DRUP STUDY MANUAL

Contents

1. Introduction

The purpose of this study manual is to specify the procedures, logistics and responsibilities within the DRUP study, including instructions for patient registration, biopsy collection, drug ordering, data collection, and (S)AE and SUSAR reporting. For remaining questions regarding any DRUP study procedures, please contact the study coordinators (see Study Contacts below).

2. Study contacts

Team			**Function**	**Name**	**Contact details**
Central Study Team	**Steering committee (SC)**	**Central Principle Investigators**	Coordinating PI	Emile Voest	e.voest@nki.nl 020-512 6930
			Central PIs	Hans Gelderblom	a.j.gelderblom@lumc.nl
				Henk Verheul	h.verheul@erasmusmc.nl
		Multi-disciplinary SC members	Pharmacist Pathologist Hematologist Neuro-oncologist Peripheral oncologist	Alwin Huitema Katrien Grunberg Elly Lugtenburg Filip de Vos Haiko Bloemendal	
	Study coordinators		Coordinating sub-investigators	Ilse Spiekman Laurien Zeverijn Birgit Geurts Karlijn Verkerk Soemeya Haj Mohammad	DRUP@nki.nl 020-512 7848
	Clinical Project Managers			Emilie van der Sande Femke Verwer	DRUP@nki.nl 020-512 4009
General study contact details				DRUP@nki.nl	020-512 7848
Study website				https://drupstudy.nl	

Sponsor site contacts	Central Data Manager	Henk Botma	h.botma@nki.nl Tel. 020-512 9118
	SAE reporting	NKI-AVL Safety Desk	Fax. 020-512 2679 Tel. 020-512 2668
	Study Monitors	Ernst Smienk	e.smienk@nki.nl Tel. 020-512 2655
	Central pharmacy Drug distribution & Stock maintenance	Anuja Misier Kees Koks	trials-gdp@nki.nl
	Packaging, labeling, transfer to GDP	Bastiaan Nuijen	b.nuijen@nki.nl
General CPCT contacts	Chair CPCT Tumor Board (MEB)	Wendy de Leng	W.W.J.deLeng@umcutrecht.nl
	National Trialmanager CPCT-02	Eleonora Louwman	e.louwman@erasmusmc.nl
	General Manager CPCT	Evelijn Ubert-Bak	e.bak@cpct.nl

Independent Data Monitoring Committee (IDMC)	Chair	Prof. dr. E.G.E. de Vries
	Geneticist	Prof. Dr. C.J. van Asperen
	Pathologist	Dr. S.M. Willems
	Statistician	Dr. J. Berkhof
	Oncologist	Dr. Å. Helland
	Oncologist	Dr. A. Awada
	Oncologist	Dr. C. Sessa

Table 1: study contacts

3. Study management: responsibilities and meetings

3.1 Responsibilities

a. Central PIs
    a. Responsible for overall study management and conduct.
    b. Legal representative: coordinating PI.
b. Study coordinators
    a. Carry out central study coordination as delegated by the central PIs.
    b. Responsible for all study related tasks.
    c. Handling of patient submissions (if applicable, incl. CPCT MEB submission).
    d. Provide the central PIs, SC and IDMC with data and overviews as needed for their respective meetings and evaluations.
    e. Work division between study coordinators:
        i. Patient submissions: the study coordinators will organize a rotating duty-schedule (so that every working day, 1 coordinator is on-duty), and file communication on cohort assignment (as source documents).
        ii. Meetings (presentation, minutes etc.): the study coordinator who is on-duty is in principle responsible for all meetings during his / her duty.
        iii. Participating sites: the study coordinator who is on-duty is in principle responsible for all communication with the (potential) sites during his/her duty.
        iv. Pharmaceutical companies: the study coordinator who is on-duty is in principle responsible for all communication with the pharmaceutical companies during his/her duty.
        v. Back-up for Trail manager: the study coordinator who is on-duty is working as a back-up for the trial manager; supports Trial manager in her tasks and takes over tasks when Trial manager is not able to carry them out (e.g. when not present).

c. Clinical Project Managers
    a. Communication with Ethical Committees and regulatory authorities.
    b. Maintenance of the Trial Master File and Central Investigator File.

    c. Primary contact persons for participating sites, incl. organization and carrying out of initiation meetings (if possible in collaboration with study monitor).
    Primary contact person for other parties involved such as study monitor, central pharmacy, Hartwig Medical Foundation, etc.

d. Steering Committee (SC)
    a. Consists of central PIs and multidisciplinary members.
    b. Helps to oversee the study management and establish adaptions where necessary.
    c. In absence or upon request of the central PIs, the multi-disciplinary SC members can be asked for advice on patient cases that have been submitted for review.
e. Independent Data Monitoring Committee (IDMC)
    a. Independent monitoring of (preliminary) data.
    b. Advice on cohort management, as described in the study protocol.
f. CPCT Tumor Board (MEB)
    a. Can be consulted for advice on patient-drug matches.
    b. Sequencing results obtained in the context of the DRUP study, can also be discussed by the CPCT Tumor Board (MEB).
    c. Please refer to chapter 5 of this study manual for further details on the responsibilities and tasks of the CPCT Tumor Board (MEB).
g. Monitor
    a. Assist study coordinators with initiation meetings.
    b. Perform and report monitor site visits according to the monitor plan, including a list of action points and responsible parties for each action point.
    c. Monitor reports will be send to the central PIs (who have to approve of the report's contents), with a cc to the study coordinators.

3.2 Meetings, updates and evaluations

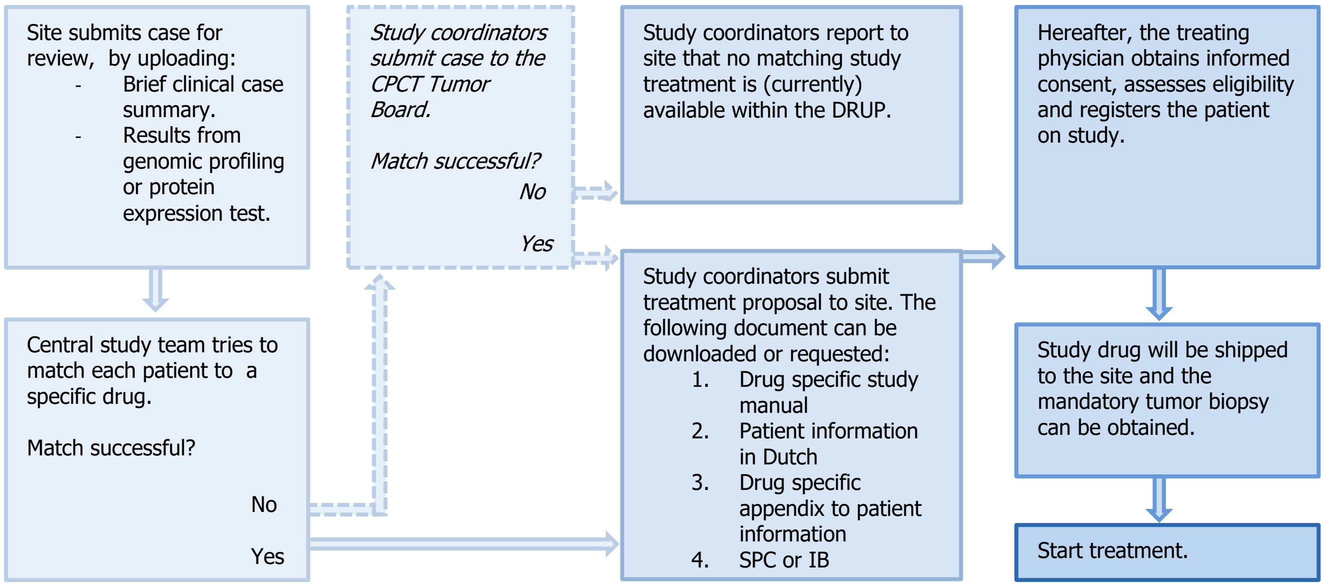
There will be regular meetings and updates to inform stakeholders on and evaluate the study's conduct and progress. In principle, the frequency will be as follows (frequency can increase or decrease as appropriate):

a. Every month
    a. Newsletter, incl. submission and accrual overview: inform sites, pharmaceutical partners and other parties involved on news and study progress.
    b. Teleconference with central PIs and study coordinators: discuss general study progress and conduct, questions and remarks.
    c. Face-to-face meeting with monitor, study coordinators and central data management: discuss general progress of DM and monitoring, major findings.
    d. Central screening and enrollment log: a PDF-copy will be filed in the TMF to enable check-ups when needed.
b. Every three months

   a. Teleconference with SC: discuss general study progress and conduct, questions and remarks for / from the SC.
   b. Teleconference with IDMC: discuss accrual rates, cohort status, safety and questions from the study team.
   c. Face-to-face meeting with central PIs and study coordinators, to discuss:
      i. Accrual patient submission and enrollment numbers.
      ii. Cohorts cohort closures, number of patients per cohort.
      iii. Drugs supply process, medication stock and left-over at sites.
      iv. Finance study income and costs to date.
      v. Safety SAEs and SUSARs, overall and per drug.
      vi. Efficacy overall response rate (blinded for per cohort RR).
      vii. Evaluability number of non-evaluable patients.
      viii. DM completeness of data in eCRF (per site).
      ix. Monitoring progress, major findings (per site).
      x. IDMC advice, meeting reports.

c. <u>Every six months</u>
   a. Face-to-face meeting with pharmaceutical companies: to discuss a selection of the items above, and questions and remarks for / from pharma.
   b. Central Data Management will at random check 10% of the case submissions on the central screening and enrollment log, compared to the PDF-copy that was created 6 months ago.

4. Patient registration



Timelines after submitting a case for review:	Report of treatment proposal: ≤7 (*or 14*) days	Screen and register patient on study: ≤14 days	Receive study drugs and start treatment: ≤14 days

Figure 2: 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).

4.1 Identifying a potentially actionable tumor profile

Results must be available from a tumor genomic or protein expression test, and must reveal a potentially actionable variant as defined in the study protocol. Variants should be known or likely pathogenic; variants of unknown significance are not eligible. 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) or immunohistochemistry (IHC), performed in diagnostic laboratory or in the CPCT sequencing facility. The test may have been performed on the primary tumor or a metastatic deposit. There are 3 routes by which a potentially actionable variant can be detected:

1. Any of the above mentioned tumor profiling tests, as performed in the participating site in the context of regular diagnostics, has revealed a potentially actionable variant.
2. Patients tumor has previously been sequenced in the context of another CPCT study, which has revealed a potentially actionable mutation.
3. If option 1 has not revealed any actionable variant and patient is not eligible for option 2, the treating physician can contact the study coordinators for advice. If option 1 has revealed a

variant of which the local diagnostic lab does not know the significance, the study coordinators can also be contacted for advice.

4.2 Submitting a case for review

To enroll a patient, first check if the patient meets all general selection criteria (provided in the study protocol). If they're all met, submit the case for review via Alea (a link is provided at the website: http://www.cpct.nl/nl/drup-studie-uitslagen/, password: drup2016) by filling in all information requested (including relevant medical history, comorbidities and co-medication, and the results and report of a genomic profiling or protein expression test, performed in a diagnostic lab or within the context of another CPCT study. If the case has previously been discussed by a site's local Tumor Board, their report should also be uploaded in Alea. Please provide only anonymous information at this point, as the patient has not yet signed Informed Consent (IC). A study number will be generated upon submission of the case-submission form in Alea.

4.3 Treatment assignment

When a case is submitted for review, the study coordinators will first discuss the case with the central PIs and / or other Steering Committee (SC) members to decide whether there is a potentially actionable variant present in the patients tumor, and if so, whether a matching study drug is available. At least two of the three central PIs have to approve of the match. In case of doubt, the study coordinators will consult the CPCT Tumor Board. Patients will be matched to treatment based on cohort availability and / or level of evidence as described in the study protocol. Within 7 days (or 14 in case of consultation of the CPCT Tumor Board) after submission of the case for review, the study coordinators will assign a cohort or reject the submission in Alea, after which the local PI and / or designated sub-investigators will automatically be notified.

4.4 Registering a patient on study

After provision of the treatment proposal, the patient can be informed (verbal and in writing) about the study protocol and the drug specific information (use the drug-specific information sheet). Written Informed Consent can be obtained and drug-specific screening can start. If the patient meets all selection criteria (provided in the drug-specific study manual), the patient can be registered on-study in Alea , after which the pre-treatment tumor biopsy must be obtained and the study drugs will be shipped to the site's pharmacy.

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.

Study treatment should in principle be initiated within 28 days after provision of the treatment proposal (deviations are allowed, but slots will in principle not be reserved for more than 28 days). To ensure timely drug supply, patients should be registered on study within 14 days after provision of the treatment proposal.

5. On-study tumor biopsy collection and DNA sequencing

From all patients who have been registered on-study, a fresh pre-treatment tumor biopsy sample should be obtained and transferred to the Hartwig Medical Foundation. DNA sequencing for biomarker analyses will be performed once cohorts have been completed. For Multiple Myeloma (MM) patients, all samples will be pre-processed by the Erasmus MC. Instructions for non-MM patients and for MM-patients are therefor provided separately below.

5.1 Non-MM patients

Blood sampling for germline DNA sequencing (non-MM patients)

At baseline, a blood sample (1 x 10 mL) for next-generation sequencing (NGS) of germline DNA will be taken, preferably combined with other necessary blood draws.

- Materials: please make sure that the blood sampling laboratory kits (provided by CPCT) are available at your site, containing:
    - CellSave® 10 mL blood collection tubes (check the expiration date before use)
    - Barcode labeling and a Blood Sample Requisition Form
    - Envelopes and blisters for shipment over mail
- Processing instructions:
    - Collect 10 mL whole blood in a CellSave blood collection tube. These tubes contain a preservative to preserve the quality of plasma at room temperature for up to 4 days.
    - The tubes will be pre-labeled. Please paste the second label onto the Blood Sample Requisition Form. The 3rd label is optionally for your own registration.
    - Complete all collection details on the Blood Sample Requisition Form and record any sample handling or quality issues.
    - A copy of the Blood Sample Requisition Form will be saved for site filing.
- Transport of blood samples: centers are requested to send the blood samples to the central laboratory on the day of collection. Samples should be kept at room temperature and send via regular mail. For this purpose, pre-addressed envelopes and transport blisters will be provided by the central laboratory. The contact details of the central laboratory are:
    - Hartwig Medical Foundation
    - Science Park 408
    - 1098XH Amsterdam
    - E: x-lab@hartwigmedicalfoundation.nl
    - T: 020-2352640
- Resupply of blood sampling laboratory kits: in case resupply of blood sampling laboratory kits are necessary (either due to usage of supplied kits or to expiration of the CellSave tubes), orders

can be placed through https://www.labkithartwigmedicalfoundation.nl/Hartwig. The laboratory kits will be delivered within 3 business days. For any questions concerning the resupply of the laboratory kits, please contact the central laboratory by email: x-lab@hartwigmedicalfoundation.nl or by phone: 020 235 2640.

Histologic tumor biopsy collection (non-MM patients)

Patients will be subjected to a histological biopsy of a locally advanced or metastatic and preferably radiological measurable (target) lesion. The biopsy is obligatory at baseline (pre-treatment) and optional after treatment (post-treatment). **NB please note that this biopsy will be sequenced and used for research purposes. It is *not* used for study enrollment or treatment allocation**.

- **Glioblastoma multiforma**: fresh tumor tissue will only be obtained through standard-of-care surgical procedures. Please refer to study protocol for further details. Tissue can be processed and transported according to the instructions below, under 'all other tumors'.
- **Non-Hodgkin lymphoma**: two to three (preferably) 18-gauge large-core needle (22 mm true-cut) lymph node biopsies are required (see instructions below):
- **All other tumors**: one or two (preferably) 18-gauge large-core needle (22 mm true-cut) or punch (skin) biopsies are required (see instructions below):

  Equipment and supplies: please make sure that the following equipment and supplies are available at your site.

  - Biopsy sampling laboratory kits, provided by CPCT, each containing 3 tissue tubes with screw cap, barcode labeling and a Biopsy Sample Requisition Form
  - Large tweezers
  - Liquid nitrogen container (N2l)
  - -70°C (or colder) freezer to store all samples until shipment
  - A temperature control log should be filled in daily to ensure stable storage conditions as per the sites standard procedure.

  Tumor biopsy collection: ultrasound or CT-guided large-core needle biopsy or a punch (skin) biopsy will be performed according to local guidelines. Following guidelines are indicative:

  - A body ultrasound (2-5 MHz) transducer is used to visualize the metastasis.
  - An add-on guiding device is attached to the transducer and the appropriate needlepath is selected (automatically).
  - Lidocaine 1% is used for local anesthesia. If necessary systemic pain control using phentanyl and mild sedation using midazolam can be used.
  - A 17-gauge guiding needle may be used, which is advanced under real-time ultrasound guidance into the tumor.

- After correct positioning of the guiding needle has been confirmed in 2D, a (preferably) 18-gauge large-core needle (22 mm true-cut) is advanced through the guiding needle and one or two biopsy specimens are obtained.
- Complete all relevant information on the Biopsy Sample Requisition Form.
- Complete all relevant information in the appropriate section of the eCRF.
- All patients should be observed after biopsy according to local protocol for full recovery.

In case the tumor cannot be accurately visualized with ultrasound, CT could be selected as guiding modality. If preferable, biopsies can be taken by GI endoscopist under imaging guidance, in which cases mild sedation (midazolam, combined with the opioid phentanyl) is allowed and biopsy will be performed according to the following protocol:

- An echo-endoscope is used to visualize the metastasis or locally advanced lesion.
- A (preferably) 19-gauge EUS histology needle is used, which is advanced under real-time ultrasound guidance into the tumor.
- After correct positioning of the needle, one or two passes through the tumor are made to obtain the biopsy specimens for DNA sequencing.
- All patients should be observed after biopsy according to local protocol for full recovery.

Tumor biopsy processing: please comply with the following processing instructions:

- Biopsy specimens and appropriate storage material should be handled wearing nonsterile gloves.
- Only supplied pre-labeled tissue tubes will be used, **one for each biopsy specimen** (maximum of 2 tissue tubes).
- Place each of the biopsy specimens directly into the appropriate tissue tube in a curved position.
- Close each of the tissue tubes and “snap-freeze” immediately.
- Use large tweezers to pick up the tissue tubes. **Do NOT tilt the tubes**.
- Snap-freeze each of the tissue tubes by placing the bottom of the tube in the surface of the N2l for 10 seconds. **Do NOT tilt the tubes**.
- Release each of the tissue tubes in the N2l container for at least 20 seconds to secure proper freezing of the specimen.
- Place the tissue tubes in the -70°C (or colder) freezer for storage until shipment.
- Complete all relevant information on the DRUP Biopsy Sample Requisition Form to be found on the website (www.hartwigmedicalfoundation.nl/aanvraagformulier) or in the biopsy sampling laboratory kit.
- Complete all relevant information in the appropriate section of the eCRF.
- A copy of the Biopsy Sample Requisition Form will be saved for site filing.
- Ship biopsy samples (together with the biopsy sample requisition form) on sufficient dry ice to assure that they remain frozen for at least two days.

- Ship samples as soon as possible **by courier** to:
  - Hartwig Medical Foundation
  - Sciencepark 408
  - 1098 XH Amsterdam
  - E: x-lab@hartwigmedicalfoundation.nl
  - T: 020-2352640

Resupply of biopsy sampling kits

In case resupply of biopsy sampling kits is necessary, please contact the central laboratory by email: x-lab@hartwigmedicalfoundation.nl.

Courier information for transport to the HMF (non-MM patients)

For transport of biological samples to the Erasmus MC (i.e., multiple myeloma samples) please refer to the sections above. For the transport of biological specimens from local sites to the Hartwig Medical Foundation sequencing facility, arrangements have been made with:

- SDX BV
- Damzigt 14B
- 3454 PS De Meern
- Tel.: 030 – 241 01 06
- Fax: 030 – 241 33 11
- Email: info@sdx.nl

Packages for transportation are expected to be 3-5 kg, with an average size of 30 x 30 x 30 cm. Materials for transport (e.g. boxes, dry ice) may be provided if indicated on the Courier Shipment Request Form (min. 1 day in advance).

Shipments can be requested until 3 days before the day of pick-up by fax, email or website. The courier will contact the site for the pick-up time. For pick-up requests the Courier Shipment Request Form may be used. Centers are requested to ship samples in a maximum frequency of once every two weeks. NB No shipment on Fridays or the day before public holidays, if delivery is planned the next day.

5.2 Multiple Myeloma (MM) patients

Instructions (MM patients)

For patients with multiple myeloma, the following three samples should be obtained and send to the Erasmus MC at baseline:

- Bone marrow aspirate: a 5 to 10 ml bone marrow aspirate is required.
  - Red sample transport envelopes (including bone marrow draw tubes) can be requested from the central laboratory of the Erasmus MC (this transport envelope corresponds to the envelope used for the HOVON studies, including HOVON126; as indicated below not

all tubes are used. Empty tubes can either be removed, or returned to the Erasmus MC empty).
    - Please use 1-2 large lithium heparine tubes (5ml of bone marrow aspirate per 10ml tube).
    - Replace the needle during the punction, in order to obtain a qualitative 'flaky' bone marrow sample (≥5, but preferably 10 ml).
    - Mix carefully by tilting the closed tube ≥5 times.
    - Divide the obtained bone marrow over 1-2 large (10 ml; 5ml of bone marrow aspirate per tube) lithium heparine tubes
- Peripheral blood sample: a blood sample (1 x 6 mL) for next-generation sequencing (NGS) of germline DNA should be obtained, preferably combined with other necessary blood draws.
    - Sample the blood by venipuncture in a 6ml heparin buffered tube.
    - Invert the tube at least 5x
- Saliva sample: a 2 ml saliva sample is required.
    - White sample transport envelopes (including a saliva sampling kit + instructions) can be requested from the central laboratory of the Erasmus MC.
    - Please obtain 2 ml of saliva in a saliva sampling kit, according to the instructions enclosed in the white envelope. In general this will take 2 to 5 minutes. Instruct the patient not to cough up saliva / sputum etc.
    - Patients should refrain from eating, drinking, smoking or chewing gum ≥30 minutes before the saliva sample is obtained.
    - On the lid of the funnel, a plastic film-coating keeps the buffer in place. Please ensure the film-coating stays in place. By closing of the kit after the saliva withdrawal the saliva and buffer are mixed. The large lid and funnel can then be taken off, after which the small lid can be placed on the tube, which can then be transported.

Sample registration (MM patients)

Please notify the Erasmus MC one day in advance that a sample will be sent (myeloma.hematology@erasmusmc.nl / 010-70 43 609 / Mark van Duin, Jasper Koenders, Michael Vermeulen, Chelsea den Hollander), including:

- Hospital and date of sample withdrawal, baseline or post-treatment
- Tracking number (as mentioned on the transport form, below the barcode, 9 digits)
- Gender and year of birth of the patient
- Study subject number (i.e. patient specific)

Labeling of the tubes (MM patients)

All tubes (bone marrow, peripheral blood and saliva) should be labelled with the following (please note, unlabeled tubes will be destroyed):

- Hospital and date of sample withdrawal
- Gender of the patient

- Year of birth of the patient
- Study subject number

Transport of samples to the Erasmus MC (MM patients)

- Transportation of bone marrow and blood samples:
  - Make sure all tubes are properly closed
  - Place tubes in transport blister, close the blister
  - Place transport blister + tubes in a safety bag, remove the closing strip
  - Place safety bag + contents in a red sample transport envelope
- Transportation of saliva samples:
  - Make sure the tube is properly closed
  - Place the tube in the original package with absorbing sheet
  - Place kit with tube and sheet in a safety bag, close the safety bag by removal of the strip
  - Place safety bag + contents in a white transport envelope
- Fill in the transport form:
  - Hospital and date of sample withdrawal
  - Name, function, email and telephone of the person who sends the material
  - Patient subject number, gender, and year of birth
  - Disease stage: relapse, pre-treatment sample for start treatment in DRUP study
  - Add the transport form to the white transport envelope and close with the zipper
- Send samples (bone marrow + peripheral blood + saliva) to the central lab of the Erasmus MC:
  - Request a TNT courier by calling 030-6398760
  - Add a TNT transportation letter (enclosed in the provided transportation envelopes), including your address and the study code (DRUP) and send to:
    - TNT Express Rotterdam
    - Saffier 2
    - 3316 LN Dordrecht
    - Contact name: Erasmus MC
    - Kenmerk: Hematologie, Ee1363, 3015CN80, Rotterdam, 010-7043609
- **NB do *not* obtain or send samples on Fridays. If possible, it's preferred to obtain and transport samples on Mondays and Tuesdays.**

5.3 Fecal sampling

For patients receiving immunotherapy in stage III (expansion cohort), three mandatory fecal samples are collected. Patient instructions for collecting these samples can be found in a separate document. Patients are asked to collect the fecal sample from one passage in the 24 hours before their visit to the hospital prior to start of the treatment. The second sample is to be collected after 2 months of treatment and the third sample as soon as progressive disease is determined. The samples can be stored at room temperature until they are sent to the NKI Biobank per mail, together with a short questionnaire on the fecal collection. The samples are stored in the Biobank of the sponsor (NKI-AvL) for future scientific cancer research. The detailed instructions for this procedure can be found in a separate document.

5.4 Criteria for DNA sequencing

The minimum tumor percentage to obtain a representative result on tumor mutations is 30%. If the tumor percentage were less than 30%, the result of sequencing would mainly represent normal tissue instead of tumor tissue, and therefore cannot be evaluable.

The minimum DNA yield to obtain a representative result on tumor mutations is 200 ng. DNA yields below 200 ng are not suitable for sequencing.

Sequencing will only be performed for patients who underwent the study related blood sampling for germline DNA and histological biopsy (meeting the requirements outlined above), who have received treatment and at least one response evaluation according to the study protocol, and for whom the eCRF is completed from baseline to the first response evaluation (or further) and only once cohorts have been completed

5.5 Sequencing timelines

Process	Management	Time
Collection and submission of biopsy and blood samples	**Local**	**Baseline**
Reporting of tumor percentage by pathologist	**Central**	**≤ 2 weeks after receipt of biopsy**
Reporting of DNA result by molecular biologist		
Study treatment	**Local**	**Treatment start**
First response evaluation		**8 weeks after treatment start**
Data recording in eCRF		**a.s.a.p. after tumor measurement**
Sequencing (if all criteria are met)	**Central**	**Once cohorts have been completed.**
Report of sequencing results to CPCT Tumor Board and treating physician (please note disclaimer)		

Table 2: sequencing timelines

5.6 Reporting of DNA sequencing results

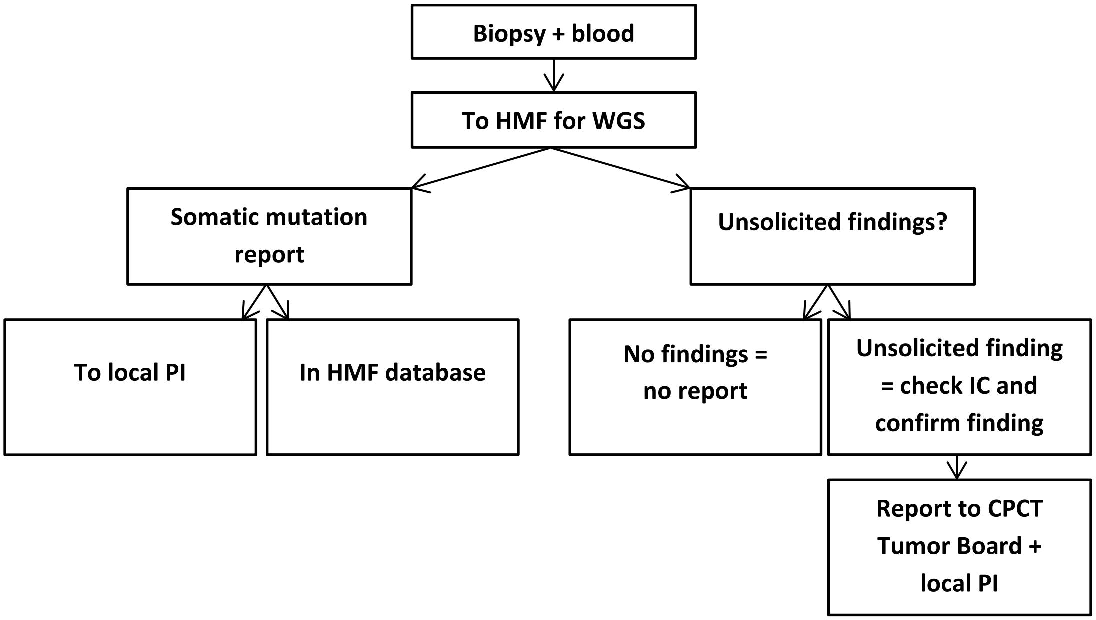


Figure 3: flowchart of reporting of sequencing results

<u>Hartwig Medical Foundation (HMF):</u> the HMF will perform the actual sequencing of germline and tumor DNA, once cohorts have been completed. HMF will send a sequencing report of the somatic mutations to the treating physician. If any unsolicited findings are encountered in the germline DNA, the HMF will inform the DRUP study coordinators (see below for further details).

<u>Local PI (or designated person):</u> it's the local PIs (or designated person's) responsibility to inform the patient about the (possible) consequences of participation in this study, and to obtain properly signed Informed Consent. This includes informing the patient about the meaning of DNA sequencing and the possible consequences of unsolicited findings. Local PIs (or designated person's) should emphasize that within the DRUP study, sequencing is performed for research purposes (i.e., *not* for genetic screening purposes). The absence of unsolicited findings does therefore *not* mean that the patient has no inheritable mutations. If any unsolicited findings are encountered and the patient has opted to be informed on the IC form, it's the local PIs (or designated person's) responsibility to inform the treating physician of the patient and to offer referral to a clinical geneticist for further genetic counseling and diagnostic validation.

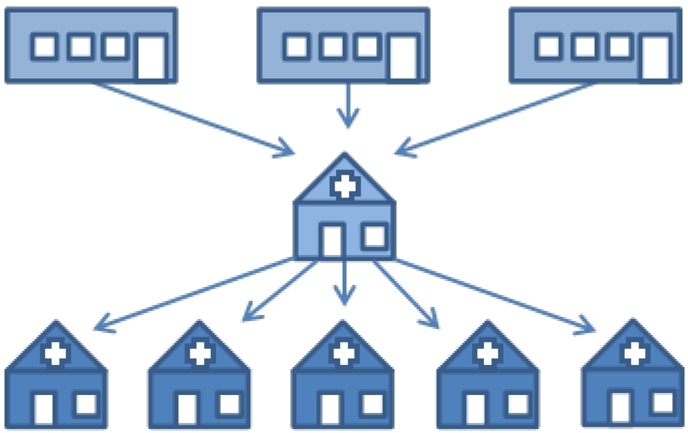
<u>DRUP study coordinators:</u> if any unsolicited findings are encountered, it is their responsibility to check the IC form of that patient for the consent on unsolicited findings. If the patient wants to be informed, the DRUP study coordinators will inform the CPCT Tumor Board (CPCT MEB), who will then arrange validation of the unsolicited finding in a diagnostic genetic laboratory in one of the CPCT-affiliated hospitals, conform current CPCT Tumor Board (CPCT MEB) logistics. If the finding has been confirmed, the DRUP study coordinators will inform the local PI and the treating physician.

CPCT Tumor Board (CPCT MEB): upon request, the somatic mutation report as provided by the HMF can be discussed by the CPCT Tumor Board. They will also pre-define which germline mutations can be reported as unsolicited findings. If any unsolicited findings are encountered and if the patient in question has opted to be informed, the CPCT Tumor Board will arrange validation of the findings and inform the DRUP study coordinators about their conclusions.

5.7 Storage of blood and tumor tissue after sequencing

Any remaining blood, tissue and feces will be stored in the DRUP Biobank, located at the sponsor site (NKI-AVL), to enable future scientific cancer research. The Biobank samples are in principle uniquely available for its custodians, but can be made available for secondary use in other studies after written approval of the custodians and review by the Translational Research Board. The Biobank can stay in place as long as the Biobank is considered relevant (as determined by its custodians), or as long as allowed by Biobank regulations. If the Biobank is no longer considered relevant, the NKI-AVL Biobank Review Board will be notified. If a patient decides to retract his or her permission, he or she can request the destruction of stored material (with the exception of material that has already been used for scientific research purposes). Medical data used for scientific research or data coming from such research cannot be destroyed or removed from the study.

6. Drug ordering and supply



Pharmaceutical companies

↓

Central pharmacy

↓

Local pharmacy (participating site)

Figure 4: schematic overview of drug supply

6.1 Drug ordering and supply during stage I and –II

All DRUP study drugs are supplied free of charge by the participating pharmaceutical companies. A small stock is supplied regularly to the sponsor's pharmacy, who will relabel all drugs as necessary. Whenever a patient is registered on study in the eCRF (Alea), the drug that has been matched to the patient will automatically be ordered and shipped to the pharmacy of the participating site that has enrolled the patient. The first drug order should contain sufficient drug to treat the patient until the first response evaluation, and 1 treatment cycle after that (to cover the period between response evaluation and re-supply). If the patient will indeed continue treatment after the response evaluation, new drugs can be ordered via the drug re-order form in Alea. Every re-supply should contain sufficient drug to treat the patient until the next response evaluation.

Left over drugs should be stored at the site's pharmacy and may be used for future DRUP patients, and should be destroyed upon their expiry date. In principle the DRUP study coordinators will inquire sites about left over drugs, and arrange return shipment if necessary.

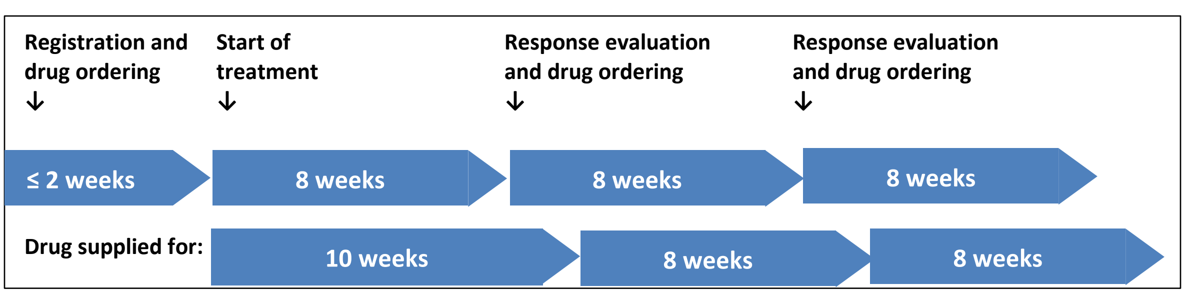


Figure 5: timelines for drug ordering and supply

6.2 Drug ordering and supply 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. The treatment of patients in the expansion cohort will be divided into two phases.

6.2.1 Drug supply during phase I (first 16 weeks)

During the first phase, the study drugs are supplied as in stage I and II (see section 6.1).

6.2.2 Drug supply during phase II (beyond 16 weeks)

If clinical benefit (defined as confirmed objective response or disease control at 16 weeks and measured more than once, at least 28 days apart) is observed at 16 weeks, treatment will continue in phase 2. During this phase **the patient will receive medication from general hospital stock** and, therefore, medication will no longer be ordered through Alea. The medication will be reimbursed by the health insurer.

7. Data collection and monitoring

7.1 Local data management

Alea, an online electronic Case Report Form (eCRF) will be used for data collection. Local data-managers can apply for an Alea account via cpctdatamanagement@nki.nl (with a cc to the DRUP study coordinators). For registration, a signed enrollment log should be submitted and an email address is needed. Subsequently, an account will be created and a data management manual and a password (which can be adjusted to personal preference) will be provided.

The responsibilities of local, participating site based data-managers (i.e., the local PI or a delegated person) are to:

- Submit cases for review to the study coordinators (see also chapter 2, Patient registration).
- If treatment with one of the study drugs is proposed by the study coordinators and the patient meets all drug-specific selection criteria, register the patient on study. When all required information has been recorded in Alea, a study number will be generated, after which the pre-treatment tumor biopsy can be obtained and the study drugs will be shipped to the site's pharmacy. NB please note: patients will only be registered once and maintain the same subject number throughout the study, also if they participate multiple times (i.e., in different treatment arms).
- Drug re-ordering if a patient will continue treatment after his or her response evaluation, by filling in the drug re-order form in Alea.

All remaining local data management will be performed by IKNL data-managers or by the local site based data-managers (according to preference of the site).

NB please note: to mimic daily practice as closely as possible, there will be *no* central review of scans and scans will *not* be uploaded in the eCRF. According to standard of care, the radiologist decides what the radiologic response of the tumor has been (and should state this clearly in the report) and the treating physician decides whether the patient can continue treatment or not (taking into account toxicity, general wellbeing of the patient etc. as well).

7.2 Central data management

Central data management will be done by the 'Scientific Administration' department of the sponsor site.