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EORTC Clinical Trial in Perspective

A multinational, multi-tumour basket study in very rare cancer types: The European Organization for Research and Treatment of Cancer phase II 90101 'CREATE' trial

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Crizotinib;
Targeted therapy;
Clinical trial;
Basket trial;
Methodology of clinical research

Until recently, clinical trials investigating cancer drugs have been conducted separately for different tumour location and histological types because they were the primary known determinant of drug efficacy. With the development of therapies targeting genomic alterations in tumour cells, novel clinical development strategies are necessary. Indeed, the genomic alteration can be uncommon in one particular tumour type and can be shared by several tumour types. Basket trials typically include patients with diverse tumour types sharing one distinguishing feature (i.e. one single or one class of biological alterations). Patients are then assigned to a drug expected to be active for tumours that harbour that alteration [1–3].

Crizotinib is a competitive small-molecule inhibitor of the *ALK*, *MET* and *ROS1* receptor tyrosine kinases. Crizotinib was primarily developed in non–small cell lung cancer (NSCLC) harbouring ALK rearrangements. Even if ALK rearrangements are present in less than 5% of NSCLC, the high incidence of NSCLC made it feasible to demonstrate the efficacy of crizotinib in a randomised phase 3 study of the targeted agent versus standard of care chemotherapy in patients with *ALK*-positive advanced NSCLC [4].

ALK alterations are also present in other, much less common tumour types, including anaplastic large cell lymphoma (ALCL), inflammatory myofibroblastic tumour (IMFT) or other diseases [5]. Alterations of the *MET* pathway have been identified in several tumour types, including papillary renal cell carcinoma type [6], alveolar soft part sarcoma (ASPS) [7], clear cell sarcoma (CCSA) [8] and alveolar rhabdomyosarcoma (ARMS) [9].

This was the rationale for the European Organisation for Research and Treatment of Cancer (EORTC) 90101 'CREATE' trial (NCT01524926), a multinational multi-tumour phase 2 basket clinical trial designed primarily to evaluate the efficacy and safety of crizotinib independently in six parallel cohorts of patients (ALCL, IMFT, papillary renal cell carcinoma type 1 [PRCC1], ASPS, CCSA and ARMS) whose tumours harbour specific alterations in *ALK* and/or *MET* pathways (Fig. 1) [10–14]. Among other secondary objectives, it was planned to also assess treatment effects in patients with the same disease types but without alterations in *ALK* and/or *MET* pathways, given the absence of reliable treatment options in such patients selected for this study. The trial represented an opportunity to explore the feasibility of such a trial design using the international EORTC network. The enrolment of participants was performed in a complex three-step procedure. In the prescreening step, the informed consent of clinically eligible patients for participation in the trial was obtained, and archival tissue blocks were collected. The second step was a central pathology confirmation, mandated before the patient enrolment step (Fig. 1), as the trial involved very uncommon cancers. Central molecular diagnostic tests were performed after patient inclusion in almost real time. Inclusions were not

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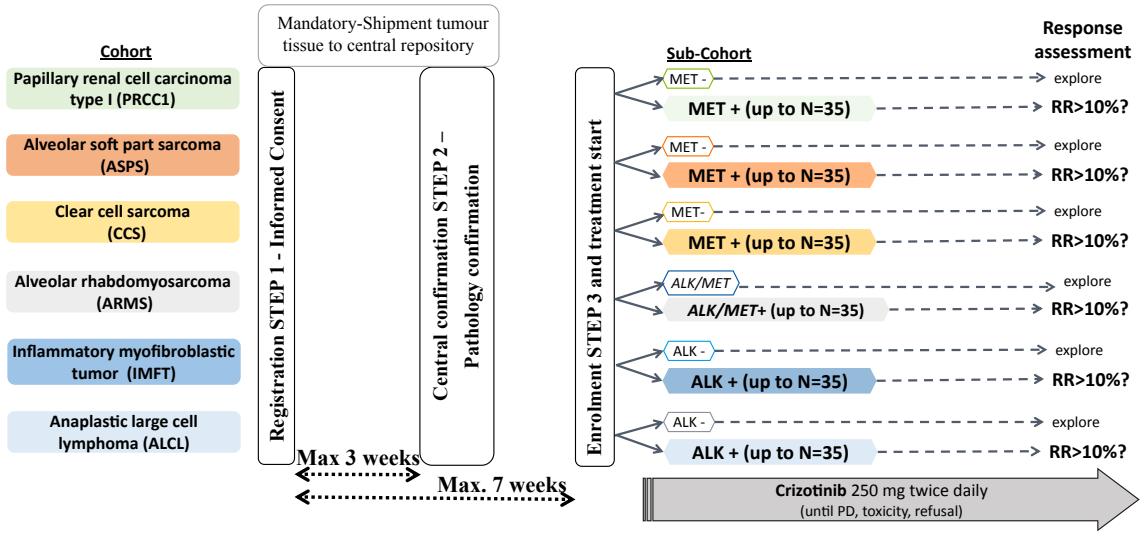

Fig. 1. Multistep design of the EORTC 90101 CREATE trial. PD = progressive disease; RR = response rate.

restricted to patients with the presence of specific ALK and/or MET pathway alteration in tumour tissue.

For each of the 12 subcohorts (6 tumour types with ALK/MET-positive and negative subsets), a maximum of 35 evaluable patients were originally planned on the basis of optimal Simon's two-stage design [15]. The six ALK/*MET*-negative subcohorts served as exploratory groups; no formal statistical comparisons were foreseen among tumour types or within ALK/MET-positive or negative subcohorts. In all cohorts, the primary end-point was overall response rate (ORR) assessed locally. The study sample size was calculated to exclude an ORR $\leq$10% with 90% power under the alternative assumption that 30% ORR can be achieved with crizotinib, in each of the six MET/*ALK*-positive subcohorts (Fig. 1). The criterion of success within each cohort required $\geq$2 objective responses (ORs) in 12 evaluable patients in stage 1 and $\geq$6 ORs in 35 eligible and evaluable patients in stage 2. In case the recruitment of a subcohort was fast enough to avoid the stage I decision rule or if additional evaluable patients are included, final analysis was planned on the whole subcohort of evaluable patients. The decision rule on the minimum number of responders would not apply, and the treatment would be considered effective enough if the lower bound of the confidence interval would be above 10%.

It is interesting to note that the trial faced different challenges in each cohort.

The over-recruitment in two cohorts reflected the rapid accrual, and some delay before it was possible to assess treatment activity. The delay was explained by the chosen primary end-point (ORR, defined as the best response at any time during the actual treatment) and relatively high number of patients who initially achieved stable disease that could theoretically convert to an objective response. Investigators then had to wait until that conversion or until the patients came off treatment to report efficacy data. Such risk of over-recruitment has to be taken into account when designing and monitoring trials with interim decision rules based on ORR. A one-stage design may be more practical in this case. In addition, the low ORR opposed to the high disease control rate as observed in the ASPS and CCSA cohorts pointed out the importance of carefully selecting end-points based on drugs mechanism of action. In retrospect, time-related end-points such as progression-free survival rate at a specific time point might have been interesting to consider for some tumour types in this trial [16].

On the contrary, the aggressiveness of some tumour types led to a high rate of screen failures and non-evaluable patients according to the Response Evaluation Criteria in Solid Tumours criteria because of early clinical progression. The very different profile of aggressiveness of the underlying diseases supports the idea to perform a careful monitoring of the trial and to define early stopping rules.

Among the recently performed basket trials, the inclusion of patients irrespective of the *ALK*/*MET* status is quite unique to this trial [1,2]. The advantage of including *ALK*/*MET*-negative patients was to avoid delay during study entry, to give the laboratory sufficient time for the molecular characterisation, to provide reference data for future research, to study the biological characteristics of these biomarker-negative patients who responded to crizotinib and to enable the assessment of the predictive value of *ALK*/*MET* biomarkers on crizotinib efficacy within the trial. The inclusion of *ALK*/*MET*-negative patients was considered ethical, given the absence of alternative treatment options for the patients included in the trial. This approach was clearly useful for the interpretation of the results in the IMFT cohort, in which the size of the *ALK*+ and *ALK*− cohorts were large enough, and a numerical difference in outcomes between the two

subcohorts was identified. In the PRCC1 cohort, the size of the *MET*-positive subcohort was small, challenging the interpretation of crizotinib efficacy. However, the inclusion of both *MET*-positive and *MET*-negative patients allowed an overall assessment of the efficacy of crizotinib among PRCC1 patients. On the contrary, in the ASPS, CCSA and ARMS cohorts, the proportion of *MET*-negative patients was low, making any interpretation on the value of the biomarker difficult and less relevant. Gathering information regarding biomarker prevalence is then important to adapt future basket trial designs. A strong biological rationale is needed to exclude upfront biomarker-negative patients from clinical trials, and given the complexity of the *MET* signalling pathway, such rationale was not available when the study was initiated. However, early stopping rules for low prevalence of *ALK*/*MET* alterations were defined to stop the inclusion early in one cohort because of insufficient feasibility.

The rate of disagreement between the local and central pathology review was quite high overall. It points out the importance of a real-time pathology review in trials focussing on orphan cancer types. However, such central review requires major coordination efforts to ensure that the reviews are performed in a timeframe compatible with the treatment of cancer patients. The molecular characterisation should also be performed in a timely fashion, as the results are necessary to make the interim trial decisions. Because the molecular characterisation in this trial needed to be tailored to each cancer type, a close collaboration with molecular biologists was required continuously from trial development through interpretation and reporting of results. Given the complexity of the trial, a strong commitment of the lead investigator and of the study team members was mandated to coordinate the important contributions of the several central laboratories in a timely manner.

In conclusion, this complex trial demonstrated that it is possible to perform international multi-tumour phase II trials in very rare cancer types with real-time central pathology review and predefined molecular characterisation. However, an intense collaborative network and a strong logistical setup are mandatory to successfully conduct such trial, as for example, it took 4.5 years and an intense collaborative effort of 24 high-volume institutions in 10 countries to screen 198 patients for the CREATE trial.

Conflict of interest statement

P.S. has received a single institutional travel grant from Pfizer for presentation of results of this trial in the recent past. The other authors have no actual or potential conflict of interest to disclose in relation with this work.

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