Protocol waivers and consequences on treatment safety and efficacy in the Drug Rediscovery Protocol (DRUP)

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BACKGROUND

• Eligibility criteria are an essential component of clinical trial design, but overly restrictive criteria contribute to low accrual and poor generalizability of study results.
• To make trials more inclusive, there has been an increasing interest in broadening eligibility criteria, but how this affects patient safety remains unclear.

In the Drug Rediscovery Protocol (DRUP), protocol deviations waivers are frequently requested, and sporadically granted by the study team, taking into account the balance of potential benefits and risks.

Here we describe the impact of these protocol deviations on patient safety and treatment efficacy.

METHODS

1. DRUP
• A Dutch multicenter, non-randomized, pan-cancer platform trial treating treatment-refractory patients with targeted- and immunotherapies outside their registered indications, based on their tumor molecular profile
• Accrual initiated in 2016 and is ongoing
• 35 targeted agents and immunotherapies available

2. Patients
• Treatment-refractory malignancies, progressive upon last line of therapy with an actionable molecular target and measurable disease
• Started treatment in DRUP between September 2016 and September 2021

3. Groups
• Group 1: patients for whom a protocol waiver was granted to enable compliance with trial in- and exclusion criteria and thereby, trial participation
• Group 2: patients that did not need a protocol waiver to participate in the trial

4. Study endpoints
• Nature of granted waivers
• Safety: all reported serious adverse events (SAEs)
• Number, grade and potential relationship to study treatment
• Efficacy: clinical benefit rate (CBR)
  • Confirmed objective response or stable disease ≥ 16 weeks (RECIST 1.1 / RANO)
  • Evaluable: evaluable according to protocol definition
  • Oral medication: received at least one full treatment cycle (28 days)
  • IV medication: received at least two administrations of treatment

RESULTS

3. Patient Safety

Our data advocate that more inclusive in- and exclusion criteria are feasible without compromising safety and study endpoints in a setting where patients have exhausted all other treatment options.

3.1. Accrual
• 1019 patients were included in the analysis
• 937 patients (92%) needed no waiver to participate
• 82 patients (8%) received a waiver to participate

3.2. Nature of waivers (Figure 1)
• Eligibility criteria
• Out-of-window testing
• Treatment exception
• Progression
• Testing exception

3.3. Patient safety analysis
• Clinical benefit rate
• Treatment efficacy
• For seven SAEs (14%) a granted waiver possibly contributed to the reporting of an SAE

4. Treatment Efficacy

Outcomes were available for 1006 patients

Group 1 (n=82): Clinical benefit rate 40.2% (95% CI 29.6-51.7)
Objective response rate 22.9% (95% CI 13.7-34.4)

Group 2 (n=924): Clinical benefit rate 33.6% (95% CI 30.7-36.6)
Objective response rate 18.3% (95% CI 15.7-21.5)

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3.4. Efficacy for Primary Endpoint

Group 1: 12/82 non-evaluable
Group 2: 165/924 non-evaluable

Most common reason for non-evaluable was early treatment discontinuation due to toxicity or progressive disease

CONCLUSION: safety and clinical benefit were preserved in patients for whom a protocol waiver was granted in DRUP

Figure 1. Nature of granted waivers breakdown

Table 1. Baseline characteristics all patients, stratified according to waiver status

Table 2. Waivers that possibly contributed to reported SAEs

ACKNOWLEDGEMENTS: We would like to thank all our sponsors, acknowledged partners (inc. Medical Oncology, the Center for Personalized Cancer Treatment, all participating hospitals and the patients and their families).

Waiver granted

<table>
<thead>
<tr>
<th>Waiver granting</th>
<th>Reported SAE</th>
<th>Treatment category</th>
<th>Relationship between DRUP and SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Group 2</td>
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</tbody>
</table>

Follow-up for this activity has closed or is in final review. DRUP is sponsored by the Dutch Cancer Society. Stevia for Life and all participating pharmaceutical companies.

Adverse events: We would like to thank all our sponsors, acknowledged partners (inc. Medical Oncology, the Center for Personalized Cancer Treatment, all participating hospitals and the patients and their families).

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