Maximizing treatment opportunities: assessing protocol waivers' impact on safety and outcome in the drug rediscovery protocol

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Maximizing Treatment Opportunities: Assessing Protocol Waivers' Impact on Safety and Outcome in the Drug Rediscovery Protocol

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ABSTRACT

Purpose: Although eligibility criteria are essential in trial design, overly restrictive criteria contribute to low accrual and limited generalizability. To enhance trial inclusivity, there has been growing interest in broadening eligibility criteria, especially for patients with advanced or treatment-refractory disease. Yet, the impact on patient safety remains uncertain. In the Drug Rediscovery Protocol (DRUP), protocol exceptions are frequently requested and occasionally granted. Here we describe the impact of these waivers on treatment safety and efficacy.

Experimental Design: DRUP is a multicenter, nonrandomized clinical basket trial treating patients with therapy-refractory cancer with molecularly targeted and immunotherapies outside their registered indications (NCT02925234). Here, all granted waivers were revised, analyzed in terms of safety and efficacy outcome, and compared without outcomes of included patients who did not receive a waiver.

Results: Between September 1, 2016, and September 1, 2021, protocol waivers were granted for 82 patients (8%) of 1,019 included patients in DRUP. Most waivers (45%) were granted for general- or drug-related eligibility criteria; other categories were out-of-window testing, treatment, and testing exceptions. Serious adverse event rate was similar between patients who received a waiver (pW) and patients who did not (pNW): 39% vs. 41%, respectively ($P = 0.81$). The clinical benefit (either objective response or stable disease ≥ 16 weeks) rate of pW was 40% versus 33% in pNW ($P = 0.43$).

Conclusions: Safety and clinical benefit were preserved in patients for whom a waiver was granted. These data support a more personalized approach in assessing eligibility criteria, especially in trials with widely used and approved drugs accruing patients without other treatment options.

See related commentary by Waqar and Govindan, p. 3655

Introduction

Eligibility criteria are an essential component in clinical trial design. They ensure patient safety by excluding patients who are at greater risk for adverse events (AE) and increase internal validity by assuring a homogeneous patient group that is most likely to respond to a certain therapy. This assures uncompromised detection of efficacy signals and is essential for comparing the studied treatment with other treatments used in similar patient populations. However, too often eligibility criteria are simply duplicated from previous protocols, without strong clinical or scientific justification. For example, patients with renal impairment are frequently excluded from clinical trials, even when pharmacodynamics of the trial drugs are not thought to be influenced by renal impairment (1).

With the rise of a multitude of new and promising targeted agents being investigated in molecularly driven oncology trials, restrictive eligibility criteria have been increasing even more (2, 3). Most of these novel agents have different pharmacodynamic properties compared with conventional cytotoxic agents, leading to the addition of new eligibility criteria. However, a critical appraisal of the "old" criteria is generally not done, even when some of the conventional eligibility criteria might be redundant in these trials (4, 5). Including more eligibility criteria than necessary will complicate trial enrollment and therefore slow down accrual. Moreover, restrictive eligibility criteria may compromise study generalizability and can lead to overestimation of the observed efficacy. This is illustrated by the study of Mitchell and colleagues that evaluated whether patients treated for metastatic renal cancer in routine clinical practice would be eligible for the corresponding clinical trial. Notably, the study demonstrated that almost 40% of patients in the cohort-population study did not meet the eligibility criteria for the clinical trial of the treatment they received (6). Similar results were observed by Lin and colleagues, who evaluated the representiveness of the AURA3 trial for non–small cell lung cancer (NSCLC) treated with osimertinib in a real-world setting. Of the included patients, 62% were ineligible for the corresponding phase III trial (7).

In the past few years, several initiatives have attempted to make trials more inclusive. In 2020, the FDA advocated more diversity of clinical trial populations and for broadening the eligibility criteria (8). Recently, the American Society of Clinical Oncology and Friends of Cancer Research proposed broadening of eligibility criteria for laboratory requirements, prior therapies, concomitant medications, and

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Translational Relevance

Overly restrictive criteria often lead to low accrual and limited generalizability of results, hindering progress in therapeutic research. This research, conducted within the Drug Rediscovery Protocol, explores the impact of protocol waivers on treatment safety and efficacy. Remarkably, the safety and clinical benefit were preserved in patients granted waivers, challenging conventional concerns. This suggests a potential for a more personalized approach in assessing eligibility criteria, especially in trials involving widely used and approved drugs for patients with limited treatment options. Furthermore, these findings advocate for a broader and more inclusive design when establishing novel trials, paving the way for a more effective and tailored application of cancer therapies in patients with advanced or refractory disease.

performance status, provided that this would not impact safety (9). At the same time, regulatory agencies emphasize study protocol adherence and disapprove prospectively approved protocol deviations/protocol waivers. However, literature describing the impact of protocol waivers on trial safety or efficacy is currently still missing.

In the Drug Rediscovery Protocol (DRUP), a national ongoing pancancer multidrug basket/umbrella trial, patients are treated off-label with registered drugs based on their tumor molecular profile (10). The innovative design allows for an unlimited number of cohorts, testing multiple hypotheses in parallel. DRUP facilitates access to potentially effective drugs for patients with therapy-refractory cancer with a specific tumor molecular profile, while systematically collecting clinical data on efficacy and safety of these drugs when used off-label. A pooled analysis of the first 500 included patients showed a clinical benefit [CB; either an objective response (OR), or stable disease (SD) ≥ 16 weeks] rate of 33% (11).

In DRUP, personalized treatment within the context of a defined protocol is being pursued. However, requests for protocol exceptions are regularly submitted to the central study team, motivated by therapeutic intent and expected benefit for the patient. In some cases, the study team decided to grant a waiver after thoughtful deliberation, balancing potential benefit against potential risks.

The purpose of the current analysis is to evaluate the effect of granted protocol waivers on safety and efficacy outcomes of the patients for whom they were granted. These protocol waivers are defined as a prospective decision by the study team to allow enrollment of a patient that does not meet all eligibility criteria, or to prospectively allow protocol deviations concerning specific study procedures. We analyzed all waivers in the DRUP trial granted between September 2016 and September 2021, and investigated whether these protocol waivers affected safety or efficacy outcomes.

Materials and Methods

Study design and population

The dataset used for the current analysis included 82 patients (out of 1,019 enrolled patients in the period under consideration) for whom a waiver was granted for enrollment or during study treatment in the DRUP trial (NCT02925234; ref. 10). DRUP is an ongoing Dutch national, nonrandomized, prospective, pan-cancer, and multidrug basket/umbrella trial, in which patients are treated with approved targeted or immunotherapies, matched to their tumor molecular profile, but outside their registered indications. Patients are enrolled at 35 participating hospitals throughout the Netherlands. The trial was approved by the Medical Ethical Committee of the Netherlands Cancer Institute (Amsterdam, the Netherlands) and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki's ethical principles for medical research. Written informed consent was obtained from all included patients.

Eligible patients for DRUP had a treatment refractory, advanced malignancy, with tumor molecular diagnostics demonstrating a pathogenic alteration for which study treatment was available, and were required to be ≥ 18 years of age. Patients had measurable disease according to the RECIST version 1.1 (RECIST v1.1; ref. 12), Response Assessment in Neuro-Oncology (RANO) criteria (13), and an Eastern Cooperative Oncology Group performance status of ≤ 2 (14). Furthermore, patients were required to have adequate bone marrow and organ function, and to have progressive metastatic disease with lesions safely accessible to biopsy (exceptions were made for primary brain tumors). For every available study drug, further drug-specific eligibility criteria applied (10).

In the DRUP trial, patients were matched to one of the available study drugs based on their tumor molecular profile, and enrolled in parallel cohorts. Cohorts were defined by tumor type, molecular profile, and study drug. Drug selection was performed by the central study team, where needed after consultation of the DRUP central molecular tumor board. The principle investigators were blinded for (individual) patient outcomes until cohorts achieved complete accrual. Safety and accrual data were reviewed regularly by the independent data monitoring committee, who monitored and advised on the conduct of the trial.

Protocol waivers

Requests for protocol waivers were initially reviewed by the team of study physicians. In specific requests related to drug safety, the manufacturer of the trial drug and clinical experts of the tumor type or treatment category in question were consulted for (new) insights. Subsequently, the requests were discussed within the central study team, which included the three central principal investigators. Protocol waiver requests were only granted when at least two of the three central principal investigators approved the waiver. Given that DRUP is an investigator-initiated study, the final decision was made by the study team. All granted waivers were collected in an electronic database. Collected data included the DRUP patient ID; baseline characteristics including gender, age, tumor type, and study treatment; and nature and rationale for the requested waiver.

For the current analysis, waivers were classified by the study team into one of four categories (eligibility criteria; out-of-window testing; treatment exception; and testing exception). Furthermore, the relationship between both nonevaluability and serious adverse events (SAE), and the granted waivers, were classified as either unlikely, possible, or certain.

Study endpoints

Main study endpoints included patient safety and treatment efficacy in patients for whom a waiver was granted. For safety analysis, all SAEs, reported in the 1,019 patients that were included in DRUP between September 2016 and September 2021, were analyzed. All SAEs occurring from registration until 30 days after last treatment administration were documented and reported to central data management of the study. An SAE is defined as an AE unrelated to tumor progression that fulfills one or more of the following criteria: initial or prolonged inpatient hospitalization; a life-threatening experience; severe or permanent disability or incapacity; congenital abnormality or birth defect; death; or any other medically important condition. Preplanned

admission or hospitalization for technical, practical, or social reasons in the absence of an AE are not considered SAEs. Each SAE was graded for severity per the NCI Common Terminology Criteria for Adverse Events (version 4.03). The relationship between SAEs and the study drug was determined by the treating physician. SAEs occurring in the patient group for whom a waiver was granted were subsequently compared with the SAEs that occurred in the patient group without a waiver in terms of quantity, nature, and grade.

For efficacy analysis, the CB rate (CBR), defined as confirmed OR or SD for at least 16 weeks, according to RECIST v1.1 (12) or RANO criteria (13), of all study patients for whom these data were available were included. Subsequently, outcomes of all study patients for whom a waiver was granted were compared with that of all included patients without a waiver. Patients receiving medication with a cycle length of 28 days were considered evaluable if they completed at least one treatment cycle. Patients receiving intravenous medication with a cycle length of less than 4 weeks were considered to be evaluable if they received at least two administrations of treatment.

Data and statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27 (IBM Corp.) and R version 4.2.0 (http://www.R-project.org/). Patient characteristics, waivers, SAEs, and tumor responses were summarized using descriptive statistics. Associations between grade of SAEs and waiver category, and CB and waiver category were explored using Fisher exact tests. To evaluate overall survival (OS; calculated from first day of treatment administration to date of death from any cause, censoring patients who were alive at last follow-up), patients were categorized into waiver and non-waiver groups. The Kaplan–Meier method was employed to calculate median OS, with separate estimates for waiver and non-waiver patients. In addition, a Cox proportional hazards model was utilized to examine the HR (waiver vs. non-waiver).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Patients and waivers

From September 1, 2016 until September 1, 2021, 1,019 patients were included and treated in DRUP. In total, 88 waivers for 82 patients (8%) were granted by the central study team, either before or during treatment, and were included in this analysis. Waivers were equally distributed over the tumor types and treatment categories included in DRUP (**Table 1**). Baseline characteristics were comparable between both groups; however, patients that required a waiver to participate in the trial were more often treated in a specialized cancer hospital.

The categories of granted waivers and the distribution of waivers across these categories are outlined in **Figure 1**. The largest category, comprising 45% of granted waivers, were waivers for eligibility criteria. The most frequently granted waiver within this category was for laboratory requirements, including impaired renal function ($n = 18$; 46%). The second prominent category for waivers concerned testing exceptions, with the most prevalent reason being the omission of a per-protocol mandatory pretreatment tumor biopsy ($n = 21$, 24%). The primary rationale for not conducting a biopsy was predominantly attributed to its highly invasive nature or perceived safety concerns associated with the procedure. For an overview of all granted waivers, please see Supplementary Table S1.

Table 1. Baseline characteristics of patients included in the analysis.

Characteristics	Patients with a waiver (n = 82), n (%)	Patients without a waiver (n = 937), n (%)	*P-value*
Median age, years (range)	63 (22–86)	62 (19–87)	0.77
Gender			1
Male	44 (54%)	505 (54%)	
Female	38 (46%)	432 (46%)	
WHO performance status			0.86
WHO 0	25 (30%)	291 (31%)	
WHO 1	50 (61%)	535 (57%)	
WHO 2	3 (4%)	58 (5%)	
Unknown	4	53	
Tumor type			0.58
NSCLC	14 (17%)	137 (15%)	
CRC	14 (17%)	162 (17%)	
CNS tumor	6 (7%)	82 (9%)	
Breast cancer	6 (7%)	63 (7%)	
Prostate cancer	5 (6%)	73 (8%)	
Urothelial cancer	4 (5%)	21 (2%)	
Sarcoma	4 (5%)	46 (5%)	
Cholangiocarcinoma	3 (4%)	35 (4%)	
Other	26 (30%)	318 (34%)	
Treatment category			0.13
Small molecules[a]	27 (33%)	393 (42%)	
Monoclonal antibodies[b]	15 (18%)	158 (17%)	
Immune therapy[c]	25 (30%)	289 (31%)	
PARP inhibitors[b]	15 (18%)	97 (10%)	
Hospital type			0.02
Academic hospital	37 (45%)	455 (49%)	
Regional hospital	12 (15%)	231 (25%)	
Cancer hospital	33 (40%)	251 (27%)	

Note: Baseline characteristics of patients for whom a waiver was granted. Abbreviations: CNS, central nervous system; CRC, colorectal cancer; NSCLC, non–small cell lung cancer; PARP, poly (ADP-ribose) polymerase; WHO, World Health Organization.
[a]Ten different treatments available.
[b]Two different treatments available.
[c]Four different treatments available.

Safety

In total, 49 SAEs, regardless of relationship to the allocated study treatment, were reported for 32 of the 82 patients (39%) for whom a waiver was granted (**Table 2**). For all included patients in DRUP without a waiver ($n = 937$), SAEs regardless of relatedness were reported for 385 patients (41%). No statistically significant differences in SAE quantity nor grade were found between patients with a waiver and patients without a waiver ($P = 0.81$ and $P = 0.27$, respectively) and grade 5 SAE rate was similar for both groups (patients that received a waiver: 4%, patients without a waiver: 5%). In our analysis, the most frequently reported SAEs were diarrhea ($n = 5$), dyspnea ($n = 5$), and fever ($n = 5$; Supplementary Table S2).

In addition, we evaluated whether the granted waiver may had led to or may had worsened the reported SAEs. This relationship was classified as either "unlikely," "possible," or "certain." For 86% of the SAEs, a relationship was thought to be unlikely. For seven SAEs (14%), the granted waiver possibly contributed to the reported SAE (**Table 3**). Of note, 2 patients that received a waiver experienced an grade 5 SAE. One of these, with a possible relationship between the

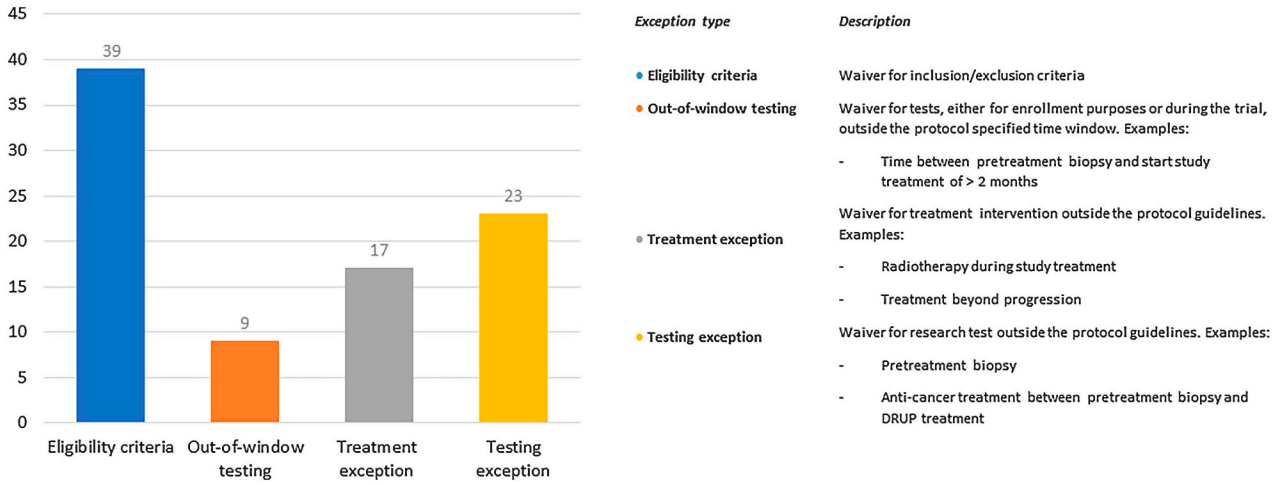

Figure 1.
Distribution and classification of waiver categories. All granted waivers were classified into one of four categories. The number of granted waivers in each category is shown.

waiver and the reported SAE, concerned a male with NSCLC included for treatment with crizotinib. He did not meet the eligibility criteria because of concomitant use of a CYP3A4 substrate (oxycodone). Prior to study treatment opioid rotation was attempted; however, sufficient pain relieve could not be achieved with other types of opioids. After consulting a pharmacist, a waiver was granted for concomitant CYP3A4 substrate use in consultation with the treating physician who informed the patient about this decision and the subsequent potential risks. After treatment initiation, the patient presented with an opioid intoxication, and recovered after naloxone administration. However, after oxycodone was restarted in a lower dose, another episode of opioid intoxication with respiratory depression occurred. The patient was intubated and developed acute respiratory distress syndrome. Because of the dismal prognosis, together with the family it was decided to discontinue all treatment, the patient died shortly thereafter. It was hypothesized that the cause of this unexpected increase in plasma opiate levels could be due to inhibition of the CYP3A4 metabolism route of oxycodone, leading to shunting on the CYP2D6 metabolism route which led to a much more potent metabolite of oxycodone (15). The relationship between this grade 5 SAE and the granted waiver was therefore considered to be possible.

Table 2. Reported SAEs.

	Patients with waiver (*n* = 82)	**Patients without a waiver (*n* = 937)**
Patients for whom SAE was reported, *n* (%)	32 (39%)	385 (41%)
Number of reported SAEs and relation to study treatment, *n* (%)	49	666
Unrelated	18 (37%)	252 (38%)
Unlikely related	14 (29%)	230 (34%)
Possible related	11 (22%)	112 (17%)
Probably related	4 (8%)	47 (7%)
Certainly related	2 (4%)	10 (2%)
Unknown	—	15 (2%)
Grade SAE		
Grade 1	—	43 (7%)
Grade 2	14 (29%)	149 (22%)
Grade 3	31 (63%)	400 (60%)
Grade 4	1 (2%)	29 (4%)
Grade 5	2 (4%)	35 (5%)
Unknown	1	10

Note: Reported SAEs for patients for whom a waiver was granted and for all included patients in DRUP.
Abbreviation: SAE, serious adverse event.

The second patient with an SAE grade 5 concerned a male with NSCLC, who did not meet the hemoglobin (Hb) requirements for olaparib treatment (6.2 mmol/L, at screening patient had 5.9 mmol/L). Because the patient had had a stable Hb level for a longer period of time and no signs of bleeding, a waiver was granted for this eligibility criterion. At 2 months after treatment initiation, he was admitted to the hospital with dyspnea. On the basis of the chest x-ray, the differential considerations were pneumonia, pneumonitis, lymphangitic carcinomatosis, and decompensated heart failure. Because of rapid clinical deterioration, no further diagnostic work-up was performed and the patient died 4 days after presentation. The reported grade 5 SAE and the granted waiver were thought to be unrelated.

Furthermore, for patients that received a waiver for one of the study's eligibility criteria, we also assessed all non-SAEs ($n = 114$) that were reported during treatment. In seven instances, we identified a possible relationship between a granted waiver and the reported AE. In five cases, this concerned a direct relationship; waivers for decreased Hb levels that led to an AE report of anemia ($n = 2$) and waivers for elevated liver enzymes that resulted in AEs concerning these elevated values ($n = 3$). The two remaining cases included a patient with a waiver for increased amylase and lipase levels (without clinical symptoms of pancreatitis) who developed diarrhea during treatment with ribociclib, and a patient that developed pneumonitis upon crizotinib treatment following a waiver for impaired renal function.

Clinical outcome

In total, for 1,006 patients efficacy outcomes were available. At data cutoff, 33 of 82 patients (40%) with a waiver granted had CB, defined by confirmed objective tumor response or absence of disease

Table 3. Waivers that possibly contributed to the reported SAE.

Waiver granted for	SAE	Treatment	Relationship between granted waiver and SAE
Presence of multiple sclerosis	Dyspnea due to pleural effusion	Durvalumab	Possible
Radiotherapy during treatment	Abdominal pain, known duodenum metastasis Ileus Ileus (second episode)	Durvalumab	Possible Possible Possible
Oral intake not possible	Gastric perforation	Vemurafenib + cobimetinib	Possible
Impaired renal function	Anemia	Nivolumab	Possible
Coadministration of CYP3A4 substrate	Depressed level of consciousness	Crizotinib	Possible

Note: Description of the waivers that were thought to be possibly related to the reported SAEs.
Abbreviation: SAE, serious adverse event.

progression for ≥ 16 weeks after treatment initiation. Fourteen patients (17%) achieved a partial response and 19 patients (23%) had SD at 16 weeks. Thirty-seven patients (45%) had progressive disease as best response and 12 patients (14%) were found to be nonevaluable for the primary endpoint of the DRUP trial (**Table 4**).

CBRs were compared between all included patients without a waiver in DRUP and the patients for whom a waiver was granted (CBR 33% vs. CBR 40%; $P = 0.43$). These results were analyzed per treatment category and were comparable for the two groups (Supplementary Table S3). Median OS for patients that received a waiver was 11 months [95% confidence interval (CI): 7–13] versus 8 months (95% CI: 7–9) for non-waiver patients [HR: 0.87 (95% CI: 0.66–1.15, $P = 0.33$)] (**Fig. 2**).

Nonevaluability

In total, 17 waivers were granted for 12 nonevaluable patients. Most of these waivers, 11 (65%), were for eligibility criteria. The most common reason for nonevaluability was discontinuation of the treatment due to either toxicity or progressive disease, before completion of the first treatment cycle (Supplementary Table S3).

The relationship between nonevaluability and the granted waiver was evaluated and classified as either "unlikely" or "possible," or "certain" (Supplementary Table S4). For 5 of the nonevaluable patients, there seemed to be a certain relationship between non-evaluability and the granted waiver [waivers were granted for evaluability ($n = 2$), treatment beyond evaluability ($n = 2$), and coadministration of oxycodone ($n = 1$)], for 6 of these patients this relationship was considered possible [waivers were granted for renal function ($n = 1$), lab abnormalities ($n = 4$), and stable dosage of steroids < 7 days prior to baseline scan ($n = 1$)], and for 6 patients this relationship was thought to be unlikely.

Table 4. Clinical outcome for the waiver patients versus non-waiver patients.

	Patients with waiver (n = 82)	Patients without waiver (n = 924)
Best overall response		
Complete response	0 (0%)	12 (1.3%)
Partial response	14 (17.1%)	133 (14.4%)
Stable disease > 16 weeks	19 (23.2%)	159 (17.2%)
Progressive disease	37 (45.1%)	489 (52.9%)
Nonevaluable	12 (14.6%)	131 (14.2%)

Note: Number of patients with clinical benefit (defined as either objective response, or stable disease ≥ 16 weeks), with progressive disease, and who were nonevaluable are shown for all study participants.

Discussion

In this analysis, we evaluated the effect of prospectively granted protocol waivers on the safety, evaluability, and efficacy outcomes of included patients in the DRUP trial. While one should strive for selection criteria that are necessary and relevant for the purpose of the study, waivers may highlight limitations of the criteria no matter how careful the protocol design. Such waivers should be granted only after careful consideration, and, importantly, waivers granted should lead to an amendment of the chosen criteria, or at least a consideration about this.

In total, protocol waivers were granted for 82 patients (8%) between September 2016 and September 2021. Most waivers (44%) were granted for eligibility criteria, and waivers for laboratory requirements were most frequent in this category. Overall, the CBR in this patient group was 40%, including 14 patients (17%) with a partial response and 19 patients (23%) with SD for at least 16 weeks.

The overall CB reported in the patient group for whom a waiver was granted, was comparable to all included patients without a waiver (CBR of 40% vs. 33%, $P = 0.43$). Although the CBR of the patient group for whom a waiver was granted appears to be slightly higher, this difference might be explained by the selection process of the central study team, in which each waiver request was carefully considered, weighing the risks and potential benefits for the patient in question. This may have led to "positive selection" of patients that were expected to have a higher probability of successful treatment. Furthermore, the number of reported SAEs, related and unrelated to the study treatment, was in line with the number of reported SAEs for all patients included at the time of analysis (39% vs. 41%). This suggests that, in our study, the granted waivers did neither negatively affect safety nor efficacy.

Twelve patients that received a waiver (15%) were found to be nonevaluable for the primary endpoint of the study, which was either possibly or even certainly related to the granted waiver in 11 patients. This is in line with the 18% of nonevaluable patients observed in the DRUP patients without a waiver. The most frequently observed reason for nonevaluability was early discontinuation of the treatment, which is unfortunately a common event in clinical oncology trials that focus on

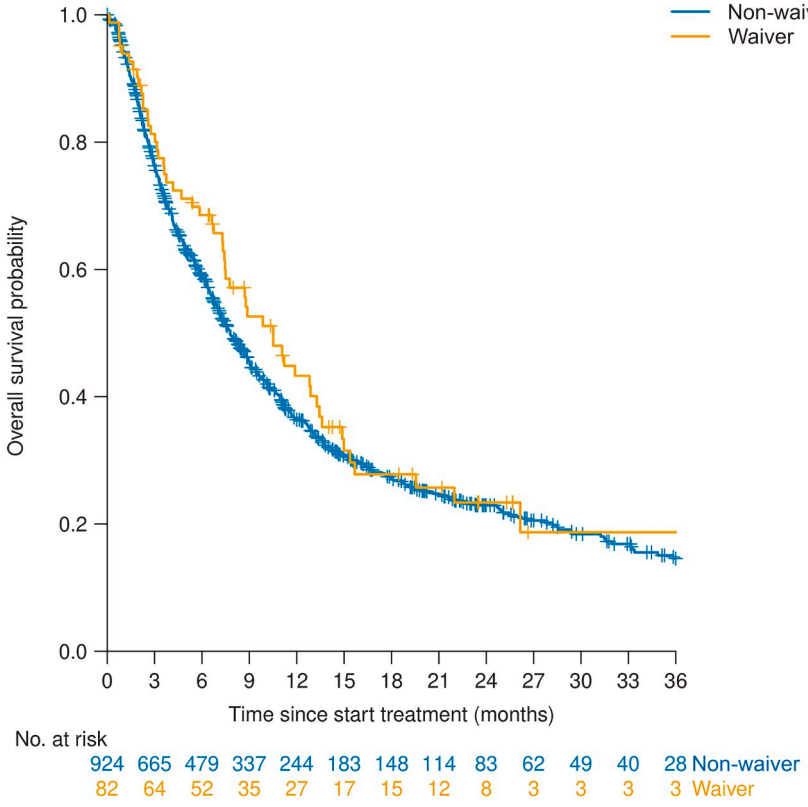

Figure 2.
OS Kaplan–Meier curve for patients with a waiver (in yellow) versus non-waiver patients (in blue).

therapy-refractory, metastatic setting. For example, Douma and colleagues, who studied clinical predictors of early trial discontinuation in phase I trials in oncology, observed early trial discontinuation in 20% of 415 studied patients (16). We therefore conclude that the granted waivers in our trial did not significantly contribute to the number of nonevaluable patients and therefore did not compromise the internal validity of the study.

In 2012, Green analyzed all protocol exception requests at a major academic center over a period of 3 years. Fifty-six percent of all requests concerned oncology trials and one-third of the requests concerned enrollment of patients who did not meet the eligibility criteria. The most common rationale provided by the requesting investigator, listed in 79% of the cases, was to enable the patient to benefit by receiving treatment (17). The actual impact of the protocol exceptions on the safety or treatment outcome of the included patients in this study was unfortunately not reported. Moreover, although there have been a few studies focusing on protocol deviations and violations, additional literature focusing on prospectively approved protocol exceptions and their consequences is still missing.

This study has some limitations; as the DRUP trial includes patients with a broad variety of tumor types, different molecular profiles, and different assigned treatments, these lumped safety and efficacy outcomes should be interpreted with caution. Moreover, the reasons for which the waivers were issued were diverse, as were their possible impact on patient safety and outcome of the treatment. Because of limited sample sizes however, subgroup analysis could not be performed reliably. Importantly, the waivers granted were generally minor deviations from the protocol. We have, unfortunately, no registration of declined waiver requests. Still, this study is the first to report safety and efficacy outcome data after allowing protocol deviations in a clinical study in which an individual approach of the patient plays a significant role. Within DRUP, this approach enabled inclusion of more patients that were otherwise treatment-refractory. It goes without saying that this is of great significance to this patient group.

In our study, we demonstrate that patients in DRUP for whom a waiver was granted did not have worse efficacy outcomes and did not report higher rates of toxicity or nonevaluability, compared with the included DRUP patients for whom no waiver was granted. However, despite careful consideration, it must be noted that one patient deceased, possibly as a result of a granted waiver. In addition, the efficacy observed in molecularly driven trials is higher when compared with unmatched conventional therapies in similar patient populations (4, 5, 18). Therefore, the individual patient is more likely to benefit from molecularly driven therapy, as these drugs have a higher antitumor activity. However, upon granting a protocol waiver, it is crucial to take into account the mechanism of action of the investigated product, its most commonly documented AEs and its potential impact on the patient in terms of safety and efficacy. The current data advocate that "old" unnecessarily strict safety criteria should, where possible, be eliminated when setting-up new molecularly driven trials. This is especially relevant when the study population concerns patients without other treatment options. Furthermore, our data support the importance of a more personalized approach when assessing eligibility criteria in molecularly driven trials, for example using a decision-making procedure that involves both the study team and independent experts.

Authors' Disclosures

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Authors' Contributions

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Note

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