with MCT and conventional in vivo efficacy test formats.