ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

Rationale and design of the CRAFT (Continuous ReAssessment with Flexible ExTension in Rare Malignancies) multicenter phase II trial

C. E. Heilig[1,2], P. Horak[1,2], S. Kreutzfeldt[1,2], V. Teleanu[1,2,3], A. Mock[1,2,4], M. Renner[1,5], I. A. Bhatti[1,2,4], B. Hutter[6,7], J. Hüllein[6], M. Fröhlich[6,7], S. Uhrig[6,7], H. Süße[8], L. Heiligenthal[8], S. Ochsenreither[9,10], A. L. Illert[11,12,13], A. Vogel[14], A. Desuki[15,16,17], V. Heinemann[18,19], S. Heidegger[19,20], M. Bitzer[21,22,23], M. Scheytt[24,25], B. Brors[2,7], D. Hübschmann[2,6,26], G. Baretton[27], A. Stenzinger[2,5], K. Steindorf[28], A. Benner[29], D. Jäger[4], C. Heining[30,31,32], H. Glimm[30,31,32], S. Fröhling[1,2] & R. F. Schlenk[2,3,4,8*]

[1]Department of Translational Medical Oncology, National Center for Tumor Diseases (NCT) Heidelberg and German Cancer Research Center (DKFZ), Heidelberg; [2]German Cancer Consortium (DKTK), Heidelberg; [3]Department of Hematology, Oncology and Rheumatology, Heidelberg University Hospital, Heidelberg; [4]Department of Medical Oncology, NCT Heidelberg and Heidelberg University Hospital, Heidelberg; [5]Institute of Pathology, Heidelberg University Hospital, Heidelberg; [6]Computational Oncology Group, Molecular Precision Oncology Program, NCT Heidelberg and DKFZ, Heidelberg; [7]Division of Applied Bioinformatics, DKFZ, Heidelberg; [8]NCT Trial Center, NCT Heidelberg and DKFZ, Heidelberg; [9]Charité Comprehensive Cancer Center, Charité — Universitätsmedizin Berlin, Berlin; [10]DKTK, Berlin; [11]Comprehensive Cancer Center Freiburg, University of Freiburg Medical Center, Faculty of Medicine, University of Freiburg, Freiburg; [12]Department of Internal Medicine I, University of Freiburg Medical Center, Faculty of Medicine, University of Freiburg, Freiburg; [13]DKTK, Freiburg; [14]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover; [15]University Cancer Center Mainz, Johannes Gutenberg University Mainz, Mainz; [16]DKTK, Mainz; [17]Third Medical Department, University Medical Center, Mainz; [18]Department of Medicine III, University Hospital, Ludwig Maximilians University Munich, Munich; [19]DKTK, Munich; [20]Department of Medicine III, School of Medicine, Technical University of Munich, Munich; [21]Center for Personalized Medicine, Eberhard-Karls University, Tübingen; [22]Department of Internal Medicine I, University Hospital, Eberhard-Karls University, Tübingen; [23]DKTK, Tübingen; [24]Comprehensive Cancer Center Mainfranken, University of Würzburg, Würzburg; [25]Department of Internal Medicine II, Würzburg University Medical Center, Würzburg; [26]Heidelberg Institute for Stem Cell Technology and Experimental Medicine, Heidelberg; [27]Institute for Pathology, Faculty of Medicine Carl Gustav Carus, Technical University Dresden, Dresden; [28]Division of Physical Activity, Prevention and Cancer, NCT Heidelberg and DKFZ, Heidelberg; [29]Division of Biostatistics, DKFZ, Heidelberg; [30]Department of Translational Medical Oncology, NCT Dresden and DKFZ, Dresden; [31]Center for Personalized Oncology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden; [32]DKTK, Dresden, Germany

Available online xxx

Background: Approvals of cancer therapeutics are primarily disease entity specific. Current molecular diagnostic approaches frequently identify actionable alterations in rare cancers or rare subtypes of common cancers for which the corresponding treatments are not approved and unavailable within clinical trials due to entity-related eligibility criteria. Access may be negotiated with health insurances. However, approval rates vary, and critical information required for a scientific evaluation of treatment-associated risks and benefits is not systematically collected. Thus clinical trials with optimized patient selection and comprehensive molecular characterization are essential for translating experimental treatments into standard care.

Patients and methods: Continuous ReAssessment with Flexible ExTension in Rare Malignancies (CRAFT) is an open-label phase II trial for adults with pretreated, locally advanced, or metastatic solid tumors. Based on the evaluation by a molecular tumor board, patients are assigned to combinations of six molecularly targeted agents and a programmed death-ligand 1 (PD-L1) antagonist within seven study arms focusing on (i) *BRAF* V600 mutations; (ii) *ERBB2* amplification and/or overexpression, activating *ERBB2* mutations; (iii) *ALK* rearrangements, activating *ALK* mutations; (iv and v) activating *PIK3CA* and *AKT* mutations, other aberrations predicting increased PI3K—AKT pathway activity; (vi) aberrations predicting increased RAF—MEK—ERK pathway activity; (vii) high tumor mutational burden and other alterations predicting sensitivity to PD-L1 inhibition. The primary endpoint is the disease control rate (DCR) at week 16; secondary and exploratory endpoints include the progression-free survival ratio, overall survival, and patient-reported outcomes. Using Simon's optimal two-stage design, 14 patients are accrued for each study arm. If three or fewer patients achieve disease control, the study arm is stopped. Otherwise, 11 additional patients are accrued. If the DCR exceeds 7 of 25 patients, the null hypothesis is rejected for the respective study arm.

Conclusions: CRAFT was activated in October 2021 and will recruit at 10 centers in Germany.

Trial registration numbers: EudraCT: 2019-003192-18; ClinicalTrials.gov: NCT04551521.

Key words: precision oncology, clinical trial in progress, target therapy, immunotherapy

*Correspondence to: Dr Richard F. Schlenk, NCT Trial Center, NCT Heidelberg, Im Neuenheimer Feld 460, 69120 Heidelberg, Germany. Tel: +49-6221-56-6228; Fax: +49-6221-56-5863

E-mail: richard.schlenk@nct-heidelberg.de (R. F. Schlenk).

INTRODUCTION

The cancer genome sequencing efforts of the past decades have led to the discovery of numerous molecularly targeted cancer therapies and associated predictive biomarkers[1-3] and raised hopes that patient outcomes may be improved by comprehensive molecular characterization of individual tumors. The majority of mutations in 'actionable' cancer genes, however, were discovered through systematic studies of patient cohorts from common disease categories defined by conventional, histology-based diagnostic criteria, and previous precision oncology trials accordingly included mainly patients with common cancers.[4-6] By contrast, the value of molecular profiling to guide therapeutic decisions in patients with rare cancers—for which there is no internationally agreed definition—is only beginning to emerge.[7] Furthermore, many common cancers are now viewed as multiple, molecularly distinct diseases of the same organ. For example, *ROS1* alterations in non-small-cell lung cancer,[8,9] *FGFR* alterations in urothelial cancer,[10] and *NRG1* fusions in *KRAS*-wild-type pancreatic adenocarcinoma[11,12] define molecular subsets of relatively common cancers for which targeted therapies are highly effective and thus can be regarded as rare cancers that require unique treatment. Given the abundance of rare cancers in a stricter sense, which account for ∼25% of all human neoplasms, and molecular subgroups of common cancers, optimized patient selection and comprehensive molecular analysis to understand mechanisms of response and resistance to targeted treatment are critical for improvement of patient outcomes.

The Molecularly Aided Stratification for Tumor Eradication Research (MASTER) program of the German Cancer Research Center (DKFZ), the National Center for Tumor Diseases (NCT) Heidelberg/Dresden, and the German Cancer Consortium (DKTK) is a clinical platform for molecular stratification of younger adults with advanced-stage cancers across entities and patients with rare cancers across age groups based on whole-exome or genome and RNA sequencing.[7,13] This approach enables, in a clinical setting, molecular profiling of all tumor types at a scale beyond that in initiatives such as Targeted Agent and Profiling Utilization Registry (TAPUR), Molecular Analysis for Therapy Choice (MATCH), or Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rationale for You (TAPISTRY), ClinicalTrials.gov: NCT04589845.[14,15] In conjunction with clinical data, such broad molecular analyses not only identify novel drug targets in common cancer types as outlined above, but also aid in identifying complex genetic relationships and biomarker profiles (molecular signatures) for prediction of therapy response within (i.e. histology-specific) and across major cancer types. Clinical evaluation of the molecular data generated in DKFZ/NCT/DKTK MASTER by a dedicated cross-institutional molecular tumor board (MTB) allows categorizing patients into distinct molecular intervention baskets, formulation and ranking of evidence-based treatment recommendations, and assignment of patients to genomics-guided clinical trials. At present, >3200 patients have been analyzed in DKFZ/NCT/DKTK MASTER; however, a key area for improvement concerns translating molecular findings into clinical action, with limited access to drugs and an inadequate number of molecularly stratified clinical trials being important obstacles.

Within Continuous ReAssessment with Flexible ExTension in Rare Malignancies, (CRAFT); EudraCT: 2019-003192-18; ClinicalTrials.gov: NCT04551521, we implemented seven different study arms to investigate targeted agents and immunotherapy, including—unlike TAPUR, MATCH, and TAPISTRY—rational combinations, in molecularly defined patient populations. Consistently, all treatment arms are evaluated using the same endpoint, that is, the disease control rate (DCR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1), and a uniform biometrical, adaptive phase II approach. The two key components of CRAFT are (i) the broad molecular characterization of individual tumors linked to clinical outcome data, which will be used to better identify responders and non-responders and understand mechanisms underlying primary and acquired therapy resistance, and (ii) the individual evaluation of each tumor's molecular characteristics by an MTB.

PATIENTS AND METHODS

Trial design and treatment

CRAFT is an open-label, multicenter phase II trial designed to investigate the antitumor activity of seven treatment regimens matching the molecular tumor profiles in adult patients with locally advanced or metastatic solid cancers. Molecular eligibility will be evaluated by the DKFZ/NCT/DKTK MTB based on analyses performed within DKFZ/NCT/DKTK MASTER (whole-exome or genome and RNA sequencing)[7] or in an accredited laboratory (e.g. gene panel sequencing). Eligible patients will be assigned to the following treatment arms (Figure 1): (i) vemurafenib (960 mg twice daily) and cobimetinib (60 mg once daily for 21 days in a 28-day cycle) for 28 days (run-in phase), followed by vemurafenib (720 mg twice daily), cobimetinib (60 mg once daily for 21 days in a 28-day cycle), and atezolizumab (840 mg every 2 weeks); (ii) trastuzumab (8 mg per kilogram of body weight as a loading dose, followed by 6 mg per kilogram every 3 weeks), pertuzumab (840 mg as a loading dose, followed by 420 mg intravenously every 3 weeks), and atezolizumab (1200 mg every 3 weeks); (iii) alectinib (600 mg twice daily); (iv) ipatasertib (400 mg once daily for 21 days in a 28-day cycle) and atezolizumab (1200 mg in the first cycle, followed by 840 mg every 3 weeks); (v) ipatasertib (400 mg once daily for 21 days in a 28-day cycle) and atezolizumab (1200 mg in the first cycle, followed by 840 mg every 3 weeks) combined with docetaxel, paclitaxel, or nab-paclitaxel according to European Medicines Agency (EMA)-approved indication; (vi) cobimetinib (60 mg once daily for 21 days in a 28-day cycle) and atezolizumab (840 mg every 2 weeks); and (vii) atezolizumab (1200 mg every 3 weeks). Benefiting patients may continue study treatment.

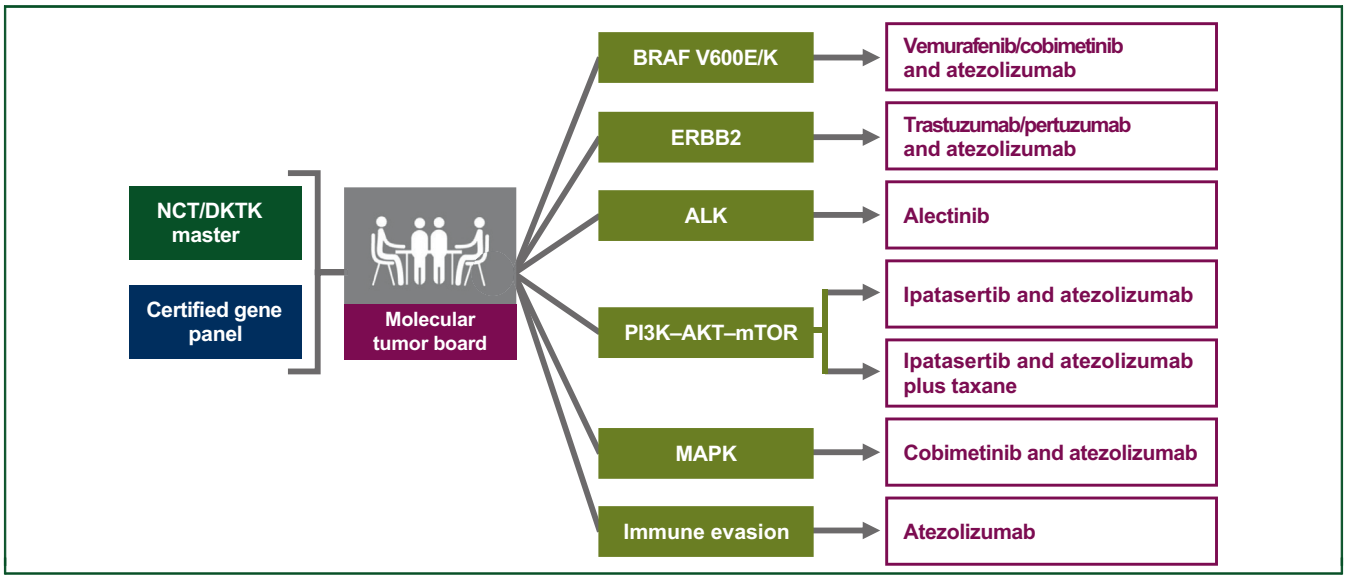

Figure 1. Pathways and study arms of the CRAFT trial.
Molecular eligibility is determined by the DKFZ/NCT/DKTK MTB. Representative examples of eligible molecular alterations include *BRAF* V600E/K mutations (Arm 1/BRAF); *ERBB2* amplification and/or overexpression, activating *ERBB2* mutations (Arm 2/ERBB2); *ALK* rearrangements, activating *ALK* mutations, alternative *ALK* transcription initiation, *RET* rearrangements (Arm 3/ALK); activating *PIK3CA* mutations, activating *AKT* mutations, other alterations predicting increased PI3K—AKT pathway activity, for example, *PTEN* loss, *AKT* amplification (Arms 4 and 5); alterations other than *BRAF* V600E/K predicting increased RAF—MEK—ERK pathway activity, for example, *BRAF* rearrangements, activating *MEK* mutations (Arm 6/MAPK); high tumor mutational burden, alterations predicting sensitivity to PD-L1 inhibition, for example, DNA mismatch repair deficiency, *PD-L1* amplification, *PD-L1* overexpression (Arm 7/Immune evasion).
CRAFT, Continuous ReAssessment with Flexible ExTension in Rare Malignancies; DKFZ, German Cancer Research Center; DKTK, German Cancer Consortium; MASTER, Molecularly Aided Stratification for Tumor Eradication Research; MTB, molecular tumor board; NCT, National Center for Tumor Diseases.

The investigational medicinal products used in the CRAFT study are approved for other indications as single agents (vemurafenib, cobimetinib, atezolizumab, trastuzumab, pertuzumab, and alectinib) and combination therapies (vemurafenib/cobimetinib and trastuzumab/pertuzumab) or are in late clinical development with expected approval in the near future (ipatasertib). Thus, the side-effects of these investigational medicinal products and their management are well known. Furthermore, combinations of targeted agents and the PD-L1 inhibitor atezolizumab are studied in several clinical trials, for example, vemurafenib/cobimetinib and atezolizumab in melanoma (ClinicalTrials.gov: NCT02902029, NCT03625141, NCT02908672);[16] trastuzumab/pertuzumab and atezolizumab in breast cancer (NCT03417544, NCT03125928, NCT03199885); ipatasertib and atezolizumab in breast cancer and across entities (NCT03800836, NCT03673787); and cobimetinib and atezolizumab in breast cancer, rare cancers, various solid tumors, lung cancer, and melanoma (NCT03566485, NCT03108131, NCT03264066, NCT03600701, NCT03273153). Within these ongoing trials, no new safety signals have been reported so far. We therefore expect that the combination therapies applied in CRAFT will be safe and tolerable.

Patient population

Adult patients refractory or intolerant to at least one standard medical cancer treatment with molecular tumor characteristics deemed targetable by the DKFZ/NCT/DKTK MTB are eligible for inclusion in the trial. Examples of molecular abnormalities suitable for the different study arms are given in Figure 1. Key clinical inclusion and general exclusion criteria are listed in Table 1.

Endpoints and assessments

The primary endpoint of the CRAFT trial is the DCR according to RECIST v1.1, including complete response (CR), partial response (PR), and stable disease (SD) as determined by investigator's assessment, at day 110 (±5) of treatment, that is, after five 21-day cycles or four 28-day cycles. Imaging will be performed at baseline, at week 8, and at week 16. Secondary endpoints are the progression-free survival (PFS) ratio and the rate of adverse events and severe adverse events according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Exploratory endpoints include PFS, the modified PFS ratio,[17] overall survival, and tumor response rate, that is, CR and PR, at day 110 (±5) of treatment according to RECIST v1.1. Additional exploratory endpoints include patient-reported outcomes, as assessed by the European Organisation for Research and Treatment of Cancer quality-of-life and fatigue questionnaires (QLQ-C30 and QLQ-FA12, respectively), the Pittsburgh Sleep Quality Index, the Patient Health Questionnaire for Anxiety and Depression, and the Functional Assessment of Cancer Therapy-Cognitive Function questionnaire. Collateral research includes collecting liquid biopsy samples at every treatment cycle for measurement of circulating tumor DNA and correlation with radiologic response and

Table 1. Key eligibility criteria

Key inclusion criteria[a]
• Diagnosis of locally advanced or metastatic, progressive malignancy
• At least one measurable lesion that can be accurately assessed at baseline by computed tomography or magnetic resonance imaging and is suitable for repeated assessment
• Prior administration of at least one standard medical therapy for primary and/or relapsed malignancy according to current guidelines
• Eastern Cooperative Oncology Group Performance Status ≤2
• Age ≥18 years, no upper age limit
• New biopsy before the start of study treatment in patients enrolled based on molecular testing outside DKFZ (German Cancer Research Center)/NCT (National Center for Tumor Diseases)/DKTK (German Cancer Consortium) MASTER (Molecularly Aided Stratification for Tumor Eradication Research) or within DKFZ/NCT/DKTK MASTER carried out >3 months (date of tissue sampling) before study inclusion[b]
Key exclusion criteria[a]
• Hematologic malignancies and primary brain tumors
• Uncontrolled symptomatic brain metastases or spinal cord compression
• Other malignancy within the last 5 years except for nonmelanoma skin cancer; carcinoma *in situ* of the cervix; ductal carcinoma *in situ* of the breast; stage 1, grade 1 endometrial carcinoma
• Persistent toxicity of grade ≥2 according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) caused by previous cancer therapy, excluding alopecia
• Active infection of grade >2 according to CTCAE v5.0
• Pregnancy or breastfeeding
• Inability to take oral medication or gastrointestinal disorders likely to interfere with absorption of the study medication
• Continued use of systemic corticosteroids at doses that exceed the equivalent of 10 mg prednisone daily
• Concurrent antineoplastic therapy

[a] Complete eligibility criteria: www.clinicaltrials.gov/ct2/show/NCT04551521.
[b] Patients may be included based on the analysis of archived tissue not older than 3 months following discussion with the principal investigator and/or the clinical coordinator.

the option of a new tumor biopsy and multilayered molecular analysis in case of progression.

Sample size and statistical analysis

All study arms are based on the same biometrical assumptions with a DCR ≤0.2 under the null hypothesis and ≥0.45 for the alternative hypothesis. The sample size and power calculations are based on Simon's optimal two-stage design[18] for each study arm and all strata in the stratified arm separately. Type I and II errors are each set at 10%. Here, the null hypothesis that the true DCR is less than or equal to $p_0 = 0.20$ will be tested against a one-sided alternative, where the desired level of response is $p_1 = 0.45$. In each study arm, 25 patients evaluable for the primary endpoint are planned. In the first stage, $n_1 = 14$ patients will be accrued. If there are $r_1 = 3$ or fewer patients with at least SD, the respective study arm will be stopped. Otherwise, 11 additional patients will be accrued for a total of $n = 25$ patients, applied in each study arm separately. The entire study's sample size will depend on the sample sizes achieved in the different study arms (minimum, $n = 98$; maximum, $n = 175$). In addition, the study aims to reduce the cumulative hazard of the PFS interval observed within the study (PFS2) compared with the cumulative hazard of the PFS interval experienced with the last systemic treatment before inclusion into the study (PFS1). This will be tested using the paired log-rank test.[19]

RESULTS AND DISCUSSION

CRAFT is a phase II trial evaluating the safety, tolerability, and efficacy of entity-informed, genomics- and transcriptomics-guided treatment in adult patients with locally advanced or metastatic solid cancers. Combining seven different targeted therapy regimens with a multilayered molecular diagnostics platform will allow for the evaluation of predictive markers for response or resistance. In addition, the systematic collection of patient-reported outcomes will generate a unique dataset with the potential for further refinement of the treatments regarding quality-of-life measures. The study was approved by authorities and the central ethics committee in July 2021 and will be conducted at ≥10 sites across Germany. We anticipate that our findings will contribute to establishing broad molecular diagnostics as an integral component of future clinical trials of targeted cancer treatments.

FUNDING

This trial is supported by the NCT Proof-of-Concept Clinical Trial Program and the NCT Molecular Precision Oncology Program. Study drugs are provided free of charge by Roche Pharma AG.

DISCLOSURE

AV reports speaker, consultancy, and advisory role for Amgen, Roche, Bayer, Sanofi, BMS, Lilly, Novartis, EISAI, AstraZeneca, Merck, Incyte, Ipsen, Pierre Fabre, MSD, Sirtex, BTG, Servier, Terumo, and GSK. AD reports consulting for or advisory board membership with Bayer, Roche, BMS, MSD, Takeda, Janssen-Cilag; as well as travel or accommodation expenses from Celgene. GB reports consulting for or advisory board membership with AstraZeneca, BMS, MSD, Novartis, Roche, and Pfizer; research associations with Roche and MSD; and travel funds from BMS, MSD, and Roche. AS reports sitting on the Advisory Board/Speaker's Bureau of Aignostics, Amgen, Astra Zeneca, AGCT, Bayer, BMS, Eli Lilly, Illumina, Incyte, Janssen, MSD, Novartis, Pfizer, Roche, Seattle Genetics, Takeda, and Thermo Fisher; Research funding from Bayer, BMS, Chugai, and Incyte. KS reports honorary, partly with travel expenses, from Adviva, Audi, Pierre Fabre, Preventon, Swiss Group for Clinical Research, and Takeda. DJ reports consulting or advisory role for Roche/Genentech, Bristol Myers Squibb, BioNTech AG,

and Amgen. CH reports consulting for or advisory board membership with Boehringer Ingelheim; honoraria from Roche and Novartis; and research funding from Boehringer Ingelheim. SF: reports consulting for or advisory board membership with Bayer, Illumina, and Roche; honoraria from Amgen, Eli Lilly, PharmaMar, and Roche; research funding from AstraZeneca, Pfizer, PharmaMar, and Roche; travel or accommodation expenses from Amgen, Eli Lilly, Illumina, PharmaMar, and Roche. RFS reports consulting for or advisory board membership with Daiichi Sankyo, Pfizer, Astellas, and Novartis; research funding from PharmaMar, AstraZeneca, Pfizer, Roche, Boehringer Ingelheim, and Daiichi Sankyo; travel, accommodations, and expenses covered by Daiichi Sankyo. All others have declared no conflicts of interest.

ETHICS STATEMENT

The trial was approved by the Ethics Committee of Heidelberg University (protocol number AFmu-070/2021).

REFERENCES

1. International Cancer Genome Consortium, Hudson TJ, Anderson W, et al. International network of cancer genome projects. *Nature*. 2010;464(7291):993-998.
2. Consortium P, Yuan Y, Ju YS, et al. Comprehensive molecular characterization of mitochondrial genomes in human cancers. *Nat Genet*. 2020;52:342-352.
3. Chang K, Creighton CJ, Davis C, et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat Genet*. 2013;45(10):1113-1120.
4. Tourneau CL, Delord J-P, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol*. 2015;16(13):1324-1334.
5. Rodon J, Soria JC, Berger R, et al. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. *Nat Med*. 2019;25(5):751-758.
6. Massard C, Michiels S, Ferte C, et al. High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: results of the MOSCATO 01 Trial. *Cancer Discov*. 2017;7(6):586-595.
7. Horak P, Heining C, Kreutzfeldt S, et al. Comprehensive genomic and transcriptomic analysis for guiding therapeutic decisions in patients with rare cancers. *Cancer Discov*. 2021;11(11):2780-2795.
8. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non—small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971.
9. Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov*. 2017;7(4):400-409.
10. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2019;381(4):338-348.
11. Heining C, Horak P, Uhrig S, et al. NRG1 fusions in KRAS wild-type pancreatic cancer. *Cancer Discov*. 2018;8(9):1087-1095.
12. Laskin J, Liu SV, Tolba K, et al. NRG1 fusion-driven tumors: biology, detection and the therapeutic role of afatinib and other ErbB-targeting agents. *Ann Oncol*. 2020;31(12):1693-1703.
13. Horak P, Klink B, Heining C, et al. Precision oncology based on omics data: the NCT Heidelberg experience. *Int J Cancer*. 2017;141(5):877-886.
14. Mangat PK, Halabi S, Bruinooge SS, et al. Rationale and design of the Targeted Agent and Profiling Utilization Registry study. *JCO Precis Oncol*. 2018;2018(2):1-14.
15. Flaherty KT, Gray RJ, Chen AP, et al. Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). *J Clin Oncol*. 2020;38(33):3883-3894.
16. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF V600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395(10240):1835-1844.
17. Mock A, Heilig CE, Kreutzfeldt S, et al. Community-driven development of a modified progression-free survival ratio for precision oncology. *ESMO Open*. 2019;4(6):e000583.
18. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10(1):1-10.
19. Jung S-H. Rank tests for matched survival data. *Lifetime Data Anal*. 1999;5(1):67-79.