The Drug Rediscovery Protocol (DRUP trial): A Dutch National Study on behalf of the Center for Personalized Cancer Treatment (CPCT) to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile

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Method Article

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Abstract

This is a prospective, non-randomized clinical trial that aims to describe the efficacy and toxicity of commercially available, targeted anticancer drugs* prescribed for treatment of patients with advanced cancer with a potentially actionable variant as revealed by a genomic or protein expression test. The study also aims to simplify patient access to approved targeted therapies that are contributed to the program by collaborating pharmaceutical companies and to perform next generation sequencing on tumor biopsies for biomarker analyses. Eligible patients have an advanced solid tumor, multiple myeloma or non-Hodgkin lymphoma for which standard treatment options are no longer available and acceptable performance status and organ function. A genomic or protein expression test must have been performed on the tumor and the results must identify at least one potentially actionable molecular variant as defined in the protocol. Results from the molecular profiling test will be used to determine an appropriate drug(s) from among those available in the protocol. The choice of drug will be supported by a list of potential profiles, a molecular tumor board, a knowledge library and by study coordinators for review and approval of the match. The protocol-specified treatment will be administered to the patient once any drug-specific eligibility criteria are confirmed and a fresh pre-treatment biopsy is performed for future biomarker studies. All patients who receive treatment with a drug available in the protocol will be followed for standard efficacy outcomes including tumor response, progression-free and overall survival as well as duration of treatment. In addition, treatment related toxicity will be evaluated.

Introduction

Evidence is building that matching targeted agents to tumor characteristics can improve outcomes. Such reports have fueled interest among patients and physicians to use molecular testing for treatment planning when standard treatment options have been exhausted. When oncologists aim to provide such personalized treatment to their patients though, obtaining the drugs can be challenging since off-label prescribing, while legal, is generally not reimbursed by insurance companies. Furthermore, outcomes of off-label treatment in routine clinical practice are not systematically recorded. As a result, the research and clinical communities have limited insight in these outcomes, leading to repetitive use of ineffective treatment for some tumor types, while effective treatment strategies might be missed for others. The latter is especially relevant for 'orphan diseases', that are too rare to conduct formal phase II and III trials. In summary, there is a lack of access to potentially effective therapy on one hand, and a lack of knowledge on broader use of such therapies on the other, altogether leading to sub-optimal use of available resources

Reagents

Equipment

Procedure

Eligibility patients:

Eligible patients have an advanced or metastatic solid tumor, multiple myeloma or B cell non-Hodgkin lymphoma, and have exhausted standard treatment options. A tumor genetic or protein expression test (CPCT or regular diagnostics) must have revealed a potentially actionable variant, for which FDA and / or EMA approved targeted therapy is available, but not for the tumor type in question. In addition, patients are required to be ≥18 years of age, with acceptable organ function and performance status (ECOG ≤2), and to have objectively evaluable disease of which a fresh baseline tumor biopsy can safely be obtained. For every study drug, further drug-specific selection criteria are applied.

Case submission:

Upon case submission, the study team attempted to match each patient to the most appropriate study treatment (Extended Data Figure 1), according to pre-defined matching rules . If multiple variant-drug matches could be made for one patient, the drug with the highest level of evidence was selected, unless there's rationale (such as drug-intolerance) to justify selecting an agent with a lower level of evidence. Levels of evidence were adapted from Meric-Berstam et al.

Study treatment

If a matching study treatment slot is available, to which the patient consents, the patient can be enrolled provided that all drug-specific selection criteria were met. Afterwards a fresh baseline tumor biopsy for biomarker analyses is obtained and study treatment can be initiated.

Follow up:

Study treatment could continue until progressive disease (patients receiving immune system stimulating agents were permitted to continue treatment in case of pseudo-progression), unacceptable treatment-related toxicity, death, pregnancy, consent withdrawal or withdrawal from the study at the discretion of the investigator.

- Safety: all treatment-related CTCAE 4.03 grade ≥3 adverse events are documented.

- Response assessments: response is evaluated every two months (up to every three months for patients who remained on-study for ≥6 months), and classified by local investigators according to the internationally accepted criteria for each tumor type.

Troubleshooting

Time Taken

Timelines after submitting a case for review (by treating physician):

- Report of treatment proposal provided by central study team: ≤7 (or 14) days

- Screen and register patient on study: ≤14 days

- Receive study drugs and start treatment: ≤ 14 days

- Duration treatment: Study treatment could continue until progressive disease (patients receiving immune system stimulating agents were permitted to continue treatment in case of pseudo-progression), unacceptable treatment-related toxicity, death, pregnancy, consent withdrawal or withdrawal from the study at the discretion of the investigator.

- Follow up: patients will be followed up for progression free and overall survival by yearly check of medical records until death or loss to follow up, up to two years after the end of this study.

Anticipated Results

Primary Objectives

• To describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs used for treatment of patients with an advanced solid tumor, multiple myeloma or non-Hodgkin lymphoma that harbours a genomic- or protein expression variant known to be a drug target or to predict sensitivity to a drug.

• To facilitate patient access to commercially available, targeted anti-cancer drugs of potential efficacy for treatment of an advanced solid tumor, multiple myeloma or non-Hodgkin lymphoma that harbours a genomic or protein expression variant known to be a drug target or to predict sensitivity to a drug.

Secondary Objective

• To perform biomarker analyses, including (but not limited to) next generation sequencing on a fresh tumor biopsy specimen

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Supplementary Files

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- DRUPFullProtocolversion9.pdf