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

The Drug Rediscovery Protocol (DRUP trial)

PROTOCOL TITLE *'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'*

Protocol ID	The Drug Rediscovery Protocol
Short title	DRUP trial
EU CT number	2023-509152-33
Version	Version 19
Date	01-04-2025
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DOCUMENT HISTORY:

Document	Date of version	Summary of Changes
Protocol version 19	01-APR-2025	- Addition of T-cell prolymphocytic leukemia as indication to the inclusion criteria - Correction of “Glioblastoma Multiforme (GBM)” to “primary brain tumors” (see also changes in protocol version 14) - Addition of grade 2 peripheral neuropathy to exclusion criterion 1 - Change of Exclusion criterion 4 from “Patients with known active progressive brain metastases” to “Patients with brain metastases” - The addition of the European Clinical Trial regulation (ECTR) to the regulation statement
Protocol version 18.1	12-MAR-2025	- Administrative corrections - Updates to bring the protocol in line with CTR requirements - Removal of iRECIST criteria
Protocol version 17	01-JUL-2023	Added a description of a procedure for the evaluation of possible protocol deviations
Protocol version 16	01-JUL-2022	Administrative corrections
Protocol version 15	01-NOV-2021	Administrative corrections
Protocol version 14	01-FEB-2021	- Administrative corrections - Inclusion criteria updated: o “GBM” changed to “primary brain tumor” o Added option to use material from prior biopsy o Added that patients must have progressive disease
Protocol version 13	01-FEB-2020	- Administrative corrections - Added faeces collections for patients on immunotherapy
Protocol version 12	01-MAY-2019	- Administrative corrections - Addition of iRECIST criteria for patients on immunotherapy - Addition of 3rd stage expansion cohort
Protocol version 11	01-JAN-2019	- Update timing of biopsy sequencing - Update eligible diagnosis: besides B-cel Non-Hodgkin lymphoma also other NHL may be included
Protocol version 10	01-OCT-2018	- Update exclusion criteria with allowed use of androgen deprivation therapy in prostate carcinoma patients
Protocol version 9	01-JUL-2018	- Administrative corrections - Update inclusion criteria with regards to biopsy in GBM patients
Protocol version 8	01-FEB-2018	- Administrative corrections - Update evaluation time for “clinical benefit”
Protocol version 7	01-SEP-2017	- Administrative corrections - Update In-/Exclusion criteria: addition of wash-out period of 2 weeks before start study treatment - Update of the cohort design: no limit for number of cohorts that can be opened

Document	Date of version	Summary of Changes
Protocol version 6	01-MAY-2017	- Further specification of the inclusion criteria for GBM patients - Addition of the publication policy - Further specification of the criteria for evaluability
Protocol version 5	30-DEC-2016	- Further specification in the definition of “response” - Addition of the possibility for treatment beyond progression for patients receiving immune system-stimulating agents - Changes in the timelines for screening and treatment - Update in the statistical section regarding pooling of data
Protocol version 4	12-SEP-2016	- Administrative corrections - Addition of an optional on-treatment tumor biopsy for research purposes
Protocol version 3	01-JUL-2016	Administrative corrections
Original protocol version 2.0	18-JAN-2016	Not applicable

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AR	Adverse Reaction
AVG	Algemene Verordening Gegevensbescherming
CGH	Comparative Genomic Hybridization
CPCT	Centre for Personalized Cancer Treatment
CTIS	Clinical Trials Information System
CTR	Clinical Trial Regulation
IDMC	Independent Data Monitoring Committee
eCRF	Electronic Case Report Form
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FISH	fluorescence in situ hybridization
GBM	Glioblastoma Multiforme
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
IC	Informed Consent
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IMWG	International Myeloma Working Group
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NGS	Next Generation Sequencing
PCR	Polymerase Chain Reaction
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAPUR	The Targeted Agent and Profiling Utilization Registry
WGS	Whole Genome Sequencing
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Study Summary: 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, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, for which standard treatment options are no longer available and acceptable performance status and organ function. Prior to enrolment in the trial, a genomic or protein expression test must have been performed on the tumor tissue and the results must identify at least one potentially actionable molecular variant as defined in the protocol. Molecular profiling of tumors aiming to find actionable variants for treatment within DRUP will not be performed as part of the trial. 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.

* NB All compounds are commercially available in the Netherlands and most will be supplied from commercial stock. However, for a small number of compounds, such as olaparib, pembrolizumab and nivolumab, the supply will be of investigational medicinal product or clinical supply (resp.) rather than commercial supply.

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, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia that harbors 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 prescribed for treatment of patients with an advanced solid tumor, multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia that harbors a genomic- or protein expression variant known to be a drug target or to predict sensitivity to a drug.
- To perform refined biomarker analyses, including (but not limited to) next generation sequencing, on a fresh tumor biopsy specimen.

Study population: Eligible patients have an advanced solid tumor, multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia 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 a specimen of the tumor and the results must identify at least one potentially actionable variant as defined in the protocol.

Intervention: A pre-treatment fresh frozen tumor biopsy specimen will be obtained for biomarker analyses, including (but not limited to) next generation sequencing by the Hartwig Medical Foundation, the Center for Personalized Treatment's core sequencing facility. Treatment with a commercially available, targeted anticancer drug matched to the patients molecular tumor profile.

Main study endpoints: Primary endpoints include percentage of patients that are treated based on their molecular tumor profile, objective tumor response, stable disease 16 weeks after treatment initiation and treatment-related grade ≥3 and serious adverse events. Secondary endpoints include progression-free- and overall survival and duration of treatment on study (time on drug).

Nature and extent of the burden, risks and benefit associated with participation: The potential benefit to patients from participation in this study is that the strategy of selecting a treatment based on the genomic profile of their tumor will result in tumor regression or stabilization. The potential risks to patients are that the selected therapy will be ineffective

and that treatment-related toxicities will diminish their overall quality of life. As only commercially available drugs will be used in this study and dosing will be initiated according to the official drug label, it is expected that study participants will not be exposed to greater risk of treatment-related toxicities than patients receiving the drug for an approved use.
For all included patients, biopsies of the locally advanced or metastatic lesion will be performed for biomarker analyses by next generation sequencing. Ample experience exists with performing biopsies in patients with locally advanced or metastatic lesions and the procedure is considered to be safe. Alongside the tumor biopsy, a blood sample will be obtained to determine germline DNA.

1. INTRODUCTION AND RATIONALE

1.1 Personalized cancer care is not a new concept, but its application has been enabled and enhanced by a far greater understanding of the biological underpinnings of cancer than ever existed before. Our deeper understanding of cancer at the genomic level, coupled with the increasingly widespread availability of affordable technologies to interrogate the genome, the transcriptome, the proteome and other aspects of the tumor and host is leading to new paradigms of cancer care that rely increasingly on tumor molecular profiling throughout the course of care to refine prognosis and inform treatment decisions. A new generation of drugs, both antibodies and small molecules, that target specific molecules and pathways crucial for cancer survival or progression, has revolutionized the treatment of some cancers and given hope to many patients with cancers once considered hopeless.

1.2 Evidence is building through reports of clinical trials, small research studies, case reports and clinical anecdotes to suggest that patient outcomes are improved when a specific targeted agent can be matched to a tumor genomic variant [1, 2]. Such reports have fueled interest among patients and physicians to use genomic testing as a guide to treatment planning in patients with advanced cancer when standard treatment options have been exhausted, and commercial laboratories have begun to market such genomic tests to oncologists. Clinical reports to date suggest that 30-80% of advanced solid tumors harbor potentially “actionable” genomic variants [3] but the outcomes of patients treated based on such tests remain largely anecdotal or unknown.

1.3 A significant challenge facing oncologists who aim to provide personalized medicine services to their patients is obtaining the drug or drugs predicted to be beneficial based on the genomic testing of the tumor. Few oncologists or pathologists have the highest level of expertise or full access to experts to interpret genomic test reports and guide scientifically informed decisions about the optimal use of targeted agents. In the great majority of cases, such drugs will either be marketed agents that could be prescribed off label or investigational agents that are available only through participation in a clinical trial. Off-label prescribing, while legal, is frequently not reimbursed by insurance companies due to its unproven effectiveness in many cases and the high cost of recently introduced targeted agents. Thus, patients face significant financial risk if treatment costs are not reimbursed and clinicians spend considerable time and effort in discussions with drug manufacturers and insurance companies to obtain the desired treatment at an affordable cost. In addition, where clinicians and patients use targeted agents in routine clinical practice, efficacy and safety is generally not systematically recorded and analyzed. As a result, the research and clinical communities

have a limited understanding of the clinical outcomes of patients who receive these treatments outside of formal clinical trials. There are now more than 30 commercially available drugs that target the molecular pathways frequently aberrant in human tumors. Table I lists some of the targeted agents approved for use in cancer in Europe or the U.S., the labeled indication and the putative drug target(s). Clearly, drugs are available that target many of the most common genomic alterations in human solid tumors, such as *EGFR, ERBB2, VEGFR, BRAF, MEK, MET, ALK, KIT, FGFR, PIK3CA* and *mTOR*, and hundreds of new targeted drugs are in clinical development.

Table 1 Some examples of EMA and/or FDA approved targeted agents for cancer treatment (note that this is not the list of available study drugs in DRUP)

Drug	EMA approved indication	Target(s)*
Ado-trastuzumab emtansine	Breast cancer	*HER2*
Afatinib	NSCLC	*EGFR*
Axitinib	RCC	*VEGFR*
Bevacizumab	Colorectal, NSCLC, RCC, Cervix, GBM, ovary, breast	*VEGF-A*
Bosutinib	CML	*Bcr-abl*
Cabozantinib	MTC, RCC	*RET, VEGFR, MET, TRKB, TIE2*
Ceritinib	NSCLC	*ALK, ROS*
Cetuximab	Colorectal cancer, HNC	*EGFR*
Crizotinib	NSCLC	*EML4-ALK, ROS1, MET*
Dabrafenib	Melanoma	*BRAF V600E*
Dasatinib	CML	*Bcr-abl, SRC, cKIT,PDGFR*
Erlotinib	NSCLC	*EGFR*
Everolimus	RCC, Breast, pNET	*mTOR, TSC1, TSC2*
Fulvestrant	Breast	*ESR1 expression*
Gefitinib	NSCLC	*EGFR mutations*
Ibrutinib	MCL, CLL	*BTK*
Imatinib	CML, ALL, GIST	*Bcr-abl, cKIT*
Lapatinib	Breast	*EGFR*
Nilotinib	CML	*Bcr-abl*
Olaparib	Ovarian cancer	*BRCA mutations*
Panitumumab	Colorectal cancer	*EGFR*
Pazopanib	RCC, STS	*VEGFR, PDGFR, FGFR,KIT*
Pertuzumab	Breast	*HER2*
Ramucirumab	Gastric	*VEGFR2*
Regorafenib	Colon,	*VEGFR, TIE2, PDGFR, RET,cKIT*
Ruxolitinib	Myelofibrosis	*JAK1, JAK2*
Sorafenib	RCC, HCC, DTC	*BRAF, KIT, FLT-3, RET, VEGFR, PDGFR*
Sunitinib	RCC, GIST, pNET	*PDGFR, VEGFR, KIT, FLT-3, RET*
Temsirolimus	RCC	*mTOR*
Trametinib	Melanoma	*MEK1, MEK2*
Trastuzumab	Breast, gastric	*HER2*
Vandetanib	MTC	*RET, EGFR, VEGFR, TIE2*
Vemurafenib	Melanoma	*BRAF V600E*

Vismodegib	BCC	*SMO*

* Drug targets obtained from review of EMA approved package insert for each drug. Abbreviations: ALL, acute lymphoblastic leukemia; BCC, basal-cell carcinoma; CML, chronic myeloid leukemia; DTC, differentiated thyroid cancer; GBM, glioblastoma; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HNC, head and neck cancer; MCL, mantle cell lymphoma; MTC, medullary thyroid carcinoma; NSCLC, non-small-cell lung cancer; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; STS, soft-tissue sarcoma.

1.4 A solution to lack of access to drugs prescribed outside of the labelled indication and lack of data collection on safety and efficacy of such treatments is creation of a drug access program in which key clinical outcomes are systematically recorded, analyzed and published. This study will focus initially on facilitating access to approved targeted therapies that are prescribed to patients with advanced cancer who have exhausted standard treatment options and for whom treatment is selected based on results of a genomic test of their tumor. The study will provide a molecular tumor board to help physicians understand the genomic profiling test results and possible treatment options and will capture patient outcomes in a prospective database that will enable insights to be gained about the utility of this approach. Furthermore, next generation sequencing will be performed on a fresh tumor biopsy specimen, to enable additional biomarker discovery.

Matching drugs to genomic alterations in patients with advanced cancer has yet to be proven efficacious in prospective, randomized controlled trials, although a number of studies are on-going to evaluate this approach. Thus, there is a risk that patients who participate in this study will experience treatment-related toxicity without any treatment benefit. The same is true for any treatment used in a patient who has exhausted all standard treatment options. Case reports and small trials indicate that matching drugs to genomic aberrations of the tumor can offer benefit to patients [4-8]. A pilot prospective study utilizing molecular profiling of tumors by immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and DNA microarray was completed by the Translational Genomics Research Institute [9]. This was the first published study utilizing molecular profiling to find potential targets and select treatments accordingly. The study was conducted at 9 sites across the United States and included patients with metastatic cancer who had clear-cut progression of their tumors on their last systemic therapy and no remaining standard treatment options. The primary objective of the study was to compare progression-free survival (PFS) using a treatment regimen selected by molecular profiling, versus the PFS observed for the patients' most recent prior treatment regimen, and calculate the PFS ratio (PFS on study/previous PFS). Eighty-six patients were profiled, with a molecular target detected in 84 (98%). Sixty-six

patients were treated according to profiling results (breast cancer, n=18; colorectal, n=11; ovarian, n=5; and other miscellaneous types of tumors, n=30). Of the 66 patients treated according to profiling results, 18/66 (27%) patients had a PFS ratio ≥ 1.3 (95% CI, 17-38% one-sided one-sample p=0.007). The PFS ratio was ≥ 1.3 for 44% of the breast cancer patients, 36% of the colorectal cancer patients, 20% of the ovarian cancer patients, and 16% of the patients with miscellaneous types of cancer. In addition to the PFS endpoint, there was 1 complete response by Response Evaluation Criteria for Solid Tumors (RECIST), 5 partial responses and 14 patients without progression at 4 months. In most patients with successful tumor molecular profiling, the profiling supported the use of a new treatment not contemplated initially by the investigator, in a patient population that was heavily pretreated and refractory to previous treatments.

Tsimberidou and colleagues reported results of the MD Anderson Cancer Center experience of genomic profiling of solid tumor patients with advanced disease, the Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) study. Of 1144 patients analyzed, 40.2 % had one or more genomic aberrations. For patients who received a targeted therapy matched to a genomic aberration, median PFS and OS were 4.1 months and 10.2 months respectively compared with 2.4 and 8.2 months for patients who did not receive a matched treatment (p<.0001) [8]. The MOSCATO-01 (Molecular profiling in Cancer for Treatment Optimization) trial is being conducted at the Institut Gustave Roussy in patients with treatment-resistant progressive metastatic cancers with lesions accessible to biopsy to perform genomic profiling by comparative genomic hybridization and whole-genome sequencing. Preliminary results of the first 129 patients were presented at the 2015 ASCO annual meeting [6]. Progression-free survival (PFS) using therapy based on genomic assessment was compared to the PFS for the most recent therapy on which the patient had just experienced disease progression (PFS ratio). Of 129 consented patients, 111 (86%) had a tumor biopsy. An actionable variant was identified in 52 patients (40%). Among the 25 patients treated according to their genomic assessment, five had partial responses (20%), 14 cases had stable disease (56%) and three cases of progressive disease (12%) were observed. PFS ratio was >1.3 among 9 out of 19 evaluable patients (47%).

Schwaederle and colleagues reviewed phase II single-agent studies (570 studies; 32,149 patients) published between January 1, 2010 and December 31, 2012 [10]. Response rate, progression-free survival, and overall survival (OS) were compared for arms that used a personalized strategy versus those that did not. Multivariable analysis (both weighted, multiple linear regression and random effect meta-regression) demonstrated that the personalized approach consistently and independently correlated with higher median RR

(31% vs 10.5%, P<0.0001), prolonged median PFS (5.9 vs 2.7 months, P<0.0001) and OS (13.7 vs 8.9 months, P=0.0001). Personalized arms using a “genomic biomarker” had higher median RR, prolonged median PFS and OS (all P≤0.05) than those using a “protein biomarker”. In a similar approach, Jardim and colleagues analyzed drug registration trials for agents approved by the FDA between 1998-2013 [11]. Analysis of experimental arms in 112 registration trials demonstrated that personalized therapy (i.e., therapy assigned based on a biomarker selection strategy) was associated with higher RRs (48% vs. 23%; P<0.001) and longer PFS (median = 8.3 vs. 5.5 months; P=0.002) and OS (median= 19.3 vs. 13.5 months; p = 0.04). Personalization was an independent predictor of better RR, PFS and OS as demonstrated by multilinear regression analysis.

Despite these encouraging findings to support the strategy of matching drugs to the molecular profile of a tumor, the initial report of a prospective randomized study of this approach has raised questions about its utility. Le Tourneau and colleagues recently presented the first results of the SHIVA study, a randomized phase II trial comparing therapy based on tumor molecular profiling versus conventional therapy in patients with refractory cancer. 195 patients were randomized to treatment matched to the tumor molecular profile or to physician’s choice among available therapies. Approximately 25 genomic targets were assessed in tumor biopsies and could be matched to 11 commercially available targeted drugs provided in the study. Progression-free survival, the primary study endpoint, was 2.3 months for the matched therapy arm and 2.0 months for the physician’s choice arm (p=0.41) [12]. The final results of the SHIVA trial were recently published and there appeared to be no difference between progression free survival of patients treated according to their genetic profile or physician choice. However, the study was criticized for lumping genetic profiles without consideration of the tissue context or relative importance of genetic aberrations [13].

Recently, Lopez-Chavez and colleagues [14] reported results of a basket trial conducted in patients with advanced NSCLC, small cell lung cancer and thymic malignancies. Six hundred forty-seven patients were enrolled and their tumors were tested for 11 pre-specified genomic alterations. Forty-five percent of patients had an alteration detected in at least one of the genes analyzed and 4% had multiple genomic abnormalities. However, few patients actually received the protocol-specified matched targeted therapy due to failure to meet other eligibility criteria and, overall, only 2 of 15 treatment arms were successfully completed due to patient ineligibility or low frequency of the targets of interest. The MD Anderson experience of attempting to match treatments to the genomic profiles of advanced cancer revealed similar challenges [15]. Standardized hotspot mutation analysis was performed in 2,000 patients, using either an 11-gene (251 patients) or a 46- or 50-gene (1,749 patients)

multiplex platform. Seven hundred eighty-nine patients (39%) had at least one mutation in potentially actionable genes but only eighty-three patients (11%) with potentially actionable mutations went on genotype-matched trials targeting these alterations. Challenges to trial accrual reported by the authors included patient preference of non-investigational treatment or local treatment, poor performance status or other reasons for trial ineligibility, lack of trials/slots, and insurance denial. These trials clearly illustrates the challenges of trying to match drugs to specific genomic alterations in patients with advanced cancer, that is, not all genomic tests will provide an informative result, not all tumors will harbor an actionable genomic variant, not all variants will be targeted by an available drug, not all patients will meet eligibility criteria for treatment and not all patients will successfully complete the treatment prescribed. Such difficulties highlight the need for innovative trial designs to enhance accrual and improve study completion rates.

1.5 A new generation of prospective clinical trials exemplified by the recently launched Novartis Signature Trial (www.signaturetrial.com), the FOCUS4 study (EudraCT number 2012-005111-12), the NCI Molecular Profiling based Assignment of Cancer Therapeutics (NCI-M-PACT) study, the MD Anderson IMPACT-2 study, the Lung Cancer Master Protocol (LungMap) study, the Genentech My Pathway Trial and a Stand Up to Cancer Melanoma Study (ClinicalTrials.gov identifiers NCT01827384, NCT02152254, NCT02154490, NCT02091141, NCT02094872, respectively) will provide a more definitive test of the value of matching drugs to genomic alterations. Obtaining these results will likely take years. Until then, the opportunity exists to capture data from prescribing of targeted agents in the context of clinical practice that, while imperfect, might still be informative to guide the development of this promising treatment strategy. Clearly though, this approach must still be considered investigational and should be studied in the context of an METC-approved protocol following patient informed consent regarding the potential risks and benefits of this approach.

1.6 The Center of Personalized Cancer Treatment (CPCT, www.cpct.nl) is a consortium of all academic cancer centers and several large teaching hospitals in the Netherlands. Established in 2010 it has now developed an infrastructure for genomics driven clinical studies and invests heavily in creating a data base in which genomic test of fresh tumor material obtained before start of treatment is linked with clinical outcome. The CPCT uses the NGS infrastructure of the Hartwig Medical Foundation, a centralized core facility for genetic testing and has protocols in place for every step from obtaining informed consent to returning the genetic results to patients. Presently, biopsies are tested by next generation sequencing for genetic abnormalities and RNA and protein are isolated simultaneously from

the same biopsies. The CPCT is ideally positioned to support the DRUP trial because all logistics are in place and funding to support the genomic testing is available.

1.7 Patients from the Netherlands, the United States and possibly other countries will be included in similar though independent protocols (DRUP protocol for the Netherlands and TAPUR for the United States; other partner-studies (such as the Canadian CAPTUR initiative) are being set-up at the time of writing). This will allow sufficient patient numbers even for the small subgroups over a period of 3 years and will facilitate exchange of data.

2. OBJECTIVES

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, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia that harbors 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, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia that harbors 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.

3. STUDY DESIGN

Prospective, open-label, non-randomized basket- and umbrella trial. Patients will be enrolled in multiple parallel cohorts, each defined by 1 tumor type, 1 tumor profile and 1 study drug (please refer to sections 'Sample size calculation' and 'Statistical analyses' for further details on cohort design and management). Patients will be treated with commercially available targeted anti-cancer drugs.

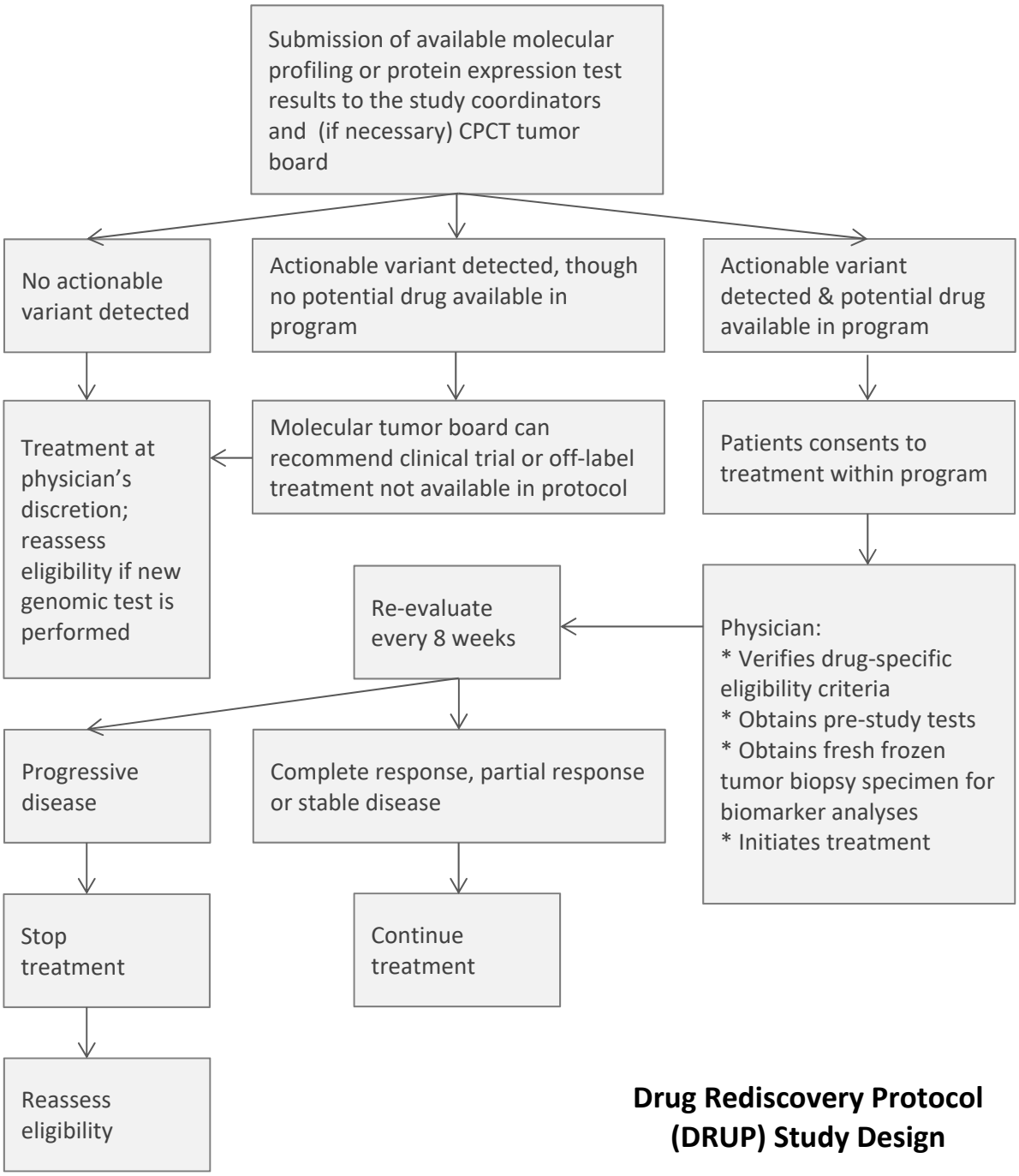

Figure 1: schematic study flowchart

4. STUDY POPULATION

4.1 Population (base)

Patients with metastatic or advanced solid tumors (including primary brain tumors), multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia who have exhausted standard treatment options or for whom no standard treatment is available are eligible to participate in this study. A potentially actionable genomic- or protein expression variant (please refer to section 'Definition of Potentially Actionable Variants' for definitions), as revealed by a previously performed tumor genomic or protein expression test must be present. Patients whose tumor harbors a genomic variant known to confer resistance to a specific anti-cancer agent are not eligible to receive that agent.
Additional inclusion and exclusion criteria may apply to specific drugs or drug – molecular variant – tumor type matches and are listed in the drug specific study manuals provided in this study. When drug-specific inclusion/exclusion criteria or precautions specified in the drug-specific manual differ from those listed below, the drug-specific criteria will take precedence. Screening should be performed ≤28 days prior to treatment initiation.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Adult (age >18 years) patient with a histologically-proven locally advanced or metastatic solid tumor, multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia with symptomatic or radiological disease progression after standard anti-cancer treatment or for whom no such treatment is available or indicated.

   For patients with a primary brain tumor:

   Histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.
2. ECOG performance status 0-2
3. Patients must have acceptable organ function as defined below. However, specific inclusion/exclusion criteria specified in the drug-specific study manual will take precedence:
   a. Absolute neutrophil count ≥ 1.5 x 10^9/l
   b. Hemoglobin > 5.6 mmol/l
   c. Platelets > 75 x 10^9/l
   d. Total bilirubin < 2 x ULN
   e. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)

f. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m^2

4. Patients must have objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma and T-cell prolymphocytic leukemia, primary brain tumors or ovarian cancer in case of CA125-based evaluation (please refer to appendices for further details) [16, 17].
5. Results must be available from a tumor genomic or protein expression test. Eligible tests may include any of the following technologies: fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), comparative genomic hybridization (CGH), next generation sequencing (NGS), immunohistochemistry (IHC) or RNA sequencing (RNAseq). The test may have been performed on the primary tumor or a metastatic deposit, in a diagnostic laboratory or within the context of another CPCT study, and must reveal a potentially actionable variant as defined in Section 5. The test results (full pathology or molecular diagnostics report) must be uploaded in the eCRF.
6. Patients must have a tumor profile for which treatment with one of the FDA and / or EMA approved (or under revision for approval) targeted anti-cancer drugs included in this study has potential clinical benefit based on preclinical data or clinical information (see section 5).
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made:

a. An exception is made for patients with a primary brain tumor or other tumor types with only intracerebral lesions, **only** if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained:
    a. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression)
    b. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure.

b. In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP.
c. An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample.

8. Ability to understand and the willingness to sign a written informed consent document.
9. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.
10. Because of the risks of drug treatment to the developing fetus, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation, and for four months following completion of study therapy. Male patients should avoid impregnating a female partner. Male patients, even if surgically sterilized, (i.e. post-vasectomy) must agree to one of the following: practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or completely abstain from sexual intercourse.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Ongoing toxicity $\geq$ grade 2, other than alopecia or grade 2 peripheral neuropathy.
2. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.
3. Patient is pregnant or nursing.
4. Patients with brain metastases. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.
   Specific exclusion criteria for patients with primary brain tumors:

a. *Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization.*
b. *No radiotherapy within the three months prior to the diagnosis of progression.*
c. *No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*

5. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.
6. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible
7. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible
8. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.

For each drug included in this protocol, specific inclusion and exclusion criteria (based on the Package Insert or manufacturers recommendations) may also apply. These can be found in the supplemental information about each agent included in the drug-specific study manuals. Drug-specific inclusion and exclusion criteria will take precedence over the inclusion/exclusion criteria listed above.

4.4 Sample size calculation stage 1 and 2

Per cohort, 8 or 24 patients can be enrolled depending on response (defined as ‘response’ individually per criteria, or as disease control (absence of disease progression) for at least 16 weeks measured ≥2x and ≥28 days apart), as depicted below. Each tumor type/variant/drug treatment will define a separate cohort, and each cohort will be monitored using a Simon-like two-stage ‘admissible’ monitoring plan [18, 19] to identify tumor/variant/drug cohorts with evidence of activity. For purposes of cohort definition, the ‘variant’ category will be defined at the level of the gene that harbors the mutation or overexpression; e.g., EGFR mutant will be defined as the ‘variant’ for purposes of cohort definition and will include all detected EGFR mutations. Please refer to chapter ‘Statistical Analysis’ for further details.

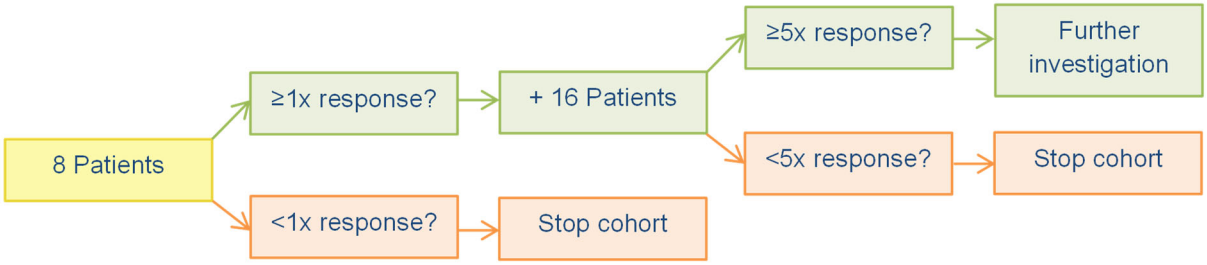

Figure 2: number of patients per cohort. Cohorts are defined by histologic tumor type, molecular tumor profile and study drug.

4.5 Expansion cohort: stage III

Cohorts that have enrolled 24 patients in stage II, and in which ≥ 5 patients have clinical benefit, are considered as potentially successful cohorts. After consultation with the manufacturer of the drug and the healthcare authorities, a successful cohort may proceed to stage III in DRUP. Stage III is an expansion cohort, in which additional patients with the same molecular profile, histological tumor type and drug will be enrolled to confirm the results obtained in the first 24 patients.

4.5.1 Objectives Of stage III:

- To confirm the clinical benefit and toxicity of a drug in a successful cohort as shown in stage II (first 24 patients).
- To perform refined biomarker analyses, including (but not limited to) whole genome sequencing, on a fresh tumor biopsy specimen.

4.5.2 Study population

For patients enrolling in stage III, the same general inclusion criteria apply as for patients enrolling in stage I and II (see section 4.2 and 4.3: Inclusion- and exclusion criteria). The drug-specific in- and exclusion criteria of the agent will take precedence over the inclusion/exclusion criteria listed above.

4.5.3 Main endpoints

- Confirmation of the clinical benefit rate (PFS) in stage II for a particular cohort with 90% confidence.
- Secondary endpoints include: objective response rate, duration of response, overall survival and treatment related grade ≥3 adverse events.
- Exploratory endpoints include: biomarker analysis on a fresh frozen tumor biopsy (including, but not limited to, next generation sequencing).

4.5.4 Design of stage III

Treatment of patients in the expansion cohort will be divided into two phases:

- Phase 1 (week 1 – 16)
  During this phase, patients will be treated with the IP (labelled as study drug), provided by the manufacturer. The medication will be shipped to the local pharmacies on a per-patient basis, DRUP infrastructure will be used. Response evaluations will be performed every 8-9 weeks and all data will be collected in the DRUP eCRF system. If progressive disease, according to RECIST 1.1, RANO, Lugano, GCIG or IMWG criteria, is observed at any point during phase 1, the treatment will be discontinued. This phase is considered the trial phase with investigational medicinal products.
- Phase 2 (beyond 16 weeks)
  If clinical benefit (defined as confirmed objective response or stable disease at 16 weeks and measured more than once, at least 28 days apart) is observed for an individual patient at 16 weeks, treatment for that individual patient with the IP will continue in phase 2. The patient will receive the (approved) medication from general hospital stock, and the medication will be reimbursed by the health insurer. This phase is considered solely as an observational phase and not a trial with investigational medicinal products and, therefore, regular marketed drug product will be used. Still, disease control and toxicity will be followed to define treatment benefit. During phase 2, response evaluations will be performed every 12 weeks. Data collection will continue in the same way as in phase 1. If progressive disease, according to RECIST 1.1, RANO, Lugano, GCIG or IMWG criteria is observed at any point during phase 2, treatment will be discontinued.

4.5.5 Sample size calculation

The sample size calculation for stage III cohorts will be performed individually for each cohort proceeding to stage III. Sample size calculations will be based on the clinical benefit rate observed in the stage II cohort, with a statistical power of 90%.

5. TREATMENT OF SUBJECTS

5.1 Definition of Potentially Actionable Variants

As described by Meric-Bernstam et al [20] a potentially actionable genomic variant may be defined as a genomic alteration that is known to promote tumor growth or progression; that is the target of a drug approved for a cancer indication; that is a specific eligibility criterion for enrollment on a clinical trial of an anti-cancer drug; or that is known to confer sensitivity to an approved drug or susceptibility to a specific molecular intervention. Hence, in this study a potentially actionable genomic or protein expression variant will be defined as:

a. Variant is the target of an approved drug for any cancer indication or is known to predict sensitivity to an approved drug for any cancer indication
b. Variant is in the same molecular pathway but located upstream of the molecular target of an approved drug for any cancer indication
c. Inactivating mutations in somatic or germline genes that result in unique susceptibility to a specific molecular intervention (e.g., BRCA1 mutation and PARP inhibitors)
d. Other genes of interest that have appropriate justification for selection based on published scientific evidence regarding susceptibility to a specific targeted therapy

5.2 Criteria for Drug Selection

The selection of appropriate matches between actionable variants and drugs will be made by the study coordinators and, in case of doubt, by the CPCT's central molecular tumor board assisted by a knowledge based data library. If more than one potentially actionable variant is present or if more than one agent available in this study targets a molecular variant identified in the patient's tumor, the drug with the highest level of evidence (as defined below, criteria adapted from Meric-Berstam et al, [20]) will be selected, unless there's rationale to justify selecting an agent with a lower level of evidence (e.g., the patient has known intolerance to the agent with the higher level of evidence).

Level 1: Agent met a clinical end point (objective response, progression-free survival or overall survival) in a prospective clinical trial testing the agent in the patient's tumor type harboring the molecular variant of interest. Agent has not yet received regulatory approval for use in patient's tumor type.

Level 2: Published clinical studies demonstrate an association between presence of the molecular variant and clinical activity of the agent against the patient's tumor type.

Level 3: Agent is commercially available in the US and / or EU for use in a tumor type with the specific genomic variant identified in the patient's tumor.

Level 4: Agent demonstrated preclinical evidence of antitumor activity and evidence of target inhibition in model systems of patient's tumor type.

For patients with primary brain tumors, expected drug penetrance trough the blood-brain barrier should be taken into account. Preferably, information should have been made available by the manufacturer. The most important features for blood-brain barrier penetration are:

- *Molecular weight ≤400*
- *Log p ≤ 5*
- *Hydrogen bond donor ≤3*
- *Hydrogen bond acceptor ≤7*

6. INVESTIGATIONAL PRODUCT

6.1 Description of available drugs

To enable a dynamic study design and to allow for regular updates of available drugs, the drugs that are available for selection through this protocol are listed in an external study table. For every available drug though, drug-specific study information will be provided. This includes the Summary of Product Characteristics (SPC) or Investigator Brochure (IB), drug-specific patient information in Dutch, and a drug-specific study manual including drug-specific in- and exclusion criteria and treatment schedules. Initial drug dose and schedule, dose modifications and management of treatment-related toxicities will be according to the FDA and / or EMA approved (or under revision for approval) label and / or manufacturer's recommendations listed in the drug-specific information. Please refer to the package insert and provided SPC or IB for details on mechanism of action, known and potential risks and benefits, concomitant medication, dosage and method of administration of each agent included in this protocol.

6.2 Summary of findings from (non-)clinical studies, risks and benefits

Within this protocol, patients will only be treated with commercially available, FDA and / or EMA approved (or under revision for approval) and registered targeted anti-cancer drugs. Please refer to the attached SPC or IB of every drug for further details.

6.3 Description and justification of route of administration and dosage

Route of administration and dosage will be conform treatment within the registered indication of every drug. Drug-specific treatment schedules are provided in the drug-specific study manuals.

6.4 Dosages, dosage modifications and method of administration

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted at the discretion of the treating physician. Recommended dose modifications contained in the SPC or IB should be followed for dose reductions and delays as clinically appropriate. Please refer to the package label of each drug for further details.

6.5 Preparation and labelling of drugs used in this study

All drugs included in this protocol should be stored and prepared according to the instructions in the package inserts of the commercial supply and labelled as study drugs by the pharmaceutical company supplying the drug. As with all anti-cancer drugs, their

preparation and administration should be closely supervised by a qualified physician experienced in the use of cancer chemotherapeutic agents. The preparation and disposal of the drug products should be in accordance with local institutional guidelines, policies and procedures.

6.6 Drug accountability

Participating sites are responsible for the accountability of study drugs. The maintenance of drug accountability can be performed according to local protocols. Left-over study drugs should be stored at the participating site unless agreed otherwise.

The treating physician can order study drugs by filling in the required information in the eCRF. Drugs (labelled as study drugs) will be shipped to the site’s pharmacy on a per-patient basis. The first shipment will include sufficient drugs to treat the patient just beyond the first response evaluation, to ensure bridging till the next shipment (if the patient will continue treatment after the response evaluation). Thereafter, drugs will be resupplied per response evaluation.

7. METHODS

7.1 Study endpoints

7.1.1 Primary study endpoints

- Percentage of patients that are treated based on their molecular tumor profile
- Objective tumor response
- Disease control, defined as Stable Disease (SD) at 16 weeks after treatment initiation
- Treatment-related grade≥3 and serious adverse events

7.1.2 Secondary study endpoints

- Progression-free and overall survival
- Duration of treatment on study (time on drug)

7.1.3 Exploratory study endpoints

- Description of concordance between mutational profile of pre-treatment tumor biopsies and mutational profile according to tumor profiling tests that were used to enroll patients

7.2 Registration procedures

Prior to submitting the case for review by the study coordinators, the treating physician will determine that the patient meets all inclusion criteria and none of the exclusion criteria that are not drug-specific. Preferably, the physician will evaluate the tumor genomic or immunohistochemistry (IHC) test results to determine if at least one potentially actionable variant (as defined in the section ‘Definition of Potentially Actionable Variants’) is present and if a potential drug match is available from among the drugs available in this study. If the treating physician is uncertain about whether a potentially actionable variant is present in the tumor that can be targeted by a drug available in the protocol, the physician may also submit the case for review. The physician will submit the case (including tumor profile, tumor type and brief anonymous clinical case summary) to the study coordinators who will (in case of doubt, in consultation with the CPCT Tumor Board) determine if indeed at least one potentially actionable variant is present and if a potential drug match is available from among the drugs available in this study. If so, the study coordinators will reserve a slot and inform the treating physician. If the patient consents to treatment with the proposed drug and if all drug specific eligibility criteria are confirmed, the treating physician will register the patient on study (see also figure 3 ‘Schematic overview of patient submission’ below) and upload the

full pathology or molecular diagnostics report in Alea. If the this report has previously been discussed by a local Tumor Board, their report should also be uploaded.

Following patient registration, treatment may begin once a fresh tumor biopsy is taken. All patients who receive treatment with a drug available in the protocol will be followed for protocol-specified toxicity and efficacy outcomes including tumor response, progression-free and overall survival as well as duration of treatment.

7.3 Treatment assignment and plan

A recent study at an NCI-designated comprehensive cancer center suggests that many oncologists feel they have insufficient knowledge to interpret and act on results of tumor genomic testing [21]. In order to ensure that the treating physician has correctly interpreted the test results and determined the best possible treatment option for the patient, the study coordinators and, in case of doubt, the CPCT's central molecular tumor board will evaluate each gene or protein expression variant-drug match. The molecular tumor board includes experts in clinical oncology, pathology, genomics and cancer biology, bioinformatics, statistics, pharmacology and other relevant scientific disciplines and is appointed by the CPCT. The treating physician should submit a copy of the full genomic profiling or protein expression test report (preferably, including the proposed drug treatment from among those drugs available in this study and the rationale for drug selection), a statement describing the tumor specimen tested (primary tumor or metastatic deposit), and a description of the patient's clinical characteristics to the study coordinators and the central molecular tumor board. Clinical characteristics provided must include patient age, gender, ECOG performance status [22], relevant medical history including histological cancer diagnosis and concomitant medications. The review of the study coordinators and the molecular tumor board will be supported by a knowledge library that will provide an analysis of the case, including potential treatments on or off protocol and potential clinical trials that might be appropriate for the patient (see also figure 3 'Schematic overview of patient submission' below).

The study coordinators will return an interpretation of the case within 5 business days after submission, or within 10 business days in case of doubt, in which case the CPCT tumor board will be consulted. Possible outcomes of the review may be but are not limited to:

1. Proposal for treatment with a drug available in this study, with rationale.
2. Proposal for treatment with more than one drug available in this study, with rationale.
3. Recommendation for participation in a specific clinical trial of an investigational agent.

The treatment recommendation must be entered in the study database but on-treatment and follow-up data will be required only for patients who receive a drug available in this protocol. Treatment with drugs provided in this protocol must be initiated within 28 days of provision of the molecular tumor board recommendation to the treating physician. Initial drug dose and schedule will be according to the approved package insert for the drug product. Any necessary dose modifications will be at the discretion of the treating physician. Dose modification in the package label will be followed if clinically appropriate.

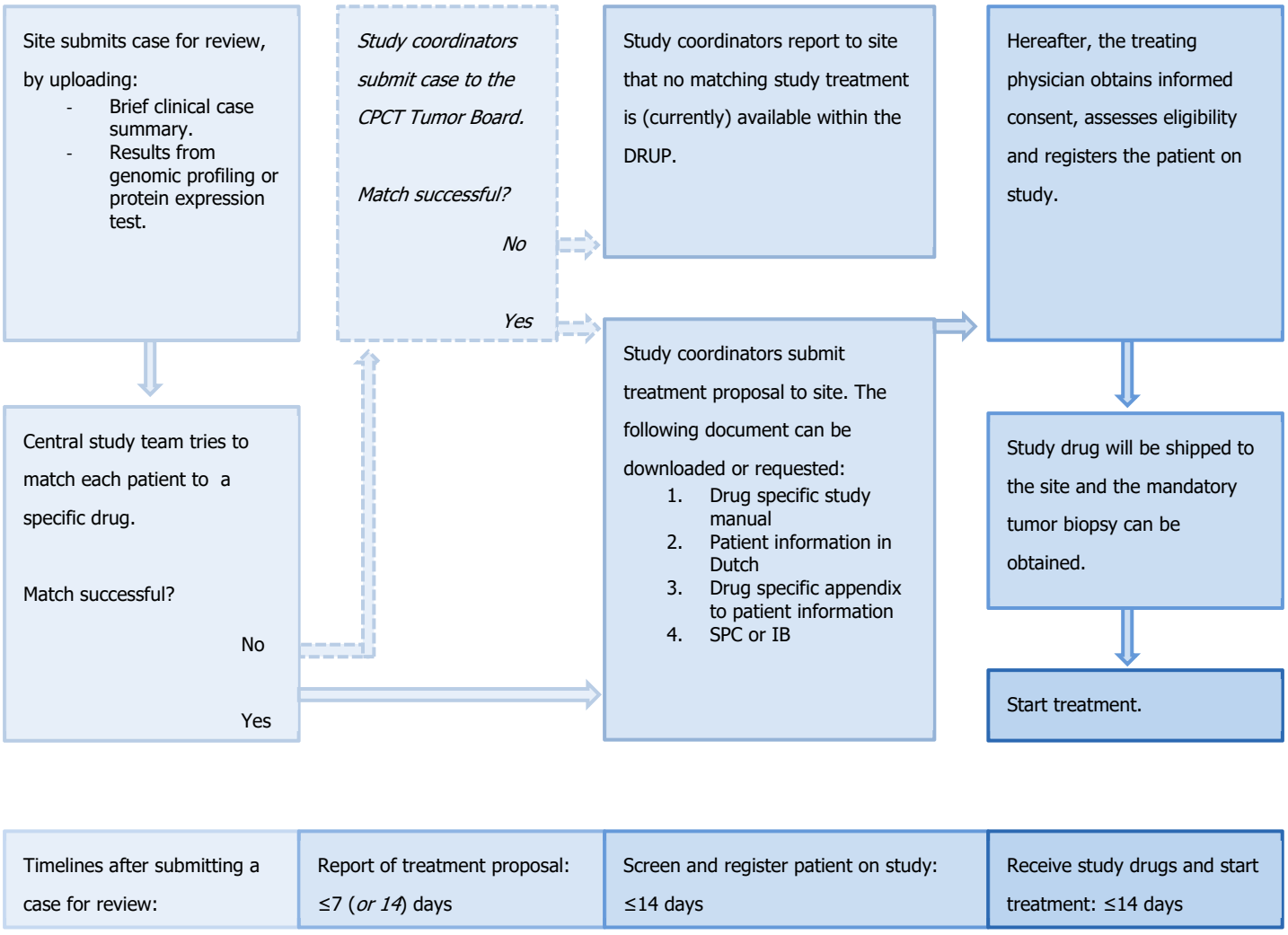

Figure 3: patient registration flowchart and proposed timelines (*CPCT Tumor Board is only consulted in case of doubt*). Participating sites may deviate from these timelines if it is in the patients' interest or because of logistical reasons, but slots will in principle only be reserved during the above displayed timeframe. NB please notify the study coordinators if a biopsy has been obtained whereas the patient will *not* start treatment (screening failure).

8. Study procedures

8.1 Pre-treatment evaluation

A signed Patient Informed Consent Form must be obtained prior to registration. The following screening procedures should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment:

1. A medical history including pertinent medical conditions must be recorded.
2. Concomitant medications/therapies including documentation of steroid use and dose.
3. Patient age and gender, physical examination including vital signs, weight, height, ECOG performance status and orientating neurological examination for patients with primary brain tumors.
4. Hematology, including total white blood cell count, absolute neutrophil count, hemoglobin, and platelet count.
5. Comprehensive serum chemistry panel, including creatinine, calculated creatinine clearance, Aspartate Amino-Transferase (AST), Alanine Amino-Transferase (ALT) and total bilirubin.
6. Baseline EKG and / or left ventricular ejection fraction as determined by ECHO or MUGA scan if clinically indicated or required after review of the drug specific in- and exclusion criteria.
7. Urine or serum pregnancy test for female patients of child bearing potential.
8. Radiological evaluation by (PET)CT-scan, MRI or any other imaging scan to define pre-treatment tumor status according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, primary brain tumors or ovarian cancer in case of CA125-based evaluation (please refer to appendices for further details).
9. Description and results of the tumor profiling test and the type of specimen used for testing. Eligible tests may include any of the following technologies: immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), comparative genomic hybridization (CGH), next generation sequencing (NGS), or RNA sequencing (RNAseq). The test may have been performed on a fresh or paraffin-embedded specimen of the primary tumor or a metastatic deposit, in a diagnostic laboratory or within the context of another CPCT study, and must reveal a potentially actionable variant (see section ‘Definition of Potentially Actionable Variants’).
10. For every agent included in this protocol, additional pre-treatment evaluations might apply. These can be found in the drug-specific study manuals.

8.2 Following verification of drug-specific eligibility and patient enrolment

A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen (in general 2-4 samples, specimen length 22mm, obtained with a 18G needle) is mandatory and has to be submitted tothe CPCT central sequencing facility, together with a 10 ml blood sample for determining patient's germline DNA background variation. On this specimen, whole genome sequencing and biomarker analyses will be performed once a cohort is completed.

In principle, tumor biopsies should only be obtained after verification of drug-specific eligibility and patient enrolment. There may however be cases in which this would delay treatment initiation more than desirable; in such cases, it is allowed to obtain the biopsy during screening. Similarly, to ensure timely drug delivery, in exceptional cases patients may be registered on-study before all drug-specific eligibility criteria have been assessed to ensure timely drug delivery. Before the actual start of treatment however all drug-specific eligibility criteria should have been verified.

8.3 On treatment evaluation

During treatment, patients will be followed according to standard of care, unless otherwise specified in the drug-specific study manual. Supportive care will be administered according to the available guidelines for each specific drug as described in the package insert or local institutional guidelines. Management of side effects will be performed according to institutional standards of care informed by the package insert for each drug. Treatment-related grade ≥3 adverse events will be documented according to CTCAE v4.03, (including start / stop dates, relationship to study drug, action taken and outcome) and followed up until 1 month after the last administration of study drug. Subjects can be asked for an optional on-treatment tumor biopsy for research purposes.

8.4 Liquid biopsy and biomarker evaluation

Optional blood samples for sequencing of circulating tumor DNA (ctDNA) and/or biomarker investigation will be taken in selected patients with certain treatments. Samples are preferably combined with baseline or routine laboratory examinations. The blood sample will for instance be used to monitor treatment efficacy and determine the patient's mutational profile in ctDNA. The blood samples can be collected at the treating hospital and will be sent to the Netherlands Cancer Center - Antoni van Leeuwenhoek hospital for analysis and storage.

8.5 Fecal sampling

Patients receiving immunotherapy will be asked to collect fecal samples three times during treatment. The first sample is to be collected in the 24 hours before their visit to the hospital prior to start of the treatment, the second sample after 2 months of treatment and the third sample as soon as progressive disease is determined. The samples can be stored at room temperature and must be sent to the NKI Biobank by mail within 30 days, together with a short questionnaire on the fecal collection. The patient will receive detailed sampling instruction for this. The fecal samples are collected for storage in the Biobank of the sponsor (NKI-AvL) for future biomarker research. The patient is also asked to track food and nutritional supplement intake in the period prior to fecal sampling by use of a questionnaire. As the fecal collection procedure is relatively simple and since the stool can be sampled at home, it is expected that the extra burden for the patient related to the fecal sampling is low.

8.6 Response assessment

For the purposes of this study, patients should be initially assessed for response at 2 months following first treatment and re-evaluated for response 2 months thereafter. If the patient continues on protocol-specified treatment beyond 6 months, then response assessment should be performed every 3 months until tumor progression (i.e., response evaluation will take place at 2, 4, 6, 9, 12, 15 etc. months after treatment initiation). Additional imaging or studies may be done at any time if clinically indicated by symptoms, physical exam, or tumor markers.

For patients with multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, IMWG response criteria [23] and CHESON/Lugano guidelines [24] will be used, resp. For patients with primary brain tumors, RANO criteria will be used [25]. For patients with solid tumors other than primary brain tumors, response and progression will be evaluated using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [26] and / or GCIG criteria in case of CA125-based evaluation for patients with ovarian cancer[16, 17]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Since this is a non-randomized trial where response is a primary endpoint, confirmation of PR and CR is required (≥30 days after the first documentation of PR or CR) and absence of disease progression for ≥16 weeks has to be measured ≥2x and ≥28 days apart. **Physician-reported assessment of response and progression according to protocol specified response criteria will be accepted for this study. Documentation of representative tumor**

measurements to confirm response or progression is required. Summaries of the listed response criteria can be found in the protocol appendices.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression and an assessment of the benefit/risk of continuing with study drug must be documented. Subjects should continue to receive monitoring according to the on-treatment assessments.

8.7 Follow up after treatment

After discontinuation of the study treatment, patients will be followed up for:

- Disease progression: only for patients who discontinued study treatment for other reasons than disease progression, clinical deterioration or death. Response evaluations should be performed at the regular interval (at every 8 weeks during the first three response evaluations and every 12 weeks thereafter; in immunotherapy patients the treatment-interruption follow-up scheme can be followed).
- Adverse events: CTCAE version 4.03 grade ≥ 3 or serious adverse events will be collected up to 30 days after the last study drug administration.
- Overall survival: every 6 months until death or loss to follow up, up to 2 years after the last treatment of the last patient in DRUP. This may be through a telephone call, a physical visit from the patient to the trial site, or by a check of medical records.

8.8 Treatment duration and withdrawal of individual subjects

Study treatment may continue until progressive disease, unacceptable treatment-related toxicity, death, pregnancy, consent withdrawal or withdrawal from the study at the discretion of the investigator.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.9 Replacement non-evaluable patients

Patients are considered to be evaluable if they have received at least 1 cycle of treatment in case of oral medication / 1 treatment administration in case of intravenous medication with a cycle length of 4 weeks/ 2 treatment administrations in case of intravenous medication with

cycle length < 4 weeks, and if response is radiologically or clinically evaluable (at the treating physician's discretion). Non-evaluable patients will be replaced.

9. SAFETY REPORTING

9.1 AEs, SAEs and SUSARs

9.1.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to study treatment. All grade ≥3 adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded, unless the adverse event is not related to study drugs or study procedures.

9.1.2 Serious adverse events (SAEs)

A serious adverse event (SAE) is an AE occurring during any trial phase (i.e. run-in, treatment, washout, follow-up), and at any dose of the investigational product, that fulfils 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
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above)

Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as ‘serious’, UNLESS at least one of the following exceptions are met:

- the admission is pre-planned (e.g. elective or scheduled surgery, documented in the patient’s file);
- hospitalization for technical (e.g. study drug administration), practical or social reasons, in the absence of an adverse event.

All Serious Adverse Events (SAE) occurring from registration until 30 days after the last protocol treatment/administration should be documented and reported (the study specific SAE form should be used) within 24 hours to the NKI-AVL Safety Desk by email (**drugsafety@nki.nl**).

The Safety Officer must notify the study coordinators within 1 working day of any serious adverse event (as defined above) experienced by a patient. The AVL Safety Desk will report the SAE's to the relevant pharmaceutical company.

Serious adverse events occurring more than 30 days after the last study medication/treatment will NOT be reported unless the investigator feels that the event may have been caused by the study treatment or a protocol procedure, unless specified otherwise in the drug specific manual. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to use of the study drug.

Common toxicities observed for chemotherapy, and progressive disease and events secondary to progressive disease are generally excluded from reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

9.1.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse drug reaction is defined as: all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product)).

The study coordinator reviews any related SAE for expectedness. A SAE that meets the SUSAR criteria will be classified as SUSAR. The study coordinator must notify the AVL Safety Desk of the existence of this SUSAR within 24 hours using the SUSAR qualification form.

The sponsor will report electronically and without delay to EudraVigilance all relevant information about any SUSAR.

The period for the reporting of SUSARs by the sponsor to EudraVigilance will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction;

- In the case of non-fatal or non-life-threatening SUSARs, not later than **15 days** after the sponsor became aware of the reaction;
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than **7 days** after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report.

9.2 Grading and Relatedness of Adverse Events

Grading of Severity of an Adverse Event

Each AE will be graded for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), and these criteria must be used in grading the severity of AEs. The criteria can be found at:
http://ctep.cancer.gov/reporting/ctc.html

Grading of Severity of an Adverse Event Not Listed in Published Criteria

For those AEs which are not listed as part of the NCI CTCAE version 4.03, the same grading system should be used, where:

- Mild corresponds to an event not resulting in disability or incapacity and which resolves without intervention
- Moderate corresponds to an event not resulting in disability or incapacity but which requires intervention
- Severe corresponds to an event resulting in temporary disability or incapacity and which requires intervention
- Life-threatening corresponds to an event in which the patient was at risk of death at the time of the event
- Fatal corresponds to an event that results in the death of the patient

Relatedness to Study Drug

The Participating Site Investigator must attempt to determine if an AE is in some way related to the use of the study drug and define an attribution category. This relationship should be described as follows:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention. The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, or a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unrelated to the use of the study drug.
	Unlikely	The AE *is **doubtfully related*** to the intervention. Adverse event does not have temporal relationship to intervention, could readily have been produced by the subject's clinical state, could have been due to environmental or other interventions, does not follow known pattern of response to intervention, does not reappear or worsen with reintroduction of intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention. The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug OR the event could be the effect of a concomitant medication
	Probable	The AE ***is likely related*** to the intervention. The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition OR the event cannot be the effect of a concomitant medication.
	Definite	The AE ***is clearly related*** to the intervention. The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug. The adverse event improves upon discontinuation of the study drug and reappears upon repeat expos

9.3 Follow-up of SAEs and SUSARs

Any serious and or unexpected adverse event should be medically well documented and the information should be available as soon as possible. All SAE's and SUSARs must be followed up until resolution or stabilization. New, relevant, information must be reported using the appropriate SAE form.

9.4 Exposure during pregnancy

Exposure during pregnancy relates to pregnancies where the fetus (from pre-embryo to birth) may have been exposed to study drug at any time during study participation. This applies to female study participants and female partners of male study participants.
Pregnancy, although not itself an SAE, must also be reported on a SAE report form within 24 hours of awareness of the pregnancy and/or exposure and be followed up to determine

outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Should a woman become pregnant or suspect she is pregnant while participating in this study or if she is the partner of a male participant in this study and becomes pregnant while he is participating in this study, she should inform her or her partner's treating physician immediately as well as her obstetrician. Women who become pregnant must immediately discontinue treatment with any study therapy.

9.5 Annual safety report

The sponsor shall submit annually through CTIS to all Member States concerned a report on the safety of each investigational medicinal product used in the clinical trial.

9.6 Temporary halt for reasons of subject safety

The sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will submit the notification through CTIS without undue delay of a temporary halt, but not later than in 15 days of the date of the temporary halt, including the reason for such an action. The study will be suspended pending a further positive decision by the concerned member state. The investigator will take care that all subjects are kept informed.

9.7 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition, the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than **7 days** from the date the measures have been taken.

10. STATISTICAL ANALYSIS

10.1 Purpose

The primary objective of this study of multiple parallel cohorts is to describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs used for treatment of patients with advanced solid tumors, multiple myeloma or non-Hodgkin lymphoma with a molecular variant known to be a drug target or to predict sensitivity to a drug. The primary outcome interest is anti-tumor activity, as assessed by objective response or stable disease at 16 weeks (measured ≥2x and ≥28 days apart) from initiation of study drug treatment. For solid tumor patients, response is defined as complete or partial response by RECIST or RANO for patients with primary brain tumors [25], and / or GCIG criteria in case of CA125-based evaluation for *ovarian* cancer [16, 17]). For patients with multiple myeloma, response is defined according to the International uniform response criteria for multiple myeloma [23]. For patients with non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, response is defined according to the Lugano criteria [24]. Serious and study treatment related ≥grade 3 adverse events will be recorded and toxicity will be described using the NCI CTCAE v. 4.03 criteria.

10.2 Sample size stage I and II

Each tumor type/variant/drug treatment will define a separate cohort, and each cohort will be monitored using a Simon-like two-stage ‘admissible’ monitoring plan [18, 19] to identify tumor/variant/drug cohorts with evidence of activity. For purposes of cohort definition, the ‘variant’ category will be defined at the level of the gene that harbors the mutation or overexpression; e.g., EGFR mutant will be defined as the ‘variant’ for purposes of cohort definition and will include all detected EGFR mutations. Admissible designs lie between MiniMax and Optimal designs and have good characteristics of both (i.e. small maximum sample size, and low expected sample size under the null hypothesis of low activity). A true response rate of less than 10% will be considered of no clinical interest. A response rate of 30% or more will be considered of sufficient interest to warrant further study in a confirmatory trial (see: stage III). If there are 0 responses (defined as ‘response’ individually per criteria, or as disease control (absence of disease progression) for at least 16 weeks measured ≥2x and ≥28 days apart) in the first 8 participants in a cohort, the cohort will be closed. Otherwise, an additional 16 participants will be included in the cohort. Four or fewer responses out of 24 will suggest a lack of activity, while 5 or more responses will suggest that further investigation of the drug in the tumor/variant cohort is warranted. This monitoring rule has 85% power and an alpha error rate of 7.8%. These operating characteristics were selected to represent a

reasonable compromise between high power, low false positive rates, and desire for small sample sizes, especially in stage 1.

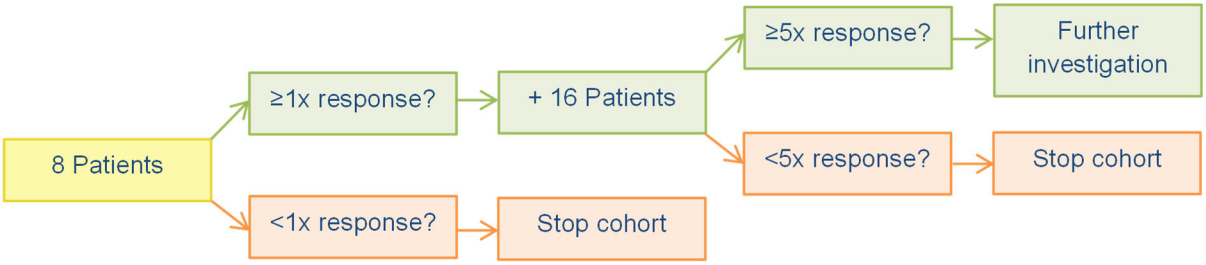

Figure 2: number of patients per cohort. Cohorts are defined by histologic tumor type, molecular tumor profile and study drug.

10.3 Sample size stage III

If in a stage II cohort 5 or more patients respond to the drug, this suggests a signal of activity, and further investigation is warranted. After consultation with the manufacturer, an expansion cohort may be opened in stage III. In the expansion cohort, patients with the same molecular variant, histological tumor type and drug are included. The aim is to confirm the clinical benefit rate that was observed in stage II, with a statistical power of 80-95% (depending on the clinical benefit rate observed in stage II). For each stage III cohort, the power calculation will be included in the drug specific manual.

10.4 Analysis plan

For each accruing cohort, accrual and responses will be monitored in real time. If a cohort fails to enrol ≥1 patient per 3 months in stage I or II, the cohort may be closed and replaced by a new cohort. When an individual cohort terminates accrual early or completes accrual, patient characteristics, response and toxicity data will be summarized descriptively with tabulations, rates and confidence intervals. Progression-free survival, overall survival and duration of time on treatment will also be summarized descriptively. Cohorts which have terminated accrual early or completed accrual may be combined for exploratory analyses, which will then be based on treatment efficacy when pooling patients with (i) the same genotype and study drug regardless of histology, or (ii) the same histology and study drug regardless of genotype (only if similar treatment efficacy may be expected based on pathway analyses, i.e. different mutations within the same oncogenic pathway)*. Such cohorts may be analyzed jointly, using, for example, logistic regression to examine possible differential or common effects of tumor type and/or variant. These analyses will be considered exploratory and interpreted with caution. The IDMC (who will be blinded for response rates in individual cohorts) will be consulted for advice on closure and pooling of cohorts. Please refer to the section ‘Data release and Independent Data Monitoring Committee’ for additional information.

Patients from the Netherlands, the United States and possibly other countries will be included in similar but independent protocols (DRUP protocol for the Netherlands and TAPUR for the United States; other partner-studies (such as the Canadian CAPTUR initiative) are being set-up at the time of writing). Data between these protocols can be exchanged to ensure sufficient patient numbers for analyses of efficacy in every cohort.

* For certain drugs that are expected to be effective in a pan-tumor-type matter (such as immunotherapy), cohorts of the same drug and tumor profile will also be analyzed jointly, regardless of the number of participants in each individual cohort. For immunotherapy, a pre-planned subgroup analyses will be performed for patients with a mutational load (missense mutational burden) >290.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study is to be conducted according to the international standards of Good Clinical Practice, in full conformance with the “Declaration of Helsinki” (latest amendment), the European Clinical Trial Regulation (ECTR), the Dutch laws and regulations and with the W.M.O. (“Wet Medisch-wetenschappelijk Onderzoek met mensen”) in particular. Institutional research policies and procedures will also be followed. Review of the protocol and consent form by the accredited METC will be obtained and documentation of METC approval and the approved consent form will be provided to each participating site. Each participating site will obtain local approval from their respective Board of Directors prior to enrollment of patients and submission of patient data.

11.2 Recruitment and consent

Patients will be recruited in the out-patient clinic of participating centers. Before patients agree to participation in this trial, they will be provided with written information (Patient Information Sheet). It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Once the essential information has been provided to the patient and the investigator is satisfied with the candidate’s understanding of the implication of participating in this study, the subject will be asked to give consent by signing and dating the informed consent form in the presence of the (sub)investigator. The informed consent must be obtained before initiation of any study specific procedures, including specific screening procedures. Patients have the right to withdraw from the study at any time, without giving an explanation and without prejudice to their subsequent care.
The Informed Consent Form as well as the Patient Information Sheet must be prospectively approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) and must be in compliance with Good Clinical Practice, local regulatory requirements and legal requirements. The investigator will retain the original of each subject’s signed Informed Consent Form.

11.3 Compensation for injury

The Investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research

subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Patient registration

Patient registration will only be accepted from authorized investigators or through their authorized data manager or authorized staff member. A patient can be registered only after treatment advice has been provided by the study coordinators, and after subsequent signing of Informed Consent and verification of eligibility. Registration will be performed online via Alea: https://www.tenalea.com/nkiavl/alea/

12.2 Forms and procedures for collecting data

A sequential patient identification number or code will be allocated to patients. This number will be used for identification of patient data and patient material, and will be handled confidentially and if possible anonymously. When it is necessary to trace data or material to an individual subject, we will use a subject identification number list to link the data or material to the subject. The code is based on the study center number, with a sequence of enrolment within the center: DRUP-01-xx-xxxx. The key to the code will be safeguarded by the coordinating investigator and the principal investigator of each center.

The handling of personal data complies with the General Data Protection Regulation (EU GDPR, in Dutch: Algemene Verordening Gegevensbescherming (AVG)).

Data for this study will be captured on electronic Case Report Forms (eCRFs).
Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data in the eCRFs. Data reported in the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification code.

The CRF must be completed by the investigator or assigned/delegated Local Data Manager as soon as the requested information is available. The goal will be to complete the relevant sections of the CRF as soon as possible but no later than two months after the data are available, with the exception of response evaluation measurements, which should be recorded in the eCRF within two weeks after the actual response evaluation. The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the Central Data Center by the responsible investigator before the start of the study. In all cases the investigator remains responsible for the content of the completed CRFs.

After completion of the CRFs the monitor will perform source document verification as described in the monitoring plan. The Central Data Center will check and process the answers from the investigator or Local Data Manager. Other irregularities found during this process will be queried as well. Queries must be answered within a reasonable time frame (the goal is within 6 weeks). When a CRF of a specific patient is complete and contains no inconsistencies or irregularities the CRF will be considered “clean” and will not be changed anymore.

12.3 Handling of data and data protection

Data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. When personal data are transferred from the EU to countries outside the EU (‘third countries’) the level of protection ensured in the EU by the General Data Protection Regulation should not be undermined. In any event, transfers to third countries may only be carried out in full compliance with the GDPR. In case data (including any biological samples) will be transferred outside the EU, no identifiers that can directly link the data or sample to the study subject will be present. Measures are taken to ensure maintenance of the same level of protection as within the EU.

12.4 Clinical trial master file and data archiving

The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file shall, at all times, contain the essential documents relating to the clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated.
The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other EU law requires archiving for a longer period. The medical files of subjects shall be archived in accordance with national law. The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request.

12.5 Storage of biological samples

Biological samples from non-Multiple Myeloma patients are sent to Hartwig Medical Foundation, who then sends these in batch to the Biobank of the sponsor for storage until analysis. Once the materials need to be analyzed they are sent to Hartwig Medical Foundation for WGS/RNA sequencing.
Biological samples from Multiple Myeloma patients are sent to the Erasmus MC and will be stored there until final analysis.

Residual material after WGS/RNA sequencing will be sent back to the Biobank of the sponsor and stored for 115 years for further research to causes and diagnosis of cancer or development of new treatments.

12.6 Monitoring and Quality Assurance

Considering the guideline by the NFU (Dutch Federation of University Medical Centers) about quality insurance in human research ("Kwaliteitsborging van mensgebonden onderzoek 2.0"), we qualify the risk of this study as 'low'. According to this low risk a 'low intensive monitoring' is advised, which will be performed by a monitor. Further details will be described within the monitor plan.

12.7 Reporting of serious breaches

The sponsor will notify the Member States concerned about a serious breach of the Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than **seven days** of becoming aware of that breach.

12.8 Notification of the start and the end of the recruitment

The sponsor will notify through CTIS within 15 days each Member State concerned of:

- the start of the clinical trial in relation to that Member State
- the first visit of the first subject in relation to that Member State
- the end of the recruitment of subjects for the clinical trial in that Member State

12.9 Substantial modifications

A 'substantial modification is defined as "any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 of the CTR and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial".
The sponsor will submit and obtain approval for substantial modifications to the original approved documents via CTIS.

12.10 Temporary halt and (prematurely) end of study

The sponsor will notify within 15 days each Member State concerned of the end of a clinical trial in relation to that Member State through CTIS. The end of the study is defined as the last patient's last visit.

The sponsor will notify through CTIS within 15 days each Member State concerned of a temporary halt of a clinical trial in all Member States concerned for reasons not affecting the benefit-risk balance.

In accordance to article 38 of the CTR, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The temporary halt or early termination of a clinical trial for reasons of a change of the benefit-risk balance will be notified to the Member States concerned through the EU portal CTIS without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures. The restart of the clinical trial following a temporary halt as referred to in paragraph 1 shall be deemed to be a substantial modification subject to the authorization procedure laid down in Chapter III of the CTR.

12.11 Summary of the results

Within one year after the end of the study, the investigator/sponsor will submit through CTIS a summary of the results of the study. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V .

12.12 Data release and Independent Data Monitoring Committee

The DRUP study coordinators will appoint an independent data monitoring committee (IDMC) comprised of one Chair, one statistician, three clinical oncologists, one pathologist and one geneticist who are not involved in conducting the study. The IDMC will be blinded for response rates in individual cohorts, and will be consulted for advice on closure and pooling of cohorts: if a cohort fails to enroll ≥1 patient per 3 months, the cohort may be closed and replaced by a new cohort. Cohorts which have terminated accrual early or completed accrual may be combined for exploratory analyses, which will then be based on treatment efficacy when pooling patients with (i) the same genotype and study drug regardless of histology, or (ii) the same histology and study drug regardless of genotype (only if similar treatment efficacy may be expected based on pathway analyses, i.e. different mutations within the same oncogenic pathway). Please refer to the IDMC charter (document D3 of the protocol submission dossier) for further details.

12.13 Publication policy

The central principle investigators decide when trial results will be published, who will be authors, and in which order. Authorship will include at least the central principal investigators, the trial coordinators and any other person that made an significant contribution (as decided by the principal investigators). General publication policy:

- Individual case reports
  Individual case reports will in principle not be published. If in exceptional cases publication is deemed to be clinically relevant, the IDMC may be consulted for advice.
- Individual and pooled cohort results
  Whenever a cohort has completed or terminated accrual, individual- and pooled cohort results (as described in the Analysis Plan) will be offered to a peer-reviewed journal for publication. Collaborating centers who have enrolled ≥20% of patients included in the publication will be invited to propose one author. Collaborating centers who have enrolled 1 to 20% of patients included in the publication will be mentioned in the acknowledgements.
- Overall, cohort-transcending study results
  At least twice per year and / or at the end of the trial, the central principle investigators (in consultation with the steering committee) will evaluate whether general study results (such as overall submission, accrual, toxicity and efficacy analyses, as well as concordance between historic and pre-treatment mutational tumor profiles) should be offered to a peer-reviewed journal for publication. Collaborating centers who have enrolled ≥20% of patients included in the publication will be invited to propose one author. Collaborating centers who have enrolled 1 to 20% of patients included in the publication will be mentioned in the acknowledgements.
- Other study results: during or after the trial, new research question (that were not contained within the study's objectives) may arise. Whether or not the DRUP data and material can be used for such purposes will be at the central principal investigators discretion following consensus.

Double-check on data derived from the central screening-and enrolment log: if data will be used for formal study reports or publications, data will be retrieved and checked independently by two (sub)investigators.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action and efficacy in human beings

Only commercially available, targeted anti-cancer drugs will be included in this trial. The mechanism of action, efficacy and safety of these drugs has been tested extensively.

b. Pharmacokinetic considerations

Study drugs will be used for treatment of patients with advanced cancers that do not fall within the registered indication of these drugs. Since pharmacokinetics might differ between different tumor types, safety will be systematically recorded and analyzed.

c. Study population

Patients with advanced cancer without any standard-of-care treatment options will be included in this trial. This trial will facilitate access to potentially effective anti-cancer drugs to which they would otherwise not have access.

d. Interaction with other products

Patient will in principle be treated with monotherapy or approved combinations of study drugs, and are not eligible if they receive any other type of anti-cancer treatment (see in- and exclusion criteria for further details). Interactions with other anti-cancer drugs are therefore not expected. Prohibited co-medication will be listed in the drug-specific study manual of every study drug, to further avoid undesirable interactions.

e. Can effects be predicted and managed?

Yes, since all study drugs are already being used in daily practice, side-effects can be predicted and managed accordingly.

13.2 Potential protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Examples of situations in which the study team may prospectively consider to grant a deviation include:

- Not clinically-significant deviations from eligibility criteria. For example: not clinically-significant lab measurement deviations or administering study medication via feeding tube in patients who are unable to swallow the medication (provided that administering this drug via a tube has been previously studied).
- Baseline tests that are minimally out-of-window.

- Treatment exceptions, such as additional dose reductions, radiotherapy during treatment or treatment beyond evaluability or progression.
- Testing exceptions such as not performing the obligatory pre-treatment biopsy due to safety issues.

Deviations are divided into four categories as depicted in table 1.

Table 1 – Four categories of protocol deviations

Deviation type	**Description**
Eligibility criteria	Deviation for inclusion/exclusion criteria. Examples: - Laboratory requirements - Administer medication via feeding tube in patients who are not able to swallow medication
Out-of-window testing	Deviation for tests, either for enrollment purposes or during the trial, outside the protocol specified window. Example: - Time between pre-treatment biopsy and start study treatment of ≥ 2 months
Treatment exception	Deviation for treatment intervention outside the protocol guidelines. Examples: - Radiotherapy during study treatment - Treatment beyond progression
Testing exception	Deviation for research test outside the protocol guidelines. Example: - Pre-treatment biopsy

Patients are required to meet both general and drug specific eligibility criteria to protect them from potential study risks, to ensure safety and the highest quality of outcome data. In addition, study specific criteria solely for scientific purposes, such as pretreatment tumor biopsies and blood draws, are part of the trial.

Although eligibility criteria are an essential component of each trial, in such a basket like study of personalized medicine, DRUP acknowledges that some eligibility criteria are sometimes matter of debate, especially because of the patient population and the use of already approved and widely prescribed drugs. Therefore, granting a protocol deviation can be considered if a request about eligibility criteria is received by the study team to support a more personalized approach. The aim of this procedure is to make this trial more inclusive for patients with potential benefit based on already approved and widely prescribed drugs and a potential favorable molecular profile.

If a patient does not meet all eligibility criteria, the study team may prospectively decide to allow enrollment or study drug continuation of the patient, or to allow protocol deviations

concerning specific study procedures. The procedure is as follows:

1. Once a request for a protocol deviation is received by the study team, the study team (coordinating sub-investigators) performs an initial assessment of the request.
    a. If, from previous experience, it is known that a deviation request will not or cannot be honored by the Principle Investigators, the study team informs the treating physician that the protocol deviation is not allowed.
    b. If the request seems reasonable and, from previous experience or after checking study drug-specific information, will most likely not compromise patient safety and study results, the request can be eligible for submission to the Principle Investigators. In that case, the study team first collects all relevant information from the patients' treating physician. This may include:
        i. *Subject of waiver request*
        ii. *Oncological medical history and other relevant medical history*
        iii. *Concurrent medication*
        iv. *Previous lab values*
        v. *Opinion of the treating physician as to why the waiver should be warranted*
        vi. *Relevant information from Investigator Brochure and/or Summary of Product Characteristics on the specific situation*
        vii. *Relevant literature on the specific situation*

2. Once all relevant information has been collected, the case is submitted to the Principle Investigators.

3. The Principle Investigators subsequently assess the case and the request.
    a. In case they deem the request to be reasonable, safe and in the best interest of the patient and without serious risk of compromising study outcomes, a protocol waiver is approved.
    For approval, agreement between the Principle Investigators is required.
    b. In case they deem the request to be either not reasonable, not safe, not in the best interest of the patient, or a potential risk to the study outcomes, a protocol deviation request is declined.
    c. In specific cases the PIs may consult specific experts for advice, this may be the manufacturer or medical experts from academic institutions.

4. In case situation 3c applies, the case is resubmitted to the Principle Investigators once the study team has obtained the required additional information and/or advice. The Principle Investigators then reassess the request, after which situation 3a or 3b will apply.

5. In case a protocol deviation is granted, the study team informs the treating physician per email that the patient can participate (or continue participation) in the trial. The study team demands that the patient is clearly informed on the potential risks and benefits when the protocol deviation is allowed by the study team and requests the treating physician to make note of this in the electronic patient file.

6. The study team writes a *Note To File*, in which the situation is explained, including the considerations of the study team through which the decision was reached.
    a. The Note to File is subsequently submitted to the coordinating Principle Investigator for sign-off.
    b. The study team files the signed Note to File in the Trial Master File, and updates the Protocol Deviation log.
    c. The treating site receives a copy of the signed Note to File and files it in their Investigator Site File.

7. During the quarterly meetings with the IDMC, every protocol deviation for which permission was granted in the past period is reviewed to ensure compliance with the aforementioned procedure and protect patient safety and validity of study results

8. When an identical protocol deviation is granted for the second time, the protocol will be re-assessed and if possible amended accordingly to prevent such protocol deviations in the future.

13.3 Synthesis

All participants in this study will have advanced cancer for which no standard treatment is available or will have exhausted standard treatment options. As such, any further treatment, whether with commercially available drugs prescribed off label or with investigational drugs, must be considered investigational. The potential benefit to patients from participation in this study is that the strategy of selecting a treatment based on the genomic profile of their tumor will result in tumor regression or stabilization when no other therapies known to be effective are available. The potential risks to patients are that the selected therapy will be ineffective and that treatment-related toxicities will diminish their overall quality of life. As only

commercially available drugs will be used in this study and dosing will be initiated according to the official drug label, it is expected that patients participating in this study will not be exposed to greater risk of treatment-related toxicities than patients receiving the drug for an approved use. All patients will be informed of the potential benefits and risks of study participation and of alternatives to study participation.

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Appendix 1: Study calendar

Procedure	Screening[6]	Following inclusion	During treatment [7]	Off Study
Sign Informed consent	x			
Submission of results of genomic- or protein expression test on archival tumor tissue [1]	x			
Demographics	x			
Medical history	x			
Concurrent meds	x		x	
Adverse events	x		x	x
Physical exam	x		x [8]	
Vital signs	x		x [8]	
Performance Status	x		x [8]	x
CBC w/diff, plts	x		x [8]	
Serum chemistry [2]	x		x [8]	
Serum pregnancy Test	x			
EKG, LVEF/LVSF by MUGA or ECHO [3]	x			
Tumor measurements and (radiologic) response evaluations	x		x [9]	
Fecal sample for biomarker analyses[10]		Mandatory		
Fresh frozen tumor biopsy specimen and blood (and saliva, only for MM patients) sample for biomarker analyses[4]		Mandatory	Optional	Optional
Treatment administration [5]			x [7]	

1. Description of type of profiling test, test results and specimen used for testing (e.g., fresh frozen vs. paraffin block, specimen obtained from primary tumor vs. metastatic deposit, date of specimen acquisition) should be submitted.
2. Albumin, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, LDH, potassium, AST, ALT, sodium, PT, APTT
3. As clinically indicated or if required by drug-specific inclusion/exclusion criteria.
4. A fresh frozen tumor biopsy specimen and blood sample (and saliva sample, only for multiple myeloma (MM) patients) taken according CPCT standard operating procedures has to be submitted to the central sequencing facility of the CPCT before the start of study treatment. Submission of a post-treatment tumor biopsy specimen is optional. Biopsies will be used for biomarker analyses, including (but not limited to) next generation sequencing.
5. Treatment with drugs provided in this protocol must in principle be initiated within 28 days of provision of the molecular tumor board recommendation to the treating physician (there may be exceptional cases where this is not feasible; slots will however in principle not be reserved for longer). Initial drug dose and schedule will be according to the approved package insert for the drug product. Any necessary dose modifications will be at the discretion of the treating physician. Dose modification in the package label will be followed if clinically appropriate.
6. Screening should be performed ≤28 days prior to treatment initiation.
7. Agent-specific schedule and dosing depends on which drug has been matched to patient and can be found in the drug-specific study manual of each drug.
8. According to standard clinical practice or as clinically indicated, or according to drug specific requirements as provided in the drug-specific study manual of each drug.
9. Tumor measurements and (radiologic) response evaluations, according to the applicable response evaluation criteria as described in the study protocol, will be initially measured within 2 months of initiation of study drug treatment. Tumor assessments will be repeated every 2 months for the first 6 months on treatment and every 3 months thereafter.
10. Only mandatory for patients receiving immunotherapy in stage III (expansion cohort)

Appendix 2: Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1

RECIST Definitions:

- Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with the selected agent.
- Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle (one month for oral agents administered continuously) of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)
- Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy (one month for oral agents administered continuously), and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters:

- Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
    - *Note:* Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.
- Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

- *Note:* Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic' lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Target lesions. Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
- Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease:
All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Conventional CT and MRI. Measurability of lesions on CT scan is defined based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in

tumor types, such as germ cell tumors, where known residual benign tumors can remain).

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
    - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity
    - *Note:* A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria for solid tumors:

1. Evaluation of Target Lesions
    - Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. Evaluation of Non-Target Lesions
   - Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
     Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
   - Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
   - Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

   NB Since this is a non-randomized trial where response is a primary endpoint, confirmation of PR and CR is required (≥30 days after the first documentation of PR or CR) and absence of disease progression for ≥16 weeks has to be measured ≥2x and ≥28 days apart.

3. Evaluation of Best Overall Response
   The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For solid tumor patients with measurable disease:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD

For solid tumor patients with non-measurable disease:

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
• 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response:

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival:

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Duration of time on treatment:

Duration of time on treatment is defined as the duration of time from the start of treatment (date of administration of first dose of study drug) to the date of discontinuation of study drug treatment.

Appendix 3: Response evaluation for patients with non-Hodgkin lymphoma or T-cell prolymphocytic leukemia (Lugano Criteria)

For patients with non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, response and progression will be evaluated in this study using the revised international working group guidelines (Lugano classification) [24].

Schedule of Evaluations

A whole body or limited whole body PET/CT scan or a PET and CT of neck, chest, abdomen and pelvis will be performed after completion of 2 cycles of therapy for initial response assessment and repeated after four cycles of treatment. Following this, a CT of neck, chest, abdomen and pelvis will be performed after every 3 cycles of treatment until completion of 1 year of treatment. After completion of 1 year of treatment, additional scans are to be performed at the discretion of the treating physician at the time of suspected disease progression or off study evaluation.

Measurement of Treatment/Intervention Effect

Target Lesions & Target Lymph Nodes

- Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.
- Non-measured lesions: These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

Metabolic Response (Assessment after Cycles 2 and 4)

Complete Metabolic Response (CMR):

1. Deauville Score of 1, 2, or 3 with or without a residual mass or nodal lesion:
   1, no FDG uptake above background;
   2, FDG uptake ≤ mediastinum;

3, FDG uptake > mediastinum but ≤ liver;
4, FDG uptake moderately > liver;
5, FDG uptake markedly higher than liver and/or new lesions;
X, new areas of uptake unlikely to be related to lymphoma.

2. In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
3. No new lesions.
4. No evidence of FDG avid disease in marrow unless as noted in (2).

Partial Metabolic Response (PMR):

1. Deauville Score of 4 or 5 with reduced uptake compared to baseline and residual mass (es) of any size.
2. No new lesions.
3. Residual marrow uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with a BM biopsy.

No Metabolic Response:

1. Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment.
2. No new lesions.
3. No change in marrow uptake from baseline.

Progressive Metabolic Disease (PMD):

1. Score 4 or 5 with an increase in intensity of uptake from baseline.
2. New FDG-avid foci consistent with lymphoma.
3. New or recurrent FDG-avid foci in the bone marrow.

<u>Follow-Up Assessment (After cycle 7 and thereafter)</u>

Progressive Disease (PD): At least one of the following must be true:

1. For previously measured lesions: An individual node/lesion must be abnormal with: LDi>1.5 cm AND increase by ≥ 50% from PPD nadir AND an increase in LDi or SDi from nadir by 0.5 cm for lesions ≤ 2 cm or 1.0 cm for lesions > 2 cm.
2. New lesions: A new node > 1.5 cm in any axis OR a new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma.
3. New or clear progression of pre-existing unmeasured lesions.
4. New or recurrent splenomegaly: In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
5. New or recurrent marrow involvement.

Appendix 4: Response evaluation for patients with multiple myeloma (IMWG uniform response criteria)

Response and progression will be evaluated in this study using the International Myeloma Working Group uniform response criteria. The International Myeloma Working Group has also endorsed the inclusion of minimal response (MR) for relapsed/refractory myeloma as adapted from the European Group for Blood and Marrow Transplantation (EBMT). Therefore, MRs will be evaluated as part of this study, as well (29, 30).

Schedule of Evaluations

For the purposes of this study, patients should be reevaluated for biochemical response after completion of 2 treatment cycles, then after 4 treatment cycles and after every 3 treatment cycles thereafter until disease progression, death, the start of a new treatment or withdrawal of consent. The start of a new treatment cycle does NOT need to be delayed awaiting the results of the disease assessment.

For patients with non-secretory disease who are being followed for response by serial bone marrow examinations (must have ≥30% involvement of the marrow space prior to treatment), a repeat bone marrow aspirate and biopsy should be performed once every 2 cycles (prior to registration, cycles 3, and 5, etc), and every 12 weeks thereafter until disease progression, death or withdrawal of consent. In these cases, the same method to assess marrow burden of disease should be used throughout treatment.

For patients with measurable extramedullary plasmacytomas, patients should be reevaluated after completion of cycles 2 and 4 of treatment and then every 12 weeks thereafter until disease progression, death, withdrawal of consent or the start of new treatment, utilizing the same imaging modality used at initial screening (CT, MRI or PET/CT).

Definitions of Measurable and Non-Measurable Disease

Measurable Disease

Disease assessments by serial monitoring of the monoclonal protein can be performed if the patient meets at least 1 of the following criteria:

1. Serum M protein≥1.0 g/dL and/or
2. Urine M protein≥200 mg/24 hours and/or
3. Involved serum free light chain≥10 mg/dL AND an abnormal serum free light chain ratio

Non-Measureable Disease

If a patient does not have measurable disease by one of the 3 above criteria, they can still be followed with serial bone marrow examinations for response, provided the baseline marrow burden of myeloma is at least 30%.

Guidelines for Evaluation of Measurable Disease

Measurement Methods:

- Determination of biochemical response requires a serum protein electrophoresis and immunofixation, 24-hour urine protein electrophoresis and immunofixation and serum free light chain test at each scheduled evaluation of response for all patients. Quantitative serum immunoglobulins and 24-hour urine light chain quantitation via nephelometry should not be used as a substitute for determining response. Additionally, measurement of an entire region of the serum protein electrophoresis cannot be used as a substitute for measurement of the M protein. For example, an IgA kappa M protein that falls within the beta region of the serum protein electrophoresis should not be monitored solely by assessment of the quantitative IgA level or measurement of the protein concentration in the entire beta region of the serum protein electrophoresis.
- For patients with measurable extramedullary plasmacytomas, the same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.
- For patients with non-secretory disease who are being followed for response by serial bone marrow examinations (must have ≥30% involvement of the marrow space prior to treatment), the same method to assess marrow burden of disease should be used throughout treatment. A repeat bone marrow is not required for confirmation of response under these circumstances.

Acceptable Modalities for Measurable Extramedullary Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

THE IMWG Uniform Response Criteria

International Myeloma Working Group (IMWG) Uniform Response Criteria + Definition of Minimal Response (MR) as Adopted from the EBMT Criteria.

The IMWG uniform response criteria will be used for determining response to therapy and progression of disease. Minimal response, as adapted from the EBMT, will also be assessed [REF]. Source documentation for all biochemical and radiographic evaluations of disease will be collected for confirmation of response and disease progression.

Response Category	Response Criteria	Response Criteria for Disease Measurable by Serum FLC Testing Only
Complete Response (CR)	Negative serum immunofixation and 24-hour urine immunofixation, disappearance of all extramedullary plasmacytomas (if present at baseline) and <5% plasma cells on repeat bone marrow examination.	All other criteria for CR met + normal serum free light chain ratio.
Stringent Complete Response (sCR)	All criteria for CR must be met + normal serum free light chain ratio + absence of clonal plasma cells on bone marrow examination by immunohistochemistry or 2- to 4-color flow cytometry.	All other criteria for sCR met + normal serum free light chain ratio.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable on immunofixation testing but not on electrophoresis OR ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours.	≥90% reduction in the difference between the involved and uninvolved serum free light chain level.
Partial Response (PR)	≥50% decrease in the serum M-protein + ≥90% reduction in the urine M-protein OR to <200 mg/24 hours +	≥50% reduction in the difference between the involved and uninvolved serum free light chain level.

	≥50% reduction in the size of extramedullary plasmacytomas (if present at baseline).*	
Minimal Response (MR)	25% - 49% decrease in the serum M-protein + 50 – 89% reduction in the urine M-protein + 25% – 49% reduction in the size of extramedullary plasmacytomas (if present at baseline) + no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).*	
Stable Disease (SD)	Not meeting criteria for CR, sCR, VGPR, PR, MR or progressive disease (PD)	
Progressive Disease (PD)	Increase of ≥25% from lowest response value (nadir)** in any of the following: 1) Serum M-protein (absolute increase must be ≥0.5 g/dL) AND/OR: 2) Urine M-protein (absolute increase must be ≥200 mg/24 hours) AND/OR: 3) For patients without a measurable serum or urine M-protein but measurable disease by serum free light chain testing: Difference between the involved and uninvolved serum free light chain level (absolute increase must be ≥10 mg/dL) AND/OR: 4) For patients without a measurable serum or urine M-component or serum free light chain level: % marrow involvement with myeloma (absolute increase must be ≥10%). Definite development of new bone lesions or extramedullary plasmacytomas or definite increase in the size of existing bone lesions or extramedullary plasmacytomas. Hypercalcemia (corrected serum calcium > 11.5 mg/dL) attributable to myeloma (e.g not due to omitted doses of biophosphonate).	

* For patients who do not have measurable disease by M-protein measurement or serum free light chain levels but ≥30% involvement of the marrow at baseline, a ≥50% reduction of bone marrow involvement is required to meet criteria for a PR.

** The lowest response value (nadir) does not have to be a value that has been confirmed by repeat measurement.

Appendix 5: Response evaluation for patients with primary brain tumors (RANO criteria)

General method of response assessment

Response to treatment is assessed on the basis of a set of target lesion(s) chosen before the first treatment administration (the complete list of target lesions must be reported on the initial measurement form before the start of treatment). These lesions must initially be measured in their two perpendicular dimensions, and these measurements must be repeated at each evaluation of the disease by the same method. Response evaluation is based on neuro-radiological imaging (MRI). For this protocol objective response (complete, partial response) and progression will be assessed by MRI. Objective response will only be assessed in patients not having undergone second surgery with complete removal of contrast enhancing lesions prior to study entry. For these patients measurable disease is required, which is defined as a clearly enhancing tumor with at two perpendicular diameters at entry equal or superior to 1 cm.

The contrast enhancing area will be considered as the basis for the tumor size assessment. Tumor size is defined as the product of the two largest perpendicular diameters. Only reductions in cross-sectional areas of 50% or more when calculating the response, the baseline scan must be used for initial comparison. In initially responding (≥ 50% reductions in cross-sectional areas) or stabilized (<50% reduction and < 25% increase in cross-sectional areas) patients, new scans must be compared to the nadir, this is the scan showing the maximum response (= minimum tumor size) during/after treatment. In assessing response, changes on T2 weighted images must be taken into consideration. For this protocol we are aiming at measuring quantitatively the FLAIR/T2 changes as well.

Definition of target lesions

Only the following lesions are eligible as target lesions:

- MRI contrast enhancing lesions with two perpendicular diameters of 10 mm or more visible on 2 or more axial slices which are 5 mm apart.
- Target lesion(s) must be measurable in two perpendicular diameters. In most patients, only one lesion will be present. In case of multifocal disease, a minimum of 2 lesions and maximum of 5 largest enlarging lesions will be chosen as target and the sum of the products of the perpendicular diameters will be determined. All other lesions than target lesions, if applicable, are assessed according to the same schedule. They are only taken into account in two situations:

- If one of them clearly progresses, the overall response to therapy will be evaluated as "progression", independent of the response of target lesions
- All lesions must have completely disappeared to report a "complete response". Adequate investigations must be carried out at each evaluation of the disease to detect eventual new lesions. If any new lesion is found, the response will be evaluated as "progression". Regardless of the status of enhancing lesions, if progressive lesions are observed on T2 weighted images or FLAIR images, the patient will be considered radiologically progressive, but treatment may continue if this is considered to be in the best interest of the patient and there are no signs or symptoms of clinical progression.

By definition, non-target lesions are those that do not meet the criteria for target lesion.

Evaluation of patient treated after re-operation

Postoperative changes on contrast enhanced neuro-imaging may interfere with disease evaluation. Within the first three days after surgery on MR imaging a thin linear enhancement may develop around the resection cavity, thereafter this enhancement may become thick and nodular. Enhancement of dura and meninges may be more pronounced, even within the first days. The postoperative linear enhancement may persist up to 3-6 months, dural and meningeal enhancement may last much longer. If MRI made within 48 hours after surgery shows enhancing lesions with a nodular or mass like appearance in areas showing tumor on the pre-operative scans this is highly suggestive of residual tumor. The use of diffusion-weighted MR imaging in the immediate postoperative MRI may help with the identification of ischemic areas around the surgical cavity that may show enhancement with further follow-up.

Schedule of disease evaluation

The initial assessment of disease (including measurement of all target lesions) must be performed in the 4 weeks preceding start of study treatment.

Response Assessment in Neuro-oncology (RANO) criteria [25]

RANO criteria were developed in response to the advances in imaging technology and current treatment practices in the era of anti-angiogenesis. The RANO criteria also place emphasis on the non-enhancing part of the tumor as shown on T2SE-weighted and FLAIR image sequences in contrast to the classical Macdonald criteria based on changes in area of enhancing lesions which is non-specific: the contrast area primarily reflects the passage of contrast material across the disrupted blood-tumor barrier. The standardized EORTC Brain Tumor Imaging Protocol may be used[27].

Definition of response

For this trial, the primary measure of response and progression will be determined by the locally assessed response according to the modified RANO criteria. All treatment decisions should be based on the modified RANO criteria. Follow up assessments will be done using both Macdonald (T1 plus contrast) and modified RANO (while considering T2/FLAIR). Response and progression will be assessed by both sets of criteria.

Target lesions are measured in their two largest perpendicular diameters. Their area is conventionally calculated as the product of these diameters. In case of multifocal disease with more than one target lesion, the total tumor size is calculated as the sum of the area of all target lesions.

Response is defined as follows according to the modified RANO criteria, which also consider T2 weighted and FLAIR images:

- Complete response (CR): Requires all of the following: 1) Complete disappearance of all enhancing measurable and non-measurable disease; 2) No new lesions; 3) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline 4) Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically.
- Partial response (PR): Requires all of the following: 1) Only reductions of cross-sectional areas of 50% or more will be considered a response; when calculating the response, the baseline MRI must be used for comparison ; 2) No progression of non-measurable disease; 3) No new lesions; 4) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline 5) Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
- Progressive disease (PD):
    - Progression is defined by any of the following: 1) ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over baseline if no decrease) on stable or increasing doses of corticosteroids; 2) ≥ 25% increase in sum of the products of perpendicular diameters of area's with abnormalities on FLAIR/T2 images compared to the nadir time point (point with the smallest FLAIR/T2 abnormalities, even if still improved as compared to baseline, and on stable or increasing dose of steroids 3) The appearance of any new lesions; 4) Clear progression of non-measurable lesions; 5) Definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose.

  - If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression

- Stable Disease: This occurs if the patients did not qualify for complete response, partial response, or progression (see below) and requires: 1) No meaningful change in the appearance of the FLAIR/T2 images compared to baseline or to the nadir (point with the smallest FLAIR/T2 abnormalities) if a decrease occurred. 2) The patient should be stable clinically. In the event the steroid dosage has been increased for new signs and symptoms without confirmation of disease progression on imaging, and further follow-up imaging shows that with hindsight this increase in steroids was indeed unequivocally needed due to disease progression, the date of progression will be the date steroids were increased.
- For patients operated at recurrence and without measurable or non-measurable disease post-surgery, any new appearance of tumor will qualify for PD. In case non measurable tumor is left after surgery i.e. tumor less than 10 mm, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment. Modest increase in the size of a non-target lesion is NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used as the date of progression. This implies that in case of gross total resection of the enhancing lesion, if at follow up minimal enhancement of unclear significance arises, treatment may continue until further follow-up gives unequivocal evidence of tumor follow-up.
- To ensure a homogeneous radiological evaluation, all MRI images will be centrally reviewed as a secondary analysis and specific study MRI protocol will be used.

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	<50% ↓ but <25% ↑	≥ 25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	≥ 25% ↑
New lesion	None	None	None	Present
Corticosteroids	None	Stable or ↓	Stable or ↓	Not applicable*
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓
Requirements for response	All	All	All	Any

*increase in steroids alone does not qualify for PD

Overall response

The overall response is evaluated at each assessment of the disease. If progressive disease exists in any lesion, or when a new lesion appears, then the overall result will be progressive disease. Progression in non-measurable lesions leading to define deterioration of the patient due to tumor bulk should be taken to indicate progression, regardless of what happens in measurable disease.

- Best overall response: best overall response is the best response designation recorded from the date of study inclusion until disease progression.
- Objective response: objective response includes best overall responses CR and PR.

Appendix 6: Response criteria incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG)

The Gynecological Cancer Intergroup has previously reached consensus regarding the criteria that should be used in clinical trial protocols to define progression-free survival after first-line therapy[1] as well as the criteria to define response to treatment in recurrent disease[2] using the serum marker CA 125, and have specified the situations where these criteria should be used (Table 1). However, the publications did not include detailed definitions nor were they written to accommodate the new version of Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.1) now available[3]. Thus, we recommend that the definitions described later in detail below are incorporated into clinical trial protocols to maintain consistency. The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated (Pujade-Lauraine, personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished. These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents. The GCIG recommends that for trials of relapsed ovarian cancer, the following definition for response according to CA 125 be used in addition to the updated RECIST 1.1[3] response criteria.

EVALUATION OF RESPONSE ACCORDING TO CA 125

Definition of Response

A CA 125 response is defined as at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment. To calculate CA 125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA 125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.

- Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4, 5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA 125 response results from both treatment modalities. CA 125 cannot distinguish between the effects of the 2 treatments.

The date when the CA 125 level is first reduced by 50% is the date of the CA 125 response. To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA 125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA 125 response and whose CA 125 level falls to within the reference range can be classified as CA 125 complete responders. In Tables 2 and 3 where CA 125 is stated as normalised or normal, means within the reference range. Patients who have a fall of CA 125 to within the reference range but whose initial CA 125 was less than twice the upper limit of the reference range have not had a CA 125 response and cannot therefore be classified as a CA 125 complete responder.

Evaluation of Response According to CA 125 in Patients Receiving First-Line Therapy
The CA 125 response definition was developed to evaluate response to chemotherapy in patients with recurrent ovarian cancer. If the patient has had combined modality therapy as part of their first-line therapy (eg, surgery and chemotherapy), CA125 response may be due to both or either treatments, and it should be clearly stated that CA125 cannot distinguish between the effects of the 2 treatments. It should be also be noted that for a patient to be classified as a complete responder according to RECIST, tumor marker levels such as CA 125 must be within the reference range.

Evaluation of Response According to CA 125 in Patients Receiving Maintenance or Consolidation Therapy
Patients whose CA 125 is greater than twice the upper limit of the reference range when they start maintenance or consolidation therapy can be evaluated using the GCIG CA 125 response definition. However, it should be noted that there are no data to validate the implications of achieving CA 125 response in this setting with respect to progression-free or overall survival. To prevent the prior therapy from interfering with the response assessment, we recommend that 2 pretreatment samples no more than 8 weeks apart are required

if test treatment is given as part of maintenance or consolidation therapy. For the test treatment to be evaluable according to CA 125, there should be no more than a 10% fall in CA 125 between the 2 pretreatment samples. The sample closest in time to the test therapy should be considered the pretreatment sample.

TABLE 2. Evaluation of best overall response in patients *without* initial measurable disease and who are evaluable by CA 125

CA 125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD†	Yes or No	PD	
Any	Any	Yes	PD	

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
†Unequivocal progression in nontarget lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Evaluation of Best Overall Response in Patients *Without* Initial Measurable Disease and Evaluable by CA 125

CA 125 may be used to evaluate response in patients without initial measurable disease either because no measurable disease is evident on radiological imaging or because appropriate imaging has not been performed as demonstrated in Table 2.

TABLE 3. Best overall response in patients with measurable disease and who are also evaluable by CA 125

Target Lesion*	Nontarget†	New Lesion	CA 125	Overall Best Response	
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days if response is primary end point
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-PD or NAE	No	Not PD	PR	
NAE	Non-PD	No	PR	PR	
PD or New >28 days from CA 125 PR‡			PR	PR	
SD§	Non-PD	No	PR	PR	
SD§	Non-PD or NAE	No	Not PR and not PD	SD	
PD or New ≤28 days From CA 125 PR‡			PR	PD	
PD	Any	Yes or No	Any	PD	
Any	PD	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD	PD	

*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.
†Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1.
‡Patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA 125 response.
§The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
NE, Not evaluated; NAE, not all evaluated.

Evaluation of Best Overall Response in Patients *With* Initial Measurable Disease and Who are Also Evaluable by CA 125

A report that combines both CA 125 and RECIST 1.1 criteria is likely to include patients who are measurable by one or both of the criteria and who may have events at different time points. It should be determined according to Table 3. In patients who have measurable disease by both criteria, the date of response will be the date of the earlier of the 2 events if this approach to combined response reporting is to be used. In the combined assessment of CA 125 and RECIST 1.1 response, the following algorithm applies when determining the best overall response. If patients have progressive disease (PD) according to RECIST 1.1 within 28 days of CA 125 response, they are classified as having PD. If the PD according to RECIST 1.1 is longer than 28 days before or after the CA 125 response, they are classified as having partial response. Patients whose best response according to RECIST 1.1 is stable disease but who have a CA 125 response are classified as CA 125 responders.

TABLE 4. Example of reporting RECIST, CA-125, and combined response

	CA 125 Response			
RECIST	**Yes**	**No or PD**	**N/E**	**Total RECIST**
CR*	***4***	0	0	*4*
PR	***3***	*1*	*1*	*5*
SD	**3**	12	1	16
PD	0	8	2	10
NE	**3**	5	2	10
Total CA 125	**13**	26	6	Total entered = 45

In the above example, the RECIST 1.1 response rate is 9 (25.7%) of 35 RECIST 1.1 evaluable patients, the CA 125 response rate is 13 (33%) of 39 CA 125 evaluable patients, and the combined overall response rate (either RECIST or CA 125 response) is 15 (35%) of 43.

*RECIST 1.1 includes normalization of CA 125 to achieve CR (Table 3).

Bolded numbers, CA 125 responders; bolded and italicized numbers, both RECIST and CA 125 responders; italicized numbers, RECIST responders.

REPORTING OF RESPONSE ACCORDING TO BOTH RECIST 1.1 AND CA 125 CRITERIA

Responses should be reported separately for both RECIST 1.1 and CA 125 response as shown in the hypothetical example in Table 4.

TABLE 5. Definition of progression after first-line therapy in ovarian cancer as proposed by the GCIG

GCIG Subcategorized Group	RECIST Measurable/Nonmeasurable Disease		CA 125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of diameters (RECIST 1.1 definition) or Any new lesions (measurable or nonmeasurable) or Unequivocal increase in nontarget disease Date of PD: date of documentation of increase or new lesions	A N D /	CA 125 ≥ 2 × ULRR documented on 2 occasions* Date of PD: first date of the CA 125 elevation to ≥ 2 × ULRR
B	As for A	O R	CA 125 ≥ 2 × nadir value on 2 occasions* Date of PD: first date of the CA 125 elevation to ≥ 2 × nadir value
C	As for A		As for A

GCIG groups A, B, and C defined above.
CA 125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4,5]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days should not be taken into account.
*Repeat CA 125 any time but normally not less than 1 week after the first elevated CA 125 level.
ULRR, upper limit of response range.

Definition of Progression on Therapy and Recurrence After Therapy According to CA 125

Progression (PD) is conventionally defined according to RECIST 1.1 but can also be based on serum CA 125 (defined below). However, in assigning the date of progression, PD by objective change in tumor size should always take precedence over CA 125 should it occur first. If measurable disease is reducing in size during treatment but the CA 125 results suggest progression (as defined below), the patient should continue to receive protocol treatment. If measurable disease is stable but CA 125 indicates confirmed progression over at least 4 weeks, some protocols may advise changing protocol treatment, unless there is the possibility that the therapy could be slowing the rate of rise of CA 125. If patients are having routine CA125 measurements as part of follow-up, the date of progression is likely to be several months earlier than symptoms or signs of progression develop.6 Therefore, when categorizing patients according to time to progression, it is necessary to specify how the date of progression was defined (CA 125 alone, CA125 and symptoms, and RECIST). Protocols will need to specify that these data have to be collected.

EVALUATION OF PROGRESSION ACCORDING TO CA 125

Progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125 according to the following criteria and Table 5:

A. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart or

B. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart or

C. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA 125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody[4, 5]) or if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

A patient may be declared to have PD on the basis of either the objective RECIST 1.1 criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

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