M17TDM: Therapeutic drug monitoring for oral anti-cancer drugs

Protocol number	**:**	**M17TDM**
Protocol writing committee	**:**	M. B.A. van der Kleij, MD M. Meertens, PharmD S.L. Groenland, MD R.B. Verheijen, PharmD N. Steeghs, MD, PhD Prof. A.D.R. Huitema, PharmD, PhD
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PROTOCOL CHANGES

Version 6.0, dated 18 January 2022:

- For pazopanib, advised dose modifications based on toxicity are changed: the recommendation to increase two dose levels in case of a trough level < 15 mg/L is deleted and changed into the advice to increase 1 dose level in case of trough levels <20 mg/L and grade 0, 1 or 2 toxicity.
- Dasatinib target and dose recommendations have been changed.
- Following cohorts are closed for further enrollment: cabozantinib, dabrafenib/trametinib, enzalutamide, erlotinib, gefitinib, olaparib, sorafenib, tamoxifen, vismodegib.
- The three-stage design has been added to the project design.
- The imatinib, sunitinib and abiraterone cohorts are completed, i.e. closed for further enrolment.
- For axitinib, inclusion of combination therapy (e.g. axitinib + pembrolizumab) is not allowed, only monotherapy axitinib.
- Palbociclib dose levels were updated, as 50 mg tablets are not available.
- Palbociclib cohort was put on hold due to difficult clinical logistics and toxicity, at least until further studies on the exposure-response relationship .

Version 5.0, dated 13 November 2019:

- Cabozantinib was added to the protocol;
- Abiraterone dose levels were updated, as 250 mg tablets are no longer available

Version 4.0, dated 8 October 2018:

- Inclusion criteria clarified: patients can only be included if they start treatment at the standard dose;
- Participating centres and co-investigators were deleted from the protocol and will be listed in a separate document.

Version 3.0, dated 28 May 2018:

- Inclusion criteria updated: diagnosis of cancer is sufficient, instead of histological or cytological proof of cancer
- For the following compounds patient inclusion has been expanded to at least 100 patients:
    - Abiraterone
    - Erlotinib
    - Imatinib

  - Pazopanib
  - Sunitinib
  - Trametinib
- The following drugs were removed from the protocol:
  - Cabozantinib (few data available)
  - Lapatinib (rarely prescribed)
  - Nintedanib (rarely prescribed)
  - Osimertinib (few evidence for exposure-response relationship)
  - Ribociclib (few data available)
- The dose level schedule of pazopanib has been changed, the first step in case of low exposure is now splitting intake moments, the second step is to take pazopanib concomitant with food.
- For dabrafenib/trametinib patients, dose adjustments will only be advised for trametinib, not for dabrafenib (concentrations will be measured only), since few evidence for an exposure-response relationship for dabrafenib is available.

SYNOPSIS

Protocol number	**M17TDM**
Protocol title	Therapeutic drug monitoring for oral anti-cancer drugs
Version	6.0
Date	18 January 2022
Collaboration	The Dutch Pharmacology Group (DPOG, www.dpog.nl)
Coordinating Investigator	N. Steeghs, MD, PhD The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Department of Medical Oncology and Clinical Pharmacology, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Project Coordinator	M.B.A. van der Kleij, MD
Sponsor	The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL)
Financial Support	Novartis Pfizer Roche Merck Ipsen
Rationale	In the Netherlands more than 100.000 people are diagnosed with cancer each year. In 2012 about 14.1 million new cases of cancer occurred globally.(1) It caused about 8.2 million deaths or 14.6% of all human deaths. Oral targeted anti-cancer agents form a novel group of very promising drugs which completely changed the treatment paradigm in cancer. Personalized treatment is now the standard for several tumor types. These new drugs have a complex pharmacological profile, narrow therapeutic index, and a marked pharmacokinetic interpatient variability leading to high variability in blood concentration at the currently used fixed doses. Individual patients have a high probability to be either underdosed

	(>30% of patients) or overdosed (>15% of patients), which can lead to either decreased anti-tumor efficacy / treatment failure or to (severe) side effects.(2–6) Therapeutic drug monitoring (TDM), personalized dosing based on measured drug levels, is a well-established method for personalized dosing of drugs.(5) Blood samples are collected during treatment, drug levels are measured and are used to guide further dosing. To establish the optimal dose for the individual patient, important patient and treatment characteristics are taken into account such as co-medication (e.g. potential for interactions) and co-morbidity. Despite a strong rationale for the use of TDM for oral targeted anti-cancer agents, it is currently not performed for these drugs routinely. This is partly caused by reimbursement and regulatory issues for higher than approved doses of these expensive drugs and reimbursement of drug level measurements. Possible drawbacks could include fear of increased side effects when dose increments are given. In addition, indisputable evidence of efficacy on survival and quality of life is lacking. With respect to the first issue, several studies have been performed showing TDM of oral anti-cancer drugs to be feasible and safe.(2,3) With respect to the second issue, it is highly unlikely that, given the patient numbers needed, randomized studies evaluating TDM will ever be performed in these drugs for often rare cancer types. We therefore aim to approach the second issue within this proposal. The aim of the current proposal is (i) to perform a prospective project implementing TDM of oral targeted anti-cancer drugs in multiple large medical centers across the country, and (ii) to build a prospective registry to structurally collect data on the patients' clinical outcome and the effectiveness of the interventions.
Previous experience	Practical guidelines for TDM for all drugs have been developed and published.(5) Validated assays are available for all oral anti-cancer drugs

	in this proposal. Validation is performed in line with international guidelines (EMA, FDA). A proven adequate infrastructure for sample collection and shipment, short turn-over and reporting is available. For 2015, only the Netherlands Cancer Institute (NKI) measured concentrations in approximately 1500 samples. We performed two prospective clinical trials to show the safety and feasibility of TDM for sunitinib and pazopanib, respectively.(2,3) We have previously shown in a retrospective analysis that a substantial number of patients is underexposed.(4)
Methodology	Multicentre prospective intervention project
Primary objective	To halve the proportion of patients with a drug exposure below TDM target level (historical case comparison) at the third moment of measuring after start of treatment (so after two moments of potential dose adjustment), for most compounds this will be after 12 weeks, except for compounds with intermittent dosing or a long half-life (see Appendix V for details on PK sampling per compound).
Secondary objectives	Per drug: - To determine the safety and feasibility of PK guided dosing; - To determine the objective response rate (according to RECIST 1.1); - To determine the time to tumor progression and progression free survival; - To determine the proportion of patients with a drug exposure below TDM target level at the second moment of measuring (so after one moment of potential dose adjustment). All patients: - To have a physician adherence of >90% in following the provided patient tailored treatment recommendations which are based on the structured TDM program

Project design	In this multicentre prospective intervention project, patients will start treatment on the usual (standard) dose according to the standard of care, which includes regular monitoring on drug-drug interactions, contra-indications, and other treatment specific parameters. Established TDM guidelines are followed. TDM consists of four steps: 1. Collection of blood sample (at steady state) and measurement of drug concentrations; 2. Treatment recommendation is provided to the treating physician based on measured blood concentration, taking all relevant patient characteristics into account. This can include the advice to increase dose when drug levels are below target (and no significant side effects are seen), to take the drug concomitant with food or to consider discontinuing interacting medications. Recommendations are prepared by an adequately trained physician, pharmacist or clinical pharmacologist; 3. Implementation of treatment recommendation; 4. Monitoring of treatment outcomes (including both efficacy and toxicities). For most compounds, trough levels will be measured at 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter, except for compounds with intermittent dosing or a long half-life (see Appendix V for details on PK sampling per compound). A prospective registry will be formed to gather the clinical and pharmacokinetic data of patients. This will include demographics, tumor type, measured trough levels, TDM recommendations, therapy advice adherence and data on tumor response and survival. On a population level this will enable us to gather important new information on the optimal use of these pharmacologically complex and expensive drugs. After 8 years the

	prospectively collected registry will include data on >6000 samples combined with clinical outcome data of at least 1250 patients.
Inclusion criteria	1. Diagnosis of cancer; 2. Indication to start treatment with anti-cancer drug from list (see section with list of participating drugs) at the standard dose; 3. Age ≥ 18 years; 4. Able and willing to give written informed consent; 5. WHO performance status of 0, 1 or 2; 6. Able and willing to undergo blood sampling for PK analysis; 7. Life expectancy ≥ 3 months, allowing adequate follow up of toxicity evaluation and antitumor activity.
Exclusion criteria	1. Woman who are pregnant or breast feeding; 2. Unreliable contraceptive methods. Both men and women enrolled in this project must agree to use a reliable contraceptive method throughout the treatment (adequate contraceptive methods are: condom, sterilization, other barrier contraceptive measures preferably in combination with condoms); 3. Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair treatment compliance; 4. Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of the drug or puts the patient at high risk for treatment-related complications; 5. Legal incapacity.
Number of patients	Assumptions: - Using standard fixed drug dosing, a substantial number of patients will have plasma levels below target, for example: - 52% for sunitinib (3);

- 20 – 57 % for pazopanib (2,7);
- 11% for erlotinib (4);
- 32% for imatinib (8);
- 52% for vemurafenib (9).

- The aim of this project is to halve the proportion of patients with a drug exposure below target level, for example:
  - 26% for sunitinib (inadequate levels from 52% to ~26%);
  - 10 – 28.5% for pazopanib (inadequate levels from 20 – 57% to ~10 – 28.5%);
  - 5.5% for erlotinib (inadequate levels from 11% to ~5.5%);
  - 16% for imatinib (inadequate levels from 32% to ~16%);
  - 26% for vemurafenib (inadequate levels from 52% to 26%).

If we consider the percentages reported in the literature as historical controls, then using an exact binomial test with a nominal 0.05 two-sided significance level will provide the power as indicated in table 1 assuming different levels of the null and alternative hypothesis and various sample sizes. Obviously, if a higher proportion of patients is `underdosed', fewer patients are needed to provide a reasonable power.

In some situations of drug and target combinations, it may prove difficult to obtain a sufficient number of patients for an acceptable level of power. A meta-analytic approach will be applied in addition to test "the-prove-of-principle" of TDM.

Table 1- Power at different levels of null and alternative hypothesis and three examples of sample size.

Proportion of patients with a drug exposure	Number of patients		
	30	60	90

below target level TDM at time point 12 weeks

Null	Alternative	Power (%, 1-β)		
0.10	0.05	1	19	33
0.20	0.10	18	43	71
0.30	0.15	32	71	92
0.40	0.20	60	92	98
0.50	0.25	80	97	
0.60	0.30	91		

To be evaluable for the secondary endpoint (feasibility of TDM per drug) we aim to include at least 30 patients per drug. Target plasma concentrations of all drugs are defined. In general, approximately 25-30% of the total patient group will be eligible for dose escalation. To be able to evaluate feasibility in at least 8 patients after PK guided dose escalation, we need to include about 3-4 times as many patients (at least 30 patients). For the following compounds we will expand the patient inclusion to at least 100 patients to be able to evaluate the effect of TDM on efficacy as well:

- Abiraterone
- Imatinib
- Pazopanib
- Sunitinib

Project Period

Planned start date: 1 June 2017

Planned end date: 31 December 2025

Final report: 1 June 2026

Pharmacokinetics

A 3 mL blood sample for pharmacokinetic analysis will be drawn at 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter for most compounds, except for compounds with intermittent dosing or a long half-life (see Appendix V for details on PK sampling per compound).

	Patients will be instructed to let the blood sample be drawn after the T_{max} of the compound has been reached. The concentration of the drug in the blood will be measured using a validated LC-MS/MS method. Time of last dose intake and time of blood sampling will be registered. The formula proposed by Wang *et al* will be used to estimate the trough plasma concentration.(10)
Participating drugs	- Abiraterone (cohort completed) - Alectinib - Axitinib - Bosutinib - Cabozantinib (cohort closed) - Crizotinib - Dabrafenib/trametinib (cohort closed) - Dasatinib - Enzalutamide (cohort closed) - Erlotinib (cohort closed) - Everolimus - Gefitinib (cohort closed) - Imatinib (cohort completed) - Nilotinib - Olaparib (cohort closed) - Palbociclib (cohort on hold) - Pazopanib - Regorafenib - Sorafenib (cohort closed) - Sunitinib (cohort completed) - Tamoxifen (cohort closed) - Vemurafenib/cobimetinib - Vismodegib (cohort closed)

Dose modifications	Patients start treatment in the usual (standard) dose according to the standard of care. See Appendix V for drug-specific information regarding pharmacokinetic targets, predefined dose levels, minimum and maximum doses and time points at which pharmacokinetic samples will be drawn. For most compounds, this will be at 4, 8 and 12 weeks after start of treatment, and every 12 weeks thereafter (except for compounds with intermittent dosing or a long half-life). At these predefined time points, the concentration of the drug in the blood will be measured using a validated LC-MS/MS method. Trough levels will be calculated using the formula proposed by Wang *et al*.(10) The outcome of the trough level calculation will be reported to the treating physician within 7 - 14 days after receipt of the samples. If the trough level of the drug is below the predefined target level of that drug and the patient does not show any treatment related ≥ grade 3 toxicity, the daily dose of the drug will be increased with one dose level or the advice can be given to take the drug concomitant with food. If patients show any ≥ grade 3 toxicity, dose will be interrupted until the toxicity is ≤ grade 1. If the toxicity was treatment related the dose will be lowered with one dose level. In addition, concomitant medication will be taken into account.
Safety assessments	For Roche compounds: all data will be reported according to the Safety Data Exchange Agreement: - All related serious adverse events (SAE's) will be reported within 15 days; - All non-related SAE's will be reported within 30 days;
Efficacy assessment	- CT-scans and/or MRI-scans (or any other form of response evaluation according to current guidelines) will be performed at least every 12 weeks until documented disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Data on best response, progression-free survival and time to tumor progression will be collected;

	- Progression-free survival (PFS) will be defined as the time from start of treatment to first documentation of objective tumor progression, or to death due to any cause, whichever occurs first; - Objective response rate (ORR) will be defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1. - Time to tumor progression (TTP) will be defined as the time from start of treatment to first documentation of objective tumor progression.
Treatment duration	Patients will remain on treatment until they no longer have clinical benefit from treatment, progressive disease or if toxicity leads to patient withdrawal.
Burden and risks associated with participation	At prespecified time points one additional blood sample needs to be drawn for pharmacokinetic analysis. Hospital visits for project purposes will be monthly during the first three months of this project and once every three months thereafter. These visits can be combined with the regular visits to the outpatient clinics. Patients will be at risk for the drug related side effects.
Data management	An electronic CRF (eCRF) will be provided by central data management. Data will be entered into the eCRF by one of the investigators.
Statistics	An exact binomial test will be applied to each individual patient group. In some situations of drug and target combinations, it may prove difficult to obtain a sufficient number of patients for an acceptable level of power. A meta-analytic approach will be applied in addition to test the "prove-of-principle" of TDM. This will be reported as shown in Figure 1. For each drug the standardized change in percentage of patients with a concentration below target level 12 weeks (or at the third moment of measuring for compounds with intermittent dosing or a long half-life) after start of treatment will be calculated using the following formula: $$Standardized\ change\ in\ \% = \frac{\%\ below\ target\ level\ in\ our\ TDM\ trial}{\%\ below\ target\ level\ in\ literature}$$

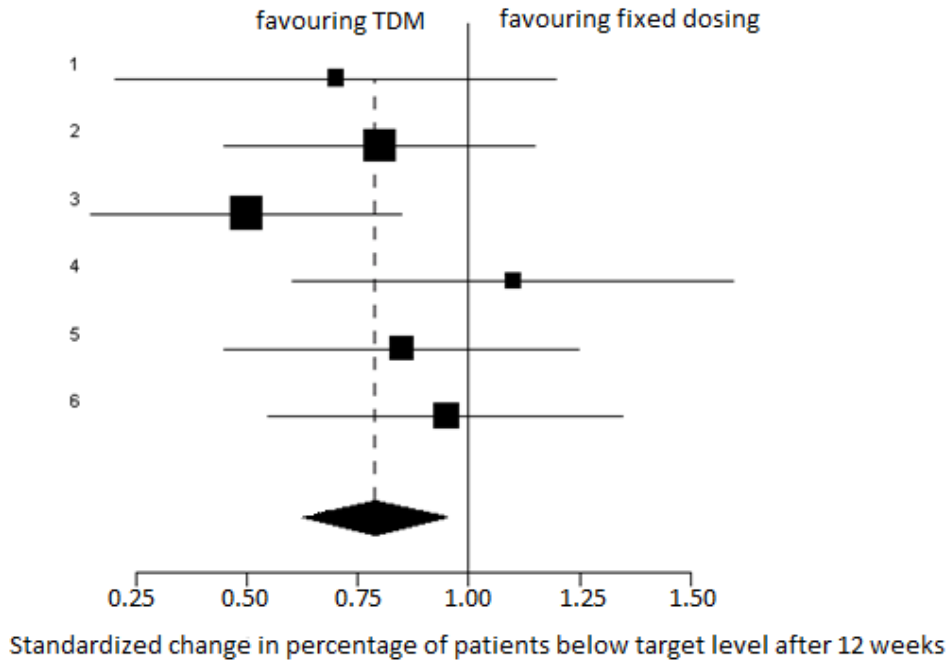

Figure 1 – Example of how the results of the meta-analytic approach to test the "prove-of-principle" of TDM will be reported.

Secondary endpoints will be described using descriptive statistics.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
BID	Bis In Die (twice daily)
CML	Chronic Myeloid Leukemia
CR	Complete Response
CRF	Case Report Form
ECG	Electrocardiogram
GIST	Gastro-Intestinal Stromal Tumor
METC	Medisch Ethische Toetsingscommissie
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NKI-AVL	Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital
OD	Once Daily
PD	Progressive Disease
PK	Pharmacokinetics
PR	Partial Response
QAD	Quaque Altera Die (every other day)
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics (in Dutch: IB1-tekst)
SD	Stable Disease
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met Mensen / Medical Research Involving Human Subjects Act

1 INTRODUCTION AND RATIONALE

In the Netherlands more than 100.000 people are diagnosed with cancer each year. In 2012 about 14.1 million new cases of cancer occurred globally.(1) It caused about 8.2 million deaths or 14.6% of all human deaths. Oral targeted anti-cancer agents form a novel group of very promising drugs which completely changed the treatment paradigm in cancer. Personalized treatment is now the standard for several tumor types. These new drugs have a complex pharmacological profile, narrow therapeutic index, and a marked pharmacokinetic interpatient variability leading to high variability in blood concentration at the currently used fixed doses.
Individual patients have a high probability to either be underdosed (>30% of patients) or overdosed (>15% of patients), which can lead to either decreased anti-tumor efficacy / treatment failure or to (severe) side effects.(2–6)

Therapeutic drug monitoring (TDM), personalized dosing based on measured drug levels, is a well-established method for personalized dosing of drugs.(5) Blood samples are collected during treatment, drug levels are measured and are used to guide further dosing. To establish the optimal dose for the individual patient, important patient and treatment characteristics are taken into account such as co-medication (e.g. potential for interactions) and co-morbidity. Despite a strong rationale for the use of TDM for oral targeted anti-cancer agents, it is currently not performed for these drugs routinely. This is partly caused by reimbursement and regulatory issues for higher than approved doses of these expensive drugs and reimbursement of drug level measurements.

A possible drawback for using TDM could include fear of increased side effects when dose increments are given. However, several studies have been performed showing TDM of oral anti-cancer drugs to be feasible and safe. Lankheet *et al* successfully performed a feasibility study in which sunitinib dosing was pharmacokinetically guided.(3) A similar study by Verheijen *et al* showed dose escalation of pazopanib to be feasible.(2) Also, for imatinib a prospective trial was performed, showing routine TDM to be a valuable contribution to clinical practice.(11) Recently, Fox *et al* published the results of a dose escalation trial with tamoxifen.(12) Furthermore, Krueger *et al* showed TDM to be feasible for everolimus treatment in children with subependymal giant cell astrocytoma.(13)

Another reason to be reluctant about the use of TDM could be that indisputable evidence of efficacy on survival and quality of life is lacking. It is highly unlikely though, given the patient numbers needed, that randomized studies evaluating TDM will ever be performed in these drugs for often rare cancer types. We therefore aim to approach the second issue within this proposal.

We do think TDM for oral anti-cancer drugs is a promising way to reduce the number of patients which are either underdosed or overdosed, and based on previous studies we think this is feasible and safe.

The aim of the current proposal is (i) to perform a prospective project implementing TDM of oral targeted anti-cancer drugs in multiple large medical centers across the nation, and (ii) to build a prospective registry to structurally collect data on the patients' clinical outcome and the effectiveness of the interventions.

2 OBJECTIVES

For the primary objective, for each oral targeted therapy cohort a maximum of 100 patients will be analyzed. For the secondary objective data of >100 patients per cohort can be analyzed.

2.1 Primary objective

To halve the proportion of patients with a drug exposure below TDM target level (historical case comparison) at the third moment of measuring after start of treatment (so after two moments of potential dose adjustment), for most compounds this will be after 12 weeks, except for compounds with intermittent dosing or a long half-life (see Appendix V for details on PK sampling per compound).

2.2 Secondary objectives

Per drug:

- To determine the safety and feasibility of PK guided dosing;
- To determine the objective response rate (according to RECIST 1.1);
- To determine the time to tumor progression and progression free survival;
- To determine the proportion of patients with a drug exposure below TDM target level at the second moment of measuring (so after one moment of potential dose adjustment).

All patients:

- To have a physician adherence of >90% in following the provided patient tailored treatment recommendations which are based on the structured TDM program.

3 PROJECT DESIGN

In this multicentre prospective intervention project, patients will start treatment on the usual (standard) dose according to the standard of care, which includes regular monitoring on drug-drug interactions, contra-indications, and other treatment specific parameters. Established TDM guidelines are followed.

TDM consists of four steps:

1. Collection of blood sample (at steady state) and measurement of drug concentrations;
2. Treatment recommendation is provided to the treating physician based on measured blood concentration, taking all relevant patient characteristics into account. This can include the advice to increase dose when drug levels are below target (and no significant side effects are seen), to take the drug concomitant with food or to consider discontinuing interacting medications. Recommendations are prepared by an adequately trained physician, pharmacist or clinical pharmacologist;
3. Implementation of treatment recommendation;
4. Monitoring of treatment outcomes (including both efficacy and toxicities).

For most compounds, trough levels will be measured at 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter, except for compounds with intermittent dosing or a long half-life. See Appendix V for drug-specific information regarding pharmacokinetic targets, predefined dose levels, minimum and maximum doses and time points at which pharmacokinetic samples will be drawn. See Appendix I for a complete overview of the project schedule.

A prospective registry will be formed to gather the clinical and pharmacokinetic data of patients. This will include demographical data, tumor type, measured trough levels, TDM recommendations, therapy advice adherence and data on tumor response and survival. On a population level this will enable us to gather important new information on the optimal use of these pharmacologically complex and expensive drugs. After 8 years the prospectively collected registry will include data on >6000 samples combined with clinical outcome data of at least 1250 patients.

For each oral targeted anti-cancer therapy the inclusion of patients is divided in three stages (Figure 2). In the first stage, approximately 30 patients are included and the feasibility of precision dosing is evaluated by the members of the DPOG. The members of the DPOG will discuss the data up to that moment and will decide if TDM is feasible for that specific drug cohort. If TDM is not feasible the first stage will be closed and further inclusion in the intervention part of the study will be stopped. If TDM is feasible or more data is needed, the second stage will be initiated, in which up to 100 patients will be included and efficacy will be evaluated. Afterwards, it can be decided to proceed to a third stage cohort, where (off-study) data can be collected of implementation into routine care. A third stage cohort can be labeled as complete, where further enrolment in this study discontinues.

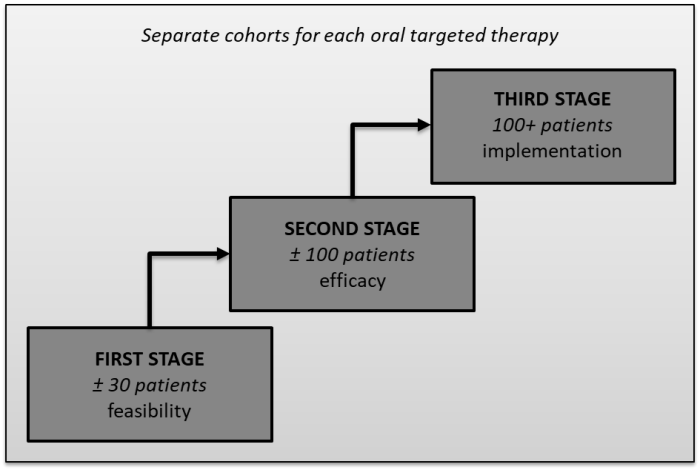

Figure 2 - Schematic overview of three-stage design for each oral targeted therapy.

4 PATIENT POPULATION

4.1 Population base

The patient population will consist of patients with histological or cytological proof of cancer for which one of the anti-cancer drugs from the list (see section 5.1) is considered standard therapy.

4.2 Inclusion criteria

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

1. Diagnosis of cancer;
2. Indication to start treatment with anti-cancer drug from list (see section with list of participating drugs) at the standard dose;
3. Age ≥ 18 years;
4. Able and willing to give written informed consent;
5. WHO performance status of 0, 1 or 2;
6. Able and willing to undergo blood sampling for PK analysis;
7. Life expectancy ≥ 3 months, allowing adequate follow up of toxicity evaluation and antitumor activity.

4.3 Exclusion criteria

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

1. Woman who are pregnant or breast feeding;
2. Unreliable contraceptive methods. Both men and women enrolled in this trial must agree to use a reliable contraceptive method throughout the treatment (adequate contraceptive methods are: condom, sterilization, other barrier contraceptive measures preferably in combination with condoms);
3. Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair treatment compliance;
4. Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or

condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications;

5. Legal incapacity.

4.4 Sample size calculation

Assumptions:

- Using standard fixed drug dosing, a substantial number of patients will have plasma levels below target, for example:
  - 52% for sunitinib (3);
  - 20 – 57% for pazopanib (2,7);
  - 11% for erlotinib (4);
  - 32% for imatinib (8);
  - 52% for vemurafenib (9).
- The aim of this project is to halve the proportion of patients with a drug exposure below target level, for example:
  - 26% for sunitinib (inadequate levels from 52% to ~26%);
  - 10 – 28.5% for pazopanib (inadequate levels from 20 – 57% to ~10 – 28.5%);
  - 5.5% for erlotinib (inadequate levels from 11% to ~5.5%);
  - 16% for imatinib (inadequate levels from 32% to ~16%);
  - 26% for vemurafenib (inadequate levels from 52% to 26%).

If we consider the percentages reported in the literature as historical controls, then using an exact binomial test with a nominal 0.05 two-sided significance level will provide the power as indicated in table 1 assuming different levels of the null and alternative hypothesis and various sample sizes. Obviously, if a higher proportion of patients is underdosed, fewer patients are needed to provide a reasonable power.

In some situations of drug and target combinations, it may prove difficult to obtain a sufficient number of patients for an acceptable level of power. A meta-analytic approach will be applied in addition to test the “prove-of-principle” of TDM.

Table 2- Power at different levels of null and alternative hypothesis and three examples of sample size.

Proportion of patients with a drug exposure below target level TDM at time point 12 weeks		Number of patients		
		30	60	90
Null	Alternative	Power (%, 1-β)		
0.10	0.05	1	19	33
0.20	0.10	18	43	71
0.30	0.15	32	71	92
0.40	0.20	60	92	98
0.50	0.25	80	97	
0.60	0.30	91		

To be evaluable for the secondary endpoint (feasibility of TDM per drug) we aim to include at least 30 patients per drug. Target plasma concentrations of all drugs are defined. In general, approximately 25-30% of the total patient group will be eligible for dose escalation. To be able to evaluate feasibility in at least 8 patients after PK guided dose escalation, we need to include about 3-4 times as many patients (at least 30 patients).

For the following compounds we will expand the patient inclusion to at least 100 patients to be able to evaluate the effect of TDM on efficacy as well:

- Abiraterone
- Imatinib
- Pazopanib
- Sunitinib

5 TREATMENT OF SUBJECTS

5.1 Participating drugs

- Abiraterone (cohort completed)
- Alectinib
- Axitinib
- Bosutinib
- Cabozantinib (cohort closed)
- Crizotinib
- Dabrafenib/trametinib (cohort closed)
- Dasatinib
- Enzalutamide (cohort closed)
- Erlotinib (cohort closed)
- Everolimus
- Gefitinib (cohort closed)
- Imatinib (cohort completed)
- Nilotinib
- Olaparib (cohort closed)
- Palbociclib (cohort on hold)
- Pazopanib
- Regorafenib
- Sorafenib (cohort closed)
- Sunitinib (cohort completed)
- Tamoxifen (cohort closed)
- Vemurafenib/cobimetinib
- Vismodegib (cohort closed)

6 MEDICINAL PRODUCTS

6.1 Name and description of investigational medicinal products

For a list of the medicinal products used in this project, see section 5.1. All drugs are approved by the EMA or are expected to be approved soon. For the drugs which are not yet approved, patients will only be included after approval. For more detailed information regarding specific drugs we refer to the Summary of Product Characteristics (SPC).

6.2 Description and justification of route of administration and dosage

For intake instructions, start dose and dose levels of the specific drugs, see Appendix V.

6.3 Preparation and labeling of Investigational Medicinal Product

6.3.1 Formulation and packaging

For information on the formulation and packaging we refer to the Summary of Product Characteristics (SPC) of the specific drugs.

6.3.2 Preparation and labelling

All drugs are stored, prepared and labeled by the pharmacies of the participating centers. This will be done as part of standard care following routine procedures, so no specific project batches need to be prepared.

7 METHODS

7.1 Parameters /endpoints

7.1.1 Main parameter/endpoint

To halve the proportion of patients with a drug exposure below TDM target level (historical case comparison) at the third moment of measuring after start of treatment (so after two moments of potential dose adjustment), for most compounds this will be after 12 weeks, except for compounds with intermittent dosing or a long half-life (see Appendix V for details on PK sampling per compound).

7.1.2 Secondary parameters/endpoints

Per drug:

- To determine the safety and feasibility of PK guided dosing;
- To determine the objective response rate (according to RECIST 1.1);
- To determine the time to tumor progression and progression free survival;
- To determine the proportion of patients with a drug exposure below TDM target level at the second moment of measuring (so after one moment of potential dose adjustment).

All patients:

- To have a physician adherence of >90% in following the provided patient tailored treatment recommendations which are based on the structured TDM program.

7.2 Patient accrual and registration procedures

The nature and the purpose of this project will be explained to each potential patient by the investigator or by a person nominated by the investigator. Patients will get written information about the project and they will get the opportunity to ask any questions. Patients will be registered in ALEA. Patients can be registered before start of treatment or before the first moment of measuring. Patients will be informed about the prospective data collection and will be asked for consent, this will be noted in their medical file.

7.3 Screening / baseline assessments

- Demographic data (including date of birth, gender, ethnic origin);
- In- and exclusion criteria;
- Medical history (including details of malignancy, stage of cancer and previous treatments);
- Any additional assessments that are clinically indicated for the respective drug;
- Baseline signs and symptoms, using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03);
- Baseline radiological and clinical tumor assessments as per RECIST Version 1.1 (see Appendix).

After all baseline and screening evaluations have been completed and the patient fulfils all in- and exclusion criteria the patient can be registered in the project according to the procedures in paragraph 02. Patients can be registered until 4 weeks after start of treatment.

The project schedule (see Appendix I) summarizes the minimal assessments required for each patient. Additional parameters and/or increased frequency of observations may be required at the investigator's discretion and according to current standard of treatment and the toxicities observed.

7.4 Treatment administration

For the dosing schedules of the specific drugs, see Appendix V.

7.4.1 Premedication and supportive care

There will be no premedication. Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician.

7.5 Dosages, dosage modifications and method of administration

7.5.1 Dose selection and escalation schedule

For the starting dose and the dose levels per drug, see Appendix V.

7.5.2 Method of administration

For the intake instructions per drug, see Appendix V.

7.6 Dose modifications for toxicity

Patients experiencing grade 3 or 4 treatment related toxicity or intolerable grade 2 toxicity despite supportive care can resume treatment at the next lowest dose level once adequate recovery is achieved as assessed by the investigator. For more information on dose adjustments per drug, see Appendix V.

7.7 Treatment duration

Treatment will be continued until disease progression, unacceptable treatment related toxicity or until patients do not want to proceed treatment anymore.

7.8 Compliance and handling of drug intake

Patients will be encouraged to take their medication at approximately the same time each day. Patients will be instructed that if they miss a day's dose, they must not double up the next day's dose but simply resume the dosing schedule the following day.

7.9 Safety measurements

Measurements used to evaluate safety will include assessment of adverse events using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03). Also, physical examinations and laboratory evaluations will be done as a part of standard care.

7.10 Assessments during the project

For most compounds, the following assessments will take place at 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter, except for compounds with intermittent dosing or a long half-life. See Appendix V for drug-specific information regarding these time points. See appendix I for a complete overview of the project schedule.

- Review of concomitant medication;

- Adverse events using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03, including start and stop dates, severity, relationship to the drug, outcome and action taken);
- Any additional assessments that are clinically indicated for the respective drug;
- PK sample for calculating C_{min} of the drug (time of last dose intake and time of blood sampling will be registered, patients will be instructed to let the blood sample be drawn after the T_{max} of the compound has been reached);
- The concentration of the drug in the blood will be measured using a validated LC-MS/MS method. The formula proposed by Wang *et al* will be used to estimate the trough plasma concentration(10);
- Treatment recommendation is provided to the treating physician within 7 – 14 days, based on measured blood concentration, taking all relevant patient characteristics into account. This can include the advice to increase dose when drug levels are below target (and no significant side effects are seen), to take the drug concomitant with food or to consider discontinuing interacting medications. See Appendix V for the predefined targets and dose levels per drug. Recommendations will be prepared by an adequately trained physician, pharmacist or clinical pharmacologist;
- Radiological and clinical tumor assessments as per RECIST Version 1.1 (see Appendix) will be performed every 12 weeks until documented disease progression.

7.15 Pharmacokinetics & pharmacodynamics

7.15.1 Pharmacokinetics

A 3 mL blood sample for pharmacokinetic analysis will be drawn at 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter for most compounds, except for compounds with intermittent dosing or a long half-life (see Appendix V for details on PK sampling per compound). Patients will be instructed to let the blood sample be drawn after the T_{max} of the compound has been reached.

The concentration of the drug in the blood will be measured using a validated LC-MS/MS method. Time of last dose intake and time of blood sampling will be registered. The formula proposed by Wang *et al* will be used to estimate the trough plasma concentration.(10) See Appendix for PK sample collection, storage and shipment procedures.

7.15.2 Volume of blood collections

Total volume of blood samples for pharmacokinetics is 3 mL per sample. For most drugs samples will be drawn 4, 8 and 12 weeks after start of treatment and every 12 weeks thereafter.

7.17 Tumor response evaluation

Tumor response is assessed either in measurable or evaluable tumor lesions according to the RECIST criteria, Version 1.1 (see Appendix). Patients are evaluable for response to treatment if at least one follow-up examination was performed in week 12 (after 3 cycles). The response assessment will be performed every 12 weeks.

8 SAFETY REPORTING

8.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a patient, whether or not considered related to the drug. All adverse events reported spontaneously by the patient, observed or questioned by the investigator or his staff will be recorded.

The information that will be recorded in the patient's file consists of:

- Description of the event;
- Start and stop date;
- Severity of the event;
- Relationship with anti-cancer medication;
- Action taken (including medication);
- Clinical outcome;
- Consequences for the anti-cancer medication.

Adverse events should be collected beginning from the time the patient starts the treatment and ending with the follow-up visit. Adverse events in clinical investigation include any change from the patient's baseline (pre-treatment) condition. This includes symptoms, physical findings or clinical signs and significant changes in laboratory values (see section 0).

All adverse events encountered during the clinical project will be recorded in the patient's file.

Every effort will be made by the investigator to categorize each adverse event according to its severity and its relationship with anti-cancer treatment.

For all compounds, the information on adverse events will be used in preparing the treatment recommendations.

8.2.1 Clinical laboratory abnormalities and other abnormal assessments

Abnormal laboratory findings (e.g. clinical chemistry and hematology) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as **clinically significant** or result

in change of anti-cancer medication will be reported as AEs or, if they meet the definition of an SAE, as such.

However, clinically significant abnormal findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the treatment and do not worsen, will **not** be reported as AEs or SAEs.

8.2.2 Assessing severity of adverse events

Adverse events will be graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03, June 14, 2010). Adverse events that are not reported according to NCI-CTCAE criteria are graded as 'mild', 'moderate', 'severe', 'life threatening' or 'death'.

The treating physician or delegate will determine the severity of events reported in the patient's file as follows:

If the adverse event is listed in the NCI-CTCAE table, then note all levels that the adverse event reached and adverse event duration until resolution to grade ≤ 1, except alopecia.

If the adverse event is not listed in the NCI-CTCAE table, then note all levels reached, according to the following description:

Grade 1 = Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 = Moderate: minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.

Grade 3 = Severe: or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**

Grade 4 = Life-threatening: consequences; urgent intervention indicated.

Grade 5 = Death: related to AE.

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2.3 Classification of relationship to treatment

Items to be considered when assessing the relationship of an adverse event to the treatment are:

- Temporal relationship of the onset of the event to the initiation of the anti-cancer treatment;
- The course of the event, considering especially the effect of discontinuation of anti-cancer treatment or reintroduction of anti-cancer treatment, as applicable;
- Whether the event is known to be associated with the anti-cancer treatment, or with other similar treatments;
- The presence of risk factors in the subject known to increase the occurrence of the event;
- The presence of non-anti-cancer treatment related factors, which are known to be associated with the occurrence of the event.

The relationship with an adverse event to anti-cancer treatment will be reported in the patient's file and defined as: 'unrelated', 'unlikely', 'possible', 'probable' or 'definite'.

Unrelated: the event is clearly related to other factors such as the patient's clinical state, other therapeutic interventions or concomitant drugs administered to the patient,

Unlikely: the toxicity is doubtfully related to the investigational agent. The event was most likely related to other factors, such as the patient's clinical state, other therapeutic interventions, or concomitant drugs,

Possible: the event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the patient's clinical state, other therapeutic interventions or concomitant drugs,

Probable: the event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the anti-cancer drug. The toxicity cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions or concomitant drugs,

Definite: the event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the anti-cancer drug, cannot be reasonably explained by other factors such as the patient's condition,

therapeutic interventions or concomitant drugs; AND occurs immediately following anti-cancer drug administration, improves on stopping the drug, or reappears on re-exposure.

8.3 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatient's hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Life threatening: the term 'life threatening' in the definition of 'serious' refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: 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 arranged prior to the start of the treatment, documented in the patient's file);
- prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event.

Events due to progression of the disease are not regarded as an SAE.

Serious adverse events will be reported only for Roche compounds (erlotinib and vismodegib). For these compounds, each SAE will be followed up until resolution or stabilization, which has to be recorded and reported.

8.3.1 Reporting of serious adverse events

For erlotinib and vismodegib, all related SAEs must be reported **within 15 days** to Roche according to the Safety Data Exchange Agreement. All non-related SAEs must be reported **within 30 days**. Other sites can report SAEs, by telephone or fax or e-mail, to the AVL Safety Desk:

Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
Fax: 0031 (0)20-5122679
E-mail: drugsafety@nki.nl

If a fax is not possible due to technical problems, the Safety Desk should be contacted by telephone: 0031 (0)20-5129047 or 5129047 between 09.00 and 17.00 hours Monday to Friday.

Follow up reports will be written when applicable.

8.3.3 Reporting SAEs to the pharmaceutical company

For Roche compounds: all data will be reported according to the Safety Data Exchange Agreement:

- All related serious adverse events (SAE's) will be reported within 15 days;
- All non-related SAE’s will be reported within 30 days;

8.5 Data Safety Monitoring Board (DSMB)

There will be no DSMB or safety committee, since the drugs used in this project are approved and only given to patients for which this is standard care.

9 STATISTICAL ANALYSIS

The data cut-off date for the final analysis for the project will be when all patients continuing treatment have been followed for at least 12 weeks (or 3 moments of pharmacokinetic measurements for compounds with intermittent dosing or a long half-life) or when treatment has been discontinued.

9.1 Populations for analysis

The full analysis set includes all patients who received at least one dose of the anti-cancer drug.

- Patients will only be considered evaluable for the primary endpoint if they have completed the first 12 weeks (or three moments of pharmacokinetic measurements for compounds with intermittent dosing or a long half-life);
- Response should be evaluated according to RECIST 1.1 criteria when possible.

9.2 Pharmacokinetic analyses

We will use the formulas proposed by Wang et al to calculate the trough plasma concentration.(10)

9.3 Methods of statistical analyses

An exact binomial test will be applied to each individual patient group. In some situations of drug and target combinations, it may prove difficult to obtain a sufficient number of patients for an acceptable level of power. A meta-analytic approach will be applied in addition to test the "prove-of-principle" of TDM. This will be reported as shown in Figure 1. For each drug the standardized change in percentage of patients with a concentration below target level 12 weeks (or three moments of measuring for compounds with intermittent dosing or a long half-life) after start of treatment will be calculated using the following formula:

$$Standardized\ change\ in\ \% = \frac{\%\ below\ target\ level\ in\ our\ TDM\ trial}{\%\ below\ target\ level\ in\ literature}$$

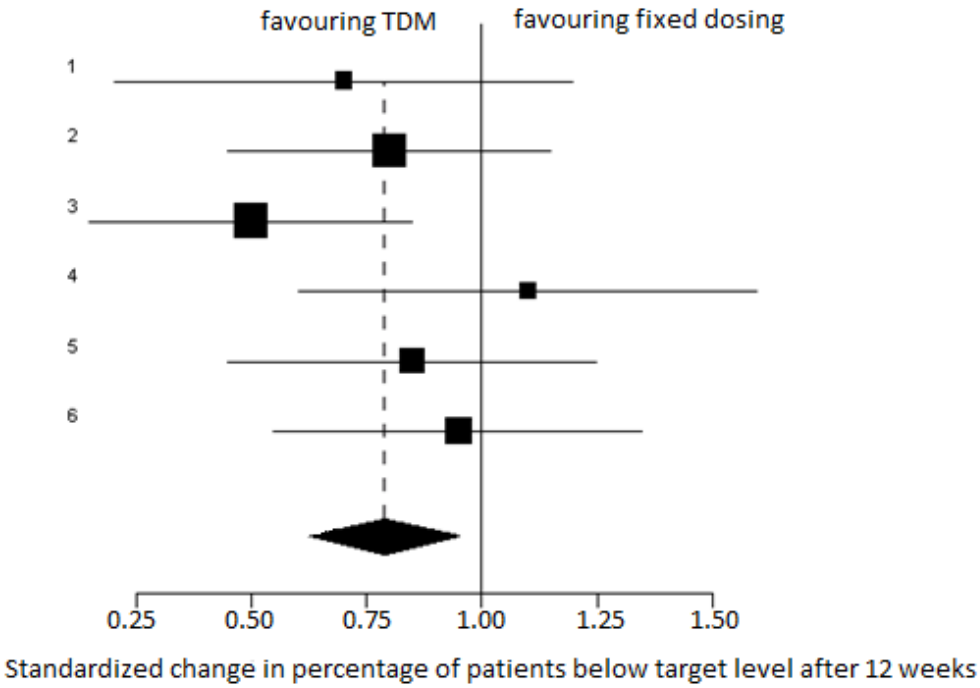

Figure 1 – Example of how the results of the meta-analytic approach to test the "prove-of-principle" of TDM will be reported.

Secondary endpoints will be described using descriptive statistics.

10 ETHICAL CONSIDERATIONS

Since measuring the blood concentrations of the participating drugs is part of standard care, the METC-AVL assessed this project as not subjected to the Medical Research Involving Human Subjects Act (WMO).

Patients will be informed about the prospective data collection and will be asked for consent, this will be noted in their medical file.

11 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

All data that are relevant for the project will be collected in an eCRF. Results will be processed anonymously, identified by a unique patient serial number. Only persons involved in the patients' standard care have access to the source data. The key to the patient serial numbers is safeguarded by one of the members of the investigator team.

11.2 Electronic CRF (eCRF)

All data that are relevant for the project will be collected in an eCRF, which will be provided by Central data management. Data will be entered into the eCRF by one of the investigators.

11.3 Confidentiality of patients

All records identifying the patients will be kept confidential and will not be made publicly available. Results will be processed coded, identified by a unique patient serial number.

11.4 Amendments

The project protocol will be updated regularly, taking into account new literature on pharmacokinetic targets and new compounds.

11.5 Financing of the trial

This project will be funded by Novartis, Roche and Pfizer.

11.6 Publication

Members of the protocol writing committee will become co-authors. All investigators will be informed in writing prior to any written communication or oral presentation about the project and invited to give comments.

12 STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Previous experience

Practical guidelines for TDM for all drugs have been developed previously.(5) Validated assays are available for all oral anticancer drugs in this proposal. Validation is performed in line with international guidelines (EMA, FDA). A proven adequate infrastructure for sample collection and shipment, short turn-over and reporting is available. For 2015, only the Netherlands Cancer Institute (NKI) measured concentrations in approximately 1500 samples. We performed two prospective clinical trials to show the safety and feasibility of TDM for sunitinib and pazopanib, respectively.(2,3) We have previously shown in a retrospective analysis that substantial number of patients are underexposed.(4)

Burden and risks associated with participation

At prespecified time points one additional blood sample needs to be drawn for pharmacokinetic analysis. Hospital visits for project purposes are monthly during the first three months of this project and once every three months thereafter. These visits will include toxicity assessments and can be combined with the regular visits to the outpatient clinics.

Patients are at risk for the drug related side effects. Before each moment of potential dose escalation, toxicity will be assessed. The dose will only be increased if the patient does not show any ≥ grade 3 toxicity. In case of ≥ grade 3 toxicity, dosing will be interrupted until toxicity is ≤ grade 1.

In our opinion, these minimal risks are acceptable for the subjects participating in the project.

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APPENDIX I PROJECT SCHEDULE

Project procedures	**Screening/ Baseline**	**Week 4**	**Week 8**	**Week 12**	**Every 12 weeks thereafter**
Demographic Data[1]	X				
In- and exclusion criteria	X				
Medical History[2]	X				
Concomitant medication[3]	X	X	X	X	X
Tumor assessment[4]	X			X	X
Toxicity assessments[5]	X	X	X	X	X
Medication	X	X	X	X	X
PK samples[6]		X	X	X	X
Treatment recommendations		X	X	X	X

1) Demographic data: including date of birth and gender

2) Medical History: including details of malignancy, stage of cancer and number of lines of previous therapies.

3) Concomitant medication: this will be used to prepare treatment recommendations, in the eCRF will be noted if there are relevant interactions (see Appendix V).

4) Tumor assessment by the most appropriate examination tool as defined before treatment every 12 weeks and according to the RECIST 1.1 criteria.

5) Toxicity assessments: baseline signs and symptoms and all related and unrelated adverse events will be assessed using the NCI-CTCAE criteria Version 4.03. This will not be recorded in the eCRF, but will be used to prepare treatment recommendations.

6) PK after 4, 8 and 12 weeks and every 12 weeks thereafter for most drugs, unless stated otherwise in Appendix V (for compounds with intermittent dosing or a long half-life).

APPENDIX II WHO/ECOG PERFORMANCE STATUS

Grade	WHO
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house hold work, office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

APPENDIX III RECIST CRITERIA VERSION 1.1

Assessment of the change in tumor burden will be done according to the RECIST guidelines version 1.1. These are described in "New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1), European Journal of Cancer 45 (2009) 228–247. Below an outline of these criteria is described. Possible decisions or modification are described in the protocol (*see chapter 7.18: "Tumor response evaluation"*).

Measurability

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable:

- *Measurable lesions:* Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm by CT scan (assuming that CT slice thickness is no greater than 5 mm, otherwise measurable lesion minimum is 2x slice thickness) or by caliper measurement by clinical exam. Lesions measured by chest X-ray should have a minimum size of 20 mm.
- *Measurable 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:* All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions.

Methods of Measurement

All measurements should be taken and recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the starting of treatment and never more than 4 weeks before the starting 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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). Lesions which cannot be accurately measured with calipers should be recorded as non-measurable. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g. for body scans). Head and neck tumors and those of extremities usually require specific protocols. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

The utilization of endoscopy and laparoscopy will only be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers *alone* cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.

Cytology and histology can be used to differentiate between PR and CR in rare cases if required by protocol.

Baseline documentation of 'target' and 'non-target' lesions

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion.
In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions in total (and a maximum of two lesions per organ) 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 and their suitability for reproducible repeated measurements (either by imaging techniques or clinically).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained. The smaller of these measures is the short axis. All other pathological nodes (those with short axis $\geq$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameter (longest for non-nodal lesions, short axis for nodal lesions) for all **target lesions** will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression. All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required and these lesions should be followed as 'present' or 'absent (or is rare cases 'unequivocal progression').
In addition it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple liver metastases').

Response Criteria

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). In addition 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 progression).
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.

Table 1: Evaluation of target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

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).
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 (Note: there must be an overall level of substantial worsening in non-target

	disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy)

Table 2: Evaluation of non-target lesions

New lesions
The appearance of new malignant lesions denotes disease progression. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression (f.i. brain metastases). If a new lesion is equivocal and repeat scans confirm the new lesion, then progression should be declared using the date of the **initial** scan.

Evaluation of best overall response

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted.

The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

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-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
Target lesions	*Non-target lesions*	*New lesions*	*Overall response*
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 3: Time point response: patients with target(+/- non-target) disease

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having 'symptomatic deterioration'. Every effort should be made to document the objective progression even after

discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

Confirmation

In **non-randomized trials** where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. The assessment should be repeated at a subsequent time point as specified in the protocol (generally 4 weeks later)**.** This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, i.e. in **randomized trials** (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol).

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded on study.

Duration of stable disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for disease progression are met, taking as reference the smallest sum on study. The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Response review

For trials where the objective response (CR + PR) is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even

if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumor assessments not repeated/incomplete; other (specify)).

Normally, all eligible patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should not be based on a selected 'evaluable' subset

APPENDIX IV PK SAMPLE COLLECTION, STORAGE AND SHIPMENT

Analysis of PK samples will occur at the Bioanalytical Laboratory of the Department of Pharmacy & Pharmacology of The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Erasmus Medical Center (Rotterdam), University Medical Center Radboud (Nijmegen), Leiden University Medical Center (Leiden) or University Medical Center Groningen (Groningen), using a validated LC-MS/MS method.

APPENDIX V PK TARGETS AND DOSING INSTRUCTIONS PER DRUG

Table of contents

1. Abiraterone (Zytiga)

Indication:

- Metastatic castration-resistant prostate cancer
- Metastatic hormone-sensitive prostate cancer

Start dose: 1000 mg OD

Target: (calculated) trough level ≥ 8.4 ng/mL, based on Carton *et al*.(14)

Dose levels:

Dose level	Abiraterone dose	Change from start dose
- 1	500 mg OD	- 500 mg
0	1000 mg OD	0
+ 1	1000 mg OD + light snack or low-fat meal	0
+ 2	1500 mg OD + light snack or low-fat meal	+ 500 mg

Abiraterone dose will not be further increased than 1500 mg once daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Abiraterone should be administered without food, at least one hour before or two hours after a meal (modified fasting state).

Food effect:
The first step in case of abiraterone trough levels below target will be to take abiraterone concomitant with a light snack or a low-fat meal, based on Chi *et al*.(15) The abiraterone capsules should be taken within 30 minutes after start of the meal.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of abiraterone:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 8.4 ng/mL: increase one dose level	TL < 8.4 ng/mL: increase one dose level	TL < 8.4 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 8.4 ng/mL: continue at the same dose level	TL ≥ 8.4 ng/mL: continue at the same dose level	TL ≥ 8.4 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level abiraterone

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding liver enzyme test disorders see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of abiraterone:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding liver enzyme test disorders see below.

Specific dose modification guidelines:

Liver enzyme test disorders

Severity	**Recommended action**
Grade 3 (> 5 x ULN)	Withhold dosing until recovery to baseline, reduce dose to 500 mg OD or two dose levels and resume treatment. In case of recurrence, abiraterone should be permanently discontinued.
Grade 4 (> 20 x ULN)	Permanently discontinue treatment with abiraterone.

PK samples:

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after each dose adjustment
- every 12 weeks until treatment discontinuation

2. Alectinib (Alecensa)

Indication: NSCLC, ALK-positive

Start dose: 600 mg BID

Target: ≥ 435 ng/mL, based on exposure-response analyses of Groenland *et al*.(16)

Dose levels:

Dose level	Alectinib dose	Change from start dose
- 2	300 mg BID	- 300 mg
- 1	450 mg BID	- 150 mg
0	600 mg BID	0
+ 1	750 mg BID	+ 150 mg
+ 2	900 mg BID	+ 300 mg

Alectinib dose will not be further increased than 900 mg twice daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Alectinib should be administered with food.

Interactions:

- No clinical significant interactions with drugs that increase the pH in the stomach are reported.
- No clinical significant interactions with CYP-enzymes and Pgp-modulators are reported.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of alectinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 435 ng/mL: increase one dose level	TL < 435 ng/mL: increase one dose level	TL < 435 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 435 ng/mL: continue at the same dose level	TL ≥ 435 ng/mL: continue at the same dose level	TL ≥ 435 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level alectinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding liver enzyme test disorders, bradycardia, CPK elevation and ILD/pneumonitis see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of alectinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding liver enzyme test disorders, bradycardia, CPK elevation and ILD/pneumonitis see below.

Specific dose modification guidelines

Liver enzyme test disorders

Liver enzyme test disorders	**Alectinib treatment**
AST/ALT elevation > 5 x ULN with total bilirubin ≤2 x ULN	Withhold dosing until recovery to baseline or ≤3 x ULN, reduce dose with one dose level or to the previous dose in case of previous dose escalation and resume treatment.
AST/ALT elevation >3 x ULN with concurrent total bilirubin elevation >2 x ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue alectinib treatment.
Total bilirubin elevation > 3 x ULN	Withhold dosing until recovery to baseline or ≤ 1.5 x ULN, reduce dose with one dose level or to the previous dose in case of previous dose escalation and resume treatment.

Bradycardia

CTC-AE grade	Alectinib treatment
Symptomatic	Withhold dosing until recovery to asymptomatic bradycardia or to heart rate ≥ 60 bpm Evaluate concomitant medication. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume alectinib at the same dose level. If no contributing concomitant medicine is identified and discontinued, or its dose is adjusted, reduce alectinib dose with one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
Life-threatening consequences, urgent intervention indicated	If no contributing concomitant medication is identified, permanently discontinue alectinib treatment. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, withhold dosing until recovery to asymptomatic bradycardia or to heart rate ≥ 60 bpm, reduce alectinib dose with one dose level or to the previous dose level in case of previous dose escalation and resume treatment. Monitor frequently. In case of recurrence, alectinib should be permanently discontinued.

Creatine phosphokinase (CPK) elevation

CPK elevation	Alectinib treatment
CPK elevation > 5 x ULN	Withhold dosing until recovery to baseline or to ≤ 2.5 x ULN, resume treatment at the same dose level.
CPK elevation > 10 x ULN or second occurrence of CPK elevation > 5 x ULN	Withhold dosing until recovery to baseline or to ≤ 2.5 x ULN, reduce dose with one dose level or to the previous dose level in case of previous dose escalation and resume treatment.

Interstitial lung disease (ILD)/pneumonitis

Withhold dosing if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after each dose adjustment
- every 12 weeks until treatment discontinuation

3. Axitinib (Inlyta)

Indication:
RCC, previously treated with sunitinib or cytokines

Only patients with monotherapy axitinib are eligible for inclusion. Patients with combination therapy (e.g. axitinib + pembrolizumab) are not eligible for inclusion.

Start dose: 5 mg BID

Target: (calculated) trough level ≥ 5 ng/ml based on Tsuchiya *et al*.(17)

Dose levels:

Dose level	Axitinib dose	Change from start dose
-2	2 mg BID	- 6 mg
-1	3 mg BID	- 4 mg
0	5 mg BID	0
+1	7 mg BID	+ 4 mg
+2	10 mg BID	+ 10 mg

Axitinib dose will not be further increased than 10 mg twice daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Axitinib can be administered with or without food.

Interactions:
- Concomitant use of (strong) CYP3A4/5-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4/5-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of axitinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 5 ng/mL: increase one dose level	TL < 5 ng/mL: increase one dose level	TL < 5 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 5 ng/mL: continue at the same dose level	TL ≥ 5 ng/mL: continue at the same dose level	TL ≥ 5 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level axitinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels for axitinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after each dose adjustment
- every 12 weeks until treatment discontinuation

4. Bosutinib (Bosulif)

Indication: Ph+ CML, when imatinib, dasatinib and nilotinib are no options

Start dose: 500 mg OD

Target: (calculated) trough level ≥ 147 ng/mL, no PK target was reported in the literature, therefore based on Yu *et al* the median C_{min} of the approved dose is used.(5)(18)

Dose levels:

Dose level	Bosutinib dose	Change from start dose
- 2	300 mg OD	- 200 mg
- 1	400 mg OD	- 100 mg
0	500 mg OD	0
+ 1	600 mg OD	+ 100 mg

Bosutinib dose will not be further increased than 600 mg once daily.

Intake instructions:
Bosutinib should be administered with food.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of drugs that increase the pH in the stomach should be avoided, proton pump inhibitors should be replaced by antacids if necessary, with an interval of 12 hours between bosutinib and the antacids.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of bosutinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 147 ng/mL: increase one dose level	TL < 147 ng/mL: increase one dose level	TL < 147 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 147 ng/mL: continue at the same dose level	TL ≥ 147 ng/mL: continue at the same dose level	TL ≥ 147 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level bosutinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption. For dose modification guidelines regarding neutropenia, thrombocytopenia or liver enzyme test disorders see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of bosutinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption. For dose modification guidelines regarding neutropenia, thrombocytopenia or liver enzyme test disorders see below.

Specific dose modification guidelines

Neutropenia and/or thrombocytopenia

Severity	Recommended action
ANC < 1.0 x 10^9/L or platelet count < 50 x 10^9/L	1. Stop dosing until ANC ≥ 1.0 x 10^9/L or platelet count > 50 x 10^9/L 2. Resume treatment at the same dose level 3. If ANC ≤ 1.0 x 10^9/L or platelet count ≤ 50 x 10^9/L again reduce dose by one dose level

Liver enzyme test disorder

Severity	Recommended action
AST/ALT > 5 x ULN	Withhold dosing until ≤ 2.5 x ULN, reduce dose with one dose level and resume treatment. If recovery takes more than 4 weeks, permanently discontinue treatment with bosutinib
AST/ALT > 3 x ULN and bilirubin > 2 x ULN	Permanently discontinue treatment with bosutinib

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

5. Cabozantinib (Cabometyx)

Indication:

- mRCC
- HCC

Advise is not formulated for patients with metastatic medullary thyroid cancer treated with Cometriq®

Start dose: 40 mg OD

According to the label, the recommended dose is 60 mg OD. However, in clinical practice many patients start at 40 mg OD (due to anticipated toxicity at 60 mg OD). In addition, the target is based on the mean/median exposure in the 40 mg OD dose level. Therefore, only patients starting cabozantinib treatment at 40 mg OD can be included in the study.

Target: ≥ 750 ng/mL, based on exposure-response analyses of Lacy *et al.*(19)

Dose levels:

Dose level	Cabozantinib dose	Change from start dose
- 1	20 mg OD	- 20 mg
0	40 mg OD	0
+ 1	60 mg OD	+ 20 mg
+ 2	60 mg OD + food	+ 20 mg
+ 3	80 mg OD + food	+ 40 mg

Cabozantinib dose will not be further increased than 80 mg OD + food.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Cabozantinib should be administered without food (except for dose level +2 and +3), at least one hour before or two hours after a meal (modified fasting state).

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- No clinically significant interactions with drugs that increase the pH in the stomach are reported.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of cabozantinib:

Toxicity				
No toxicity	**Grade1**	**Grade2***	**Grade3**	**Grade 4**
TL < 750 ng/mL: increase one dose level	TL < 750 ng/mL: increase one dose level	TL < 750 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 750 ng/mL: continue at the same dose level	TL ≥ 750 ng/mL: continue at the same dose level	TL ≥ 750 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level cabozantinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of cabozantinib:

Toxicity				
No toxicity	**Grade1**	**Grade 2***	**Grade3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption.

PK samples:
- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

6. Crizotinib (Xalkori)

Indication: NSCLC, ALK-positive or ROS1-positive

Start dose: 250 mg BID

Target: ≥ 235 ng/mL, based on the exposure-response analyses in the FDA Clinical Pharmacology & Biopharmaceutics Review and preclinical models.(20,21)

Dose levels:

Dose level	Crizotinib dose	Change from start dose
- 3	200 mg OD	- 300 mg
- 2	250 mg OD	- 250 mg
- 1	200 mg BID	- 100 mg
0	250 mg BID	0
+ 1	200 mg – 400 mg	+ 100 mg

Crizotinib dose will not be further increased than a daily dose of 600 mg.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Crizotinib should be administered with a glass of water, with or without food.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- No clinical significant interactions with drugs that increase the pH in the stomach are reported.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of crizotinib:

Toxicity				
Non-hematologic				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 235 ng/mL: increase one dose level	TL < 235 ng/mL: increase one dose level	TL < 235 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 235 ng/mL: continue at the same dose level	TL ≥ 235 ng/mL: continue at the same dose level	TL ≥ 235 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level and resume treatment**
Hematologic (excluding lymphopenia*)**				
No toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
TL < 235 ng/mL: increase one dose level	TL < 235 ng/mL: increase one dose level	TL < 235 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 2. Resume treatment at the same dose level. **	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 235 ng/mL: continue at the same dose level	TL ≥ 235 ng/mL: continue at the same dose level	TL ≥ 235 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 2. Resume treatment at the same dose level. **	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level crizotinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. For specific dose modification guidelines regarding liver enzyme test disorders, QTc prolongation, bradycardia, ILD/pneumonitis, ocular disorder, diarrhea, fatigue, nausea and vomiting and liver function test disorders see below.

*** Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of crizotinib:

Toxicity				
Non-hematologic				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level and resume treatment**
Hematologic (excluding lymphopenia*)**				
No toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 2. Resume treatment at the same dose level. **	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. For specific dose modification guidelines regarding liver enzyme test disorders, QTc prolongation, bradycardia, ILD/pneumonitis, ocular disorder, diarrhea, fatigue, nausea and vomiting and liver function test disorders see below.

*** Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Specific dose modification guidelines

Liver enzyme test disorders

CTC-AE grade	**Crizotinib treatment**
Grade 3 – 4 AST/ALT elevation with ≤ grade 1 total bilirubin elevation	Withhold dosing until ≤ grade 1 or baseline, reduce dose with two dose levels and resume treatment, escalate one dose level if clinically tolerated. In case of recurrence, crizotinib should be permanently discontinued.
Grade 2 – 4 AST/ALT elevation with concurrent grade 2 – 4 bilirubin elevation (in the absence of cholestasis or haemolysis)	Permanently discontinue crizotinib treatment.

QTc prolongation

CTC-AE grade	Crizotinib treatment
Grade 3	Withhold dosing until ≤ grade 1, check and if necessary correct electrolytes, reduce dose with one dose level or or to the previous dose level in case of previous dose escalation and resume treatment. In case of recurrence, crizotinib should be permanently discontinued.
Grade 4	Permanently discontinue crizotinib treatment.

Bradycardia

CTC-AE grade	Crizotinib treatment
Grade 2 – 3	Withhold dosing until ≤ grade 1 or to heart rate ≥ 60/min Evaluate concomitant medication. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at the same dose level. If no contributing concomitant medicine is identified and discontinued, or its dose is adjusted, reduce crizotinib dose with one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
Grade 4	If no contributing concomitant medication is identified, permanently discontinue crizotinib treatment. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reduce crizotinib dose with two dose levels and monitor frequently.

Interstitial lung disease (ILD)/pneumonitis
Withhold dosing if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed.

Ocular disorder (visual loss)
Discontinue during evaluation of severe vision loss.

PK samples
- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

7. Dabrafenib/Trametinib (Tafinlar/Mekinist)

Indication:

- unresectable or metastatic melanoma with a BRAF V600 mutation
- advanced non-small cell lung cancer with a BRAF V600 mutation

Start dose:

- **Dabrafenib**: 150 mg BID
- **Trametinib**: 2 mg OD

Target:

- **Dabrafenib**: concentrations will only be measured, no dose adaptations will be advised.
- **Trametinib**: (calculated) trough level ≥ 10.6 ng/mL, based on Ouellet *et al*.(22)

Dose levels:

Trametinib schedule

Dose level	Trametinib dose	Change from start dose
-2	1 mg OD	- 1 mg
-1	1.5 mg OD	- 0.5 mg
0	2 mg OD	0
+1	2.5 mg OD	+ 0.5 mg
+2	3 mg OD	+ 1 mg

Trametinib dose will not be further increased than 3 mg once daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:

Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal, with an interval of approximately 12 hours between doses. Dabrafenib capsules should not be mixed with food or liquids due to chemical instability of dabrafenib.

Trametinib should be taken with a full glass of water without food, at least 1 hour before or 2 hours after a meal. When trametinib and dabrafenib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

Interactions:

- Concomitant use of drugs that increase the pH in the stomach should be avoided
- Concomitant use of (strong) CYP3A4- or CYP2C8-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4- or CYP2C8-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

- Concomitant use of P-glycoprotein-inhibitors (including (but not limited to) ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) should be avoided.

Dose modifications based on treatment-associated toxicity and trough levels of trametinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 10.6 ng/mL: increase one dose level	TL < 10.6 ng/mL: increase one dose level	TL < 10.6 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 10.6 ng/mL: continue at the same dose level	TL ≥ 10.6 ng/mL: continue at the same dose level	TL ≥ 10.6 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level trametinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. See also specific dose modification guidelines regarding fever, uveitis, cutaneous squamous cell carcinoma, new primary melanoma, RAS-mutation-positive non-cutaneous malignancies, left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of trametinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding fever, uveitis, cutaneous squamous cell carcinoma, new primary melanoma, RAS-mutation-positive non-cutaneous malignancies, left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis see below.

Specific dose modification guidelines

If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued, unless stated otherwise.

Fever

If the patient's temperature is ≥38.5$^{\circ C}$, therapy with dabrafenib should be interrupted, trametinib should be continued at the same dose. Treatment with anti-pyretics such as paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice.
Upon resolution of pyrexia dabrafenib should be restarted with appropriate anti-pyretic prophylaxis, either 1) at the same dose level, or 2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

Uveitis

No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib.

RAS-mutation-positive non-cutaneous malignancies
The benefits and risks should be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

LVEF reduction
Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN). No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring.
With Grade 3 or 4 left ventricular cardiac dysfunction or if LVEF does not recover trametinib should be permanently discontinued.

Retinal vein occlusion (RVO)
In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib.

Retinal pigment epithelial detachment (RPED)

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks.
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily.
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib.

ILD/pneumonitis
Withhold trametinib in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue trametinib for patients diagnosed with treatment-related ILD or pneumonitis. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib for cases of ILD or pneumonitis.

Cutaneous squamous cell carcinoma or new primary melanoma
Continue at the same dose level.

PK samples
- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

8. Dasatinib (Sprycel)

Indication: Ph+ CML

Start dose:
- Chronic phase CML: 100 mg OD
- Accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL: 140mg OD

Primary goal of TDM for Dasatinib is prevention of toxicity. For this purpose Cmin levels must be determined with. Wang et al showed that pleural effusion is significantly associated with the Cmin of dasatinib. The hazard ratio increased 1.22 time for every 1 ng/ml increase of the Cmin. (23)

Target: C_{min} < 2.5 ng/mL
C_2 > 50 ng/mL
based on , Yu *et al.* (5), Wang *et al*.(23)(24), García-Ferrer *et al*. (25), Ishidia *et al.* (26), Miura *et al.* (27) and Rousselot *et al.* (28)

Dose levels:

Dose level	Dasatinib dose	Change from start dose
- 2	50 mg OD	- 50 mg
- 1	70 mg OD	- 30 mg
0	100 mg OD	0
+ 1	140 mg OD	+ 40 mg
+ 2	180 mg OD	+ 80 mg

Dasatinib dose will not be further increased than 180 mg once daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Dasatinib can be taken with or without a meal.

Interactions:
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- H_2 antagonists and proton pump inhibitors are not recommended and aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib

Dose adjustments:

Dose modifications based on treatment-associated toxicity and C_{min} and C2 levels of dasatinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
C_{min} < 2.5 and C2 < 50 ng/mL: increase one dose level	C_{min} < 2.5 and C2 < 50 ng/mL: increase one dose level	C_{min} < 2.5 and C2 < 50 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**
C_{min} < 2.5 and C2 ≥ 50 ng/mL: continue at the same dose level	C_{min} < 2.5 and C2 ≥ 50 ng/mL: continue at the same dose level	C_{min} < 2.5 and C2 ≥ 50 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on levels of dasatinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines see below.

Specific dose modification guidelines:

Neutropenia and thrombocytopenia

Chronic phase CML (starting dose 100 mg once daily)	ANC < 0.5 x 10^9/l and/or platelets < 50 x 10^9/l	1. Stop treatment until ANC ≥ 1.0 x 10^9/l and platelets ≥ 50 x 10^9/l. 2. Resume treatment at the original starting dose. 3. If platelets < 25 x 10^9/l and/or recurrence of ANC < 0.5 x 10^9/l for > 7 days, repeat step 1 and resume treatment at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated and blast phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC < 0.5 x 10^9/l and/or platelets < 50 x 10^9/l	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukaemia, stop treatment until ANC ≥ 1.0 x 10^9/l and platelets ≥ 20 x 10^9/l and resume at the original starting dose. 3. If recurrence of cytopenia, repeat step 1 and resume treatment at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode).

		4. If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily.

Non-hematological adverse reactions

Grade 2	1. Withhold dosing until the adverse reaction has resolved or returned to baseline 2. Resume treatment at the same dose level 3. In case of recurrence, reduce dose with one dose level
Grade 3/4	1. Withhold dosing until the adverse reaction has resolved or returned to baseline 2. Resume treatment as appropriate at a reduced dose depending on the initial severity of the adverse reaction

Pleural effusion

1. Withhold dosing until patient is asymptomatic or has returned to baseline.
2. If the episode does not improve within approximately one week, a course of diuretics or corticosteroids or both concurrently should be considered.
3. Following resolution of the first episode, reintroduction of dasatinib at the same dose level should be considered.
4. Following resolution of a subsequent episode, dasatinib at one dose level reduction should be reintroduced.
5. Following resolution of a severe (grade 3 or 4) episode, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the adverse reaction.

PK samples:

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

Different PK-schedule!

9. Enzalutamide (Xtandi)

Indication: metastatic castration-resistant prostate cancer

Start dose: 160 mg OD

Target: (calculated) trough level ≥ 5 mg/L, based on Scher *et al*.(29)

Dose levels:

Dose level	Enzalutamide dose	Change from start dose
-2	80 mg OD	- 80 mg
- 1	120 mg OD	- 40 mg
0	160 mg OD	0
+ 1	200 mg OD	+ 40 mg
+ 2	240 mg OD	+ 80 mg

Enzalutamide dose will not be further increased than 240 mg once daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Enzalutamide should be administered with a glass of water, with or without food.

Interactions:

- Concomitant use of (strong) CYP2C8-inducers or - inhibitors (including (but not limited to) gemfibrozil) should be avoided.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of enzalutamide:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 5 mg/L: increase one dose level	TL < 5 mg/L: increase one dose level	TL < 5 mg/L: increase one dose level	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 5 mg/L: continue at the same dose level	TL ≥ 5 mg/L: continue at the same dose level	TL ≥ 5 mg/L: continue at the same dose level	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level enzalutamide

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of enzalutamide:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 2. For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 10 and 16 weeks after treatment initiation
- 6 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

10. Erlotinib (Tarceva)

Indication:

- NSCLC
- Pancreatic cancer

Start dose:

- NSCLC: 150 mg OD
- Pancreatic cancer: 100 mg OD + gemcitabine 1000 mg/m^2 once weekly

Target: (calculated) trough level ≥ 500 ng/mL, based on preclinical results.(30)

Dose levels:

150 mg OD schedule

Dose level	Erlotinib dose	Change from start dose
-2	50 mg OD	- 100 mg
-1	100 mg OD	- 50 mg
0	150 mg OD	0
+1	200 mg OD	+ 50 mg
+2	250 mg OD	+ 100 mg
+ 3	300 mg OD	+ 150 mg

100 mg OD + gemcitabine 1000 mg/m^2 once weekly schedule

Dose level	Erlotinib dose	Change from start dose
-1	50 mg OD	- 50 mg
0	100 mg OD	0
+1	150 mg OD	+ 50 mg
+2	200 mg OD	+ 100 mg
+ 3	250 mg OD	+ 150 mg

Erlotinib dose will not be further increased than 300 mg daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:

Erlotinib should be administered without food, at least one hour before or two hours after a meal.

Interactions:

- Concomitant use of drugs that increase the pH in the stomach should be avoided (6)
  - H2-antagonists: should be administered 2 hours after intake of erlotinib
  - antacids: should be administered 4 hours before or 2 hours after intake of erlotinib
  - PPIs should not be used
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of P-glycoprotein-inhibitors (including (but not limited to) ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) should be avoided.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of erlotinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 500 ng/mL: increase one dose level	TL < 500 ng/mL: increase one dose level	TL < 500 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 500 ng/mL: continue at the same dose level	TL ≥ 500 ng/mL: continue at the same dose level	TL ≥ 500 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level erlotinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of erlotinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

11. Everolimus (Afinitor)

Start dose: 10 mg OD

Indication:

- Hormone receptor-positive HER2/neu negative advanced **breast cancer**, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.
- Unresectable or metastatic, well- or moderately-differentiated **neuroendocrine tumours of pancreatic origin** in adults with progressive disease.
- Unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional **neuroendocrine tumours of gastrointestinal or lung origin** in adults with progressive disease.
- Advanced **renal cell carcinoma** with progression on or after treatment with VEGF-targeted therapy.

Target: (calculated) trough level ≥ 10 ng/mL, based on Ravaud *et al*.(31)

Dose levels:

Dose level	Everolimus dose	Change from start dose
- 3	2.5 mg OD	- 7.5 mg
- 2	5 mg OD	- 5 mg
- 1	7.5 mg OD	- 2.5 mg
0	10 mg OD	0
+ 1	12.5 mg OD	+ 2.5 mg
+ 2	15 mg OD	+ 5 mg

Everolimus dose will not be further increased than 15 mg daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Everolimus should be administered orally once daily at the same time every day, consistently either with or without food. Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of P-gp modulators (including (but not limited to) cyclosporine, kinidine and verapamil).

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of everolimus:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 10.0 ng/mL: increase one dose level	TL < 10.0 ng/mL: increase one dose level	TL < 10.0 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 10.0 ng/mL: continue at the same dose level	TL ≥ 10.0 ng/mL: continue at the same dose level	TL ≥ 10.0 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level everolimus

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of everolimus:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines see below.

Specific dose modification guidelines

Adverse event	Grade	Recommended everolimus dose adjustment
Non-infectious pneumonitis	2	Consider interruption of therapy until symptoms improve to ≤ grade 1. Reduce dose by one dose level or to the previous dose level in case of previous dose escalation. Discontinue treatment if failure to recover within 4 weeks.
	3	Withhold dose until ≤ grade 1. Consider resuming treatment with a dose reduction of one dose level or to the previous dose level in case of previous dose escalation. If toxicity recurs at grade 3, consider discontinuation.
	4	Discontinue treatment with everolimus permanently.
Stomatitis	2	Withhold dose until ≤ grade 1. Resume treatment at the same dose level. If stomatitis recurs at grade 2, withhold dose until ≤ grade 1, reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
	3	Withhold dose until ≤ grade 1, reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
	4	Discontinue treatment with everolimus permanently.
Other non-hematological toxicities (excluding metabolic events)	2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, withhold dose until ≤ grade 1 and resume treatment at the same dose

		level. If toxicity recurs at grade 2, interrupt dose until recovery to ≤ grade 1, reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
	3	Withhold dose until ≤ grade 1, reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment. If toxicity recurs at grade 3, consider discontinuation.
	4	Discontinue treatment with everolimus permanently.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	2	No dose adjustment required.
	3	Withhold dose temporarily, reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
	4	Discontinue treatment with everolimus permanently.
Thrombocytopenia	2	Withhold dose until ≤ grade 1 (≥ 75 * 10^9/L) and resume treatment at the same dose level.
	3 – 4	Withhold dose until ≤ grade 1 (≥ 75 * 10^9/L), reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
Neutropenia	2	No dose adjustment required.
	3	Withhold dose until ≤ grade 2 (≥ 1.0 * 10^9/L) and resume treatment at the same dose level.
	4	Withhold dose until ≤ grade 2 (≥ 1.0 * 10^9/L), reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
Febrile neutropenia	3	Withhold dose until ≤ grade 2 (≥ 1.25 * 10^9/L) and no fever, reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
	4	Discontinue treatment with everolimus permanently.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

12. Gefitinib (Iressa)

Start dose: 250 mg OD

Indication: NSCLC with EGFR-mutation

Target: (calculated) trough level ≥ 200 ng/mL, based on Zhao *et al.*(32)

Dose levels:

Dose level	Gefitinib dose	Change from start dose
- 2	250 mg twice weekly	- 179 mg
- 1	250 mg QAD	- 125 mg
0	250 mg OD	0
+ 1	500 mg OD	+ 250 mg
+ 2	750 mg OD	+ 500 mg

Gefitinib dose will not be further increased than 750 mg once daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instruction:
Gefitinib can be administered with or without food, at approximately the same time each day.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of (strong) CYP2D6-inhibitors (including (but not limited to) abiraterone, miodarone, bupropion, cimetidine, cinacalcet, fluoxetine, paroxetine, duloxetine, sertraline, ritonavir and terbinafine).
- Drugs that increase the pH of the stomach should be avoided. PPI's and H2-antagonists are not allowed. If necessary, antacids can be administered 2 hours before or 2 hours after intake of gefitinib. (6)
- No clinically significant interactions with Pgp-modulators are reported.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of gefitinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 200 ng/mL: increase one dose level	TL < 200 ng/mL: increase one dose level	TL < 200 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 200 ng/mL: continue at the same dose level	TL ≥ 200 ng/mL: continue at the same dose level	TL ≥ 200 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level gefitinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of gefitinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

13. Imatinib (Glivec)

Indication:
- GIST
- CML

Start dose:
- 400 mg OD for GIST and chronic phase CML
- 600 mg OD for accelerated phase CML, blast crisis CML or Ph+ ALL

Target:
- (calculated) trough level ≥ 1100 ng/mL for GIST, based on Demetri *et al*.(33)
- (calculated) trough level ≥ 1000 ng/mL for CML, based on Picard *et al* and Larson *et al*.(34)(35)

Dose levels:

Dose level	Imatinib dose	Change from start dose
-3	100 mg OD	- 300 mg
-2	200 mg OD	- 200 mg
-1	300 mg OD	- 100 mg
0	400 mg OD	0
+1	600 mg OD	+ 200 mg
+2	400 mg BID*	+ 400 mg

* When daily dose is incremented to 800mg the dose should be split into two intake moments.

Imatinib dose will not further increased than 400 mg twice daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Imatinib should be administered orally with a meal and a large glass of water to minimise the risk of gastrointestinal irritations.

Interactions:
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of proton pump inhibitors, H2-antagonists or antacids is permitted.(6)

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of imatinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 550 ng/mL: increase two dose levels TL 550 - 1100 ng/mL: increase one dose level	TL < 550 ng/mL: increase two dose levels TL 550 - 1100 ng/mL: increase one dose level	TL < 550 ng/mL: increase one dose level TL 550 - 1100 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**
TL ≥ 1100 ng/mL: continue at the same dose level	TL ≥ 1100 ng/mL: continue at the same dose level	TL ≥ 1100 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**

TL = trough level imatinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding decreased ANC/platelet count see below.

Patients with hematologic malignancies (target: 1000 ng/mL):

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 550 ng/mL: increase two dose levels TL 550 - 1000 ng/mL: increase one dose level	TL < 550 ng/mL: increase two dose levels TL 550 - 1000 ng/mL: increase one dose level	TL < 550 ng/mL: increase one dose level TL 550 - 1000 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**
TL ≥ 1000 ng/mL: continue at the same dose level	TL ≥ 1000 ng/mL: continue at the same dose level	TL ≥ 1000 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to the previous dose level in case of previous dose escalation and resume treatment**

TL = trough level imatinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption. For specific dose modification guidelines regarding decreased ANC/platelet count see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of imatinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding decreased ANC/platelet count see below.

Specific dose modification guidelines

Absolute neutrophil count (ANC) and platelet count

Chronic phase CML / GIST (standard dosing 400 mg OD)	
ANC/platelet count	**Dosing advice**
ANC < 1.0 x 10^9/L or platelet count < 50 x 10^9/L	1. Stop dosing until ANC > 1.5 x 10^9/L or platelet count > 75 x 10^9/L 2. Resume treatment at the same dose level 3. If ANC < 1.0 x 10^9/L or platelet count < 50 x 10^9/L again reduce dose by 300 mg
Accelerated phase CML / blastic crisis CML / Ph+ ALL (standard dosing 600 mg OD)	
ANC/platelet count	**Dosing advice**
*ANC < 0.5 x 10^9/L or platelet count < 10 x 10^9/L	1. Examine if the cytopenia is related to the leukaemia (by performing a bone marrow aspiration or biopsy) 2. If not: reduce dose to 400 mg OD 3. If cytopenia lasts for 2 weeks: reduce dose to 300 mg OD 4. If cytopenia lasts for 4 weeks and is still unrelated to the leukaemia: stop dosing until ANC ≥ 1.0 x 10^9/L or platelet count ≥ 20 x 10^9/L 5. Resume treatment at 300 mg OD

* at least one month after start of treatment.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

14. Nilotinib (Tasigna)

Indication: Ph+ CML

Start dose:
- 300 mg BID for newly diagnosed chronic phase CML
- 400 mg BID after previous treatment with imatinib

Target: (calculated) trough level ≥ 469 ng/mL, based on Verheijen *et al.*(36)

Dose levels:
300 mg BID

Dose level	Nilotinib dose	Change from start dose
- 1	400 mg OD	- 200 mg
0	300 mg BID	0
+ 1	400 mg BID	+ 200 mg
+ 2	500 mg BID	+ 400 mg
+ 3	600 mg BID	+ 600 mg

400 mg BID

Dose level	Nilotinib dose	Change from start dose
- 2	400 mg OD	- 400 mg
- 1	300 mg BID	- 200 mg
0	400 mg BID	0
+ 1	500 mg BID	+ 200 mg
+ 2	600 mg BID	+ 400 mg

Nilotinib dose will not be further increased than 600 mg twice daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Nilotinib should be administered without food, at least one hour before or two hours after a meal, with an interval of approximately 12 hours between doses.

Interactions:
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

- Concomitant use of P-glycoprotein-inhibitors (including (but not limited to) ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) should be avoided.
- Concomitant use of drugs that increase the pH in the stomach (6):
    - H2-antagonists: should be administered 10 hours before or 2 hours after intake of nilotinib
    - antacids: should be administered 2 hours before or 2 hours after intake of nilotinib
    - PPI: allowed

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of nilotinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 469 ng/mL: increase one dose level	TL < 469 ng/mL: increase one dose level	TL < 469 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**
TL ≥ 469 ng/mL: continue at the same dose level	TL ≥ 469 ng/mL: continue at the same dose level	TL ≥ 469 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**

TL = trough level nilotinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption. For specific dose modification guidelines see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of nilotinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue study treatment without interruption. For specific dose modification guidelines see below..

Specific dose modification guidelines:

Neutropenia and/or thrombocytopenia

Indication	**Severity**	**Recommended action**
Newly diagnosed chronic phase CML at 300 mg twice daily	ANC* <1.0 x 10^9/l and/or platelet counts <50 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >50 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Imatinib-resistant or intolerant CML in accelerated phase at 400 mg twice daily	ANC* <0.5 x 10^9/l and/or platelet counts <10 x 10^9/l	1. Treatment with nilotinib must be interrupted and blood count monitored. 2. Treatment must be resumed within 2 weeks at prior dose if ANC >1.0 x 10^9/l and/or platelets >20 x 10^9/l. 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.

Elevated serum lipase
For Grade 3-4 serum lipase elevations, doses should be reduced to 400 mg once daily or interrupted. Serum lipase levels should be tested monthly or as clinically indicated.

Elevated bilirubin and hepatic transaminases
For Grade 3-4 bilirubin and hepatic transaminase elevations, doses should be reduced to 400 mg once daily or interrupted. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated.

PK samples
- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

15. Olaparib (Lynparza)

Indication: maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Start dose: 400 mg BID

Target: (calculated) trough level ≥ 1.29 mg/L, no PK target is reported in the literature, therefore based on Yu *et al* the mean C_{min} of the approved dose is used.(5)(37)

Dose levels:

Dose level	Olaparib dose	Change from start dose
- 2	100 mg BID	- 600 mg
- 1	200 mg BID	- 400 mg
0	400 mg BID	0
+ 1	500 mg BID	+ 200 mg
+ 2	600 mg BID	+ 400 mg

Olaparib dose will not be further increased than 600 mg twice daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Olaparib should be administered without food, at least one hour before or two hours after a meal.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of P-gp modulators (including (but not limited to) cyclosporine, kinidine and verapamil).

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of olaparib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 1.29 mg/L: increase one dose level	TL < 1.29 mg/L: increase one dose level	TL < 1.29 mg/L: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL > 1.29 mg/L: continue at the same dose level	TL > 1.29 mg/L: continue at the same dose level	TL > 1.29 mg/L: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level olaparib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of olaparib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

16. Palbociclib (Ibrance)

Different PK-schedule!

Start dose: 125 mg OD, 3-weeks on 1-week off

Target: (calculated) trough level ≥ 61 ng/mL, no PK target was reported in the literature, therefore based on Yu *et al* the mean C_{min} of the approved dose is used.(5)(38)

Indication:
Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer

Dose levels:

Dose level	Palbociclib dose	Change from start dose
- 2	75 mg OD	- 50 mg
- 1	100 mg OD	- 25 mg
0	125 mg OD	0
+ 1	150 mg OD	+ 25 mg
+ 2	175 mg OD	+ 50 mg
+ 3	200 mg OD	+ 75 mg

Palbociclib dose will not be further increased than 200 mg once daily.

Toxicity (e.g. hematologic toxicity in blood samples) will be evaluated on the first day of the next cycle, while PK-evaluation takes places at the end of week 3.

No dose increments are allowed after a previous dose reduction for toxicity.

Intake instructions:
Palbociclib should be taken at approximately the same time each day, together with a meal.

Interactions:

- Concomitant use of proton pump inhibitors should be avoided, H2-antagonists and antacids may be used.
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of palbociclib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 61 ng/mL: increase one dose level	TL < 61 ng/mL: increase one dose level	TL < 61 ng/mL: increase one dose level	If persistent despite medical therapy, withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 if not considered a safety risk for the patient). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	If persistent despite medical therapy, withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 if not considered a safety risk for the patient). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**
TL ≥ 61 ng/mL: continue at the same dose level	TL ≥ 61 ng/mL: continue at the same dose level	TL ≥ 61 ng/mL: continue at the same dose level	If persistent despite medical therapy, withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 if not considered a safety risk for the patient). For treatment related toxicity: reduce dose by one dose level and resume treatment**	If persistent despite medical therapy, withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 if not considered a safety risk for the patient). For treatment related toxicity: reduce dose by one dose level resume treatment**

TL = trough level palbociclib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For dose modification guidelines regarding hematologic toxicities see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of palbociclib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	If persistent despite medical therapy, withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 if not considered a safety risk for the patient). For treatment related toxicity: reduce dose by one dose level and resume treatment**	If persistent despite medical therapy, withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 if not considered a safety risk for the patient). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For dose modification guidelines regarding hematologic toxicities see below.

Specific dose modification guidelines

Hematologic toxicities

CTC-AE Grade	**Recommended dose adjustment**
Grade 1 or 2	No dose adjustment required.
Grade 3	Day 1 of cycle: Withhold dosing. Repeat complete blood count within 1 week. When ≤ grade 2 start next cycle at the same dose level Day 14 of first two cycles: Continue dosing at the same dose level to complete cycle. Repeat complete blood count at day 21. Consider dose reduction in cases of prolonged (> 1 week) recovery of grade 3 neutropenia or recurrent grade 3 neutropenia in subsequent cycles.
Grade 3 ANC + temperature ≥ $38.5^{\circ C}$ and/or infection	Withhold dosing until ANC ≥ 1.0 * 10^9/L (≥ grade 2), resume with dose reduction.
Grade 4	Withhold dosing until ANC ≥ 1.0 * 10^9/L (≥ grade 2), resume with dose reduction.

PK samples

- 3, 7 and 11 weeks after treatment initiation (in the week before treatment interruption)
- 3 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

17. Pazopanib (Votrient)

Indication:

- RCC
- Soft tissue sarcoma (STS)

Start dose: 800 mg OD

Target: (calculated) trough level ≥ 20.5 mg/L, based on Suttle *et al*.(7)

Dose levels:

Dose level	Pazopanib dose	Change from start dose
-3	200 mg OD	- 600 mg
-2	400 mg OD	- 400 mg
-1	600 mg OD	- 200 mg
0	800 mg OD	0
+1	400 mg BID	0
+2	400 mg BID + food	0
+3	400 mg / 600 mg + food	+ 200 mg
+4	600 mg BID + food	+ 400 mg
+5	600 mg / 800 mg + food	+ 600 mg
+6	800 mg BID + food	+ 800 mg
+7	800 mg / 1000 mg + food	+ 1000 mg
+8	1000 mg BID + food	+ 1200 mg

Pazopanib dose will not be further increased than 2000 mg daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions

Pazopanib should be administered without food, at least one hour before or two hours after a meal, with a glass of water.

Food effect

The second step in case of pazopanib trough levels below target will be to take pazopanib concomitant with food, based on Willemsen *et al* (39). The pazopanib tablets should be taken within 30 minutes after start of the meal.

Interactions

- Concomitant use of drugs that increase the pH in the stomach should be avoided
    - H2-antagonists: pazopanib should be administered 2 hours before or 10 hours after intake of H2-antagonists
    - antacids: should be administered 4 hours before or 2 hours after intake of pazopanib
    - PPI: if not alternatives, administer together with pazopanib in the evening (6)
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of P-gp/BCRP modulators (including (but not limited to) cyclosporine, kinidine, verapamil and lapatinib).

Dose adjustments

Dose modifications based on treatment-associated toxicity and trough levels of pazopanib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 20.0 mg/L: increase one dose level	TL < 20.0 mg/L: increase one dose level	TL < 20.0 mg/L: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**
TL ≥ 20.0 mg/L: continue at the same dose level	TL ≥ 20.0 mg/L: continue at the same dose level	TL ≥ 20.0 mg/L: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**

TL = trough level pazopanib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels for pazopanib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

18. Regorafenib (Stivarga)

Different PK-schedule!

Indications

- Colorectal cancer (CRC)
- Gastrointestinal stromal tumors (GIST)

Start dose: 160 mg OD, 3-weeks on 1-week off

Target: (calculated) trough level ≥ 1400 ng/mL, no PK target is reported in the literature, therefore based on Yu *et al* the mean C_{min} of the approved dose is used.(5)(40)

Dose levels

Dose level	Regorafenib dose	Change from start dose
- 3	40 mg OD	- 120 mg
- 2	80 mg OD	- 80 mg
- 1	120 mg OD	- 40 mg
0	160 mg OD	0
+ 1	200 mg OD	+ 40 mg

Regorafenib dose will not be further increased than 200 mg daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions

Regorafenib should be taken at approximately the same time each day. Regorafenib tablets should be swallowed whole with water after a low-fat-meal.

Interactions

- No data are available on the concomitant use of proton pump inhibitors, H2-antagonists or antacids.
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

Dose adjustments

Dose modifications based on treatment-associated toxicity and trough levels of regorafenib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 1400 ng/mL: increase one dose level	TL < 1400 ng/mL: increase one dose level	TL < 1400 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 1400 ng/mL: continue at the same dose level	TL ≥ 1400 ng/mL: continue at the same dose level	TL ≥ 1400 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level regorafenib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding palmar-plantar erythrodysesthesia syndrome and AST/ALT elevations see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of regorafenib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding palmar-plantar erythrodysesthesia syndrome and AST/ALT elevations see below.

Specific dose modification guidelines

Palmar-plantar erythrodysesthesia syndrome

Dermatologic toxicity grade	Occurrence	Suggested dose modification
Grade 1: minimal skin changes or dermatitis (e.g. erythema, edema or hyperkeratosis) without pain	Any occurrence	Continue treatment at the same dose level and start supportive measures for symptomatic relief.
Grade 2: skin changes (e.g. peeling, blisters, bleeding, edema or hyperkeratosis) with pain, limiting instrumental ADL	1st occurrence	Reduce dose by one dose level or to previous dose level in case of previous dose escalation and start supportive measures for symptomatic relief. If no improvement occurs within 7 days, see below.
	No improvement within 7 days after 1st occurrence or 2nd or 3rd occurrence	Withhold dose until toxicity is ≤ grade 1, reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment. A dose re-escalation is permitted at the discretion of the treating physician.
	4th occurrence	Discontinue treatment with regorafenib permanently.
Grade 3: severe skin changes (e.g. peeling, blisters, bleeding, edema or hyperkeratosis) with pain, limiting self care ADL	1st occurrence	Start supportive measures for symptomatic relief. Withhold dosing for a minimum of 7 days and until toxicity is ≤ grade 1, reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment. A dose re-escalation is permitted at the discretion of the treating physician.
	2nd occurrence	Start supportive measures for symptomatic relief. Withhold dosing for a minimum of 7 days and

		until toxicity is ≤ grade 1, reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment.
	3rd occurrence	Discontinue treatment with regorafenib permanently

Elevations of ALT and/or AST

Observed elevations of ALT and/or AST	**Occurrence**	**Recommended measures and dose modification**
≤ 5 x upper limit of normal (ULN) (maximum grade 2)	Any occurrence	Continue treatment at the same dose level. Monitor liver function weekly until transaminases return to < 3 x ULN (Grade 1) or baseline.
> 5 x ULN - ≤ 20 x ULN (Grade 3)	1st occurrence	Withhold dosing and monitor transaminases weekly until return to < 3 x ULN or baseline. Restart if the potential benefit outweighs the risk of hepatotoxicity, reduce dose by one dose level or to previous dose level in case of previous dose escalation. Monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with regorafenib permanently.
> 20 x ULN (Grade 4)	Any occurrence	Discontinue treatment with regorafenib permanently.
> 3 x ULN (Grade 2 or higher) with concurrent bilirubin > 2 x ULN*	Any occurrence	Discontinue treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline.

***** Exception: patients with Gilbert's syndrome who developed elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST

PK samples

- 3, 7 and 11 weeks after treatment initiation (in the week before treatment interruption)
- 3 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

19. Sorafenib (Nexavar)

Indications

- Hepatocellular carcinoma (HCC)
- Renal cell carcinoma (RCC)
- Differentiated thyroid carcinoma (DTC)

Start dose: 400 mg BID

Target: (calculated) trough level ≥ 3750 ng/mL, no PK target is reported in the literature, therefore based on Yu *et al* the mean C_{min} of the approved dose is used.(5)(41)(42)(43)

Dose levels

Dose level	Sorafenib dose	Change from start dose
- 3	200 mg OD	- 600 mg
- 2	200 mg BID	- 400 mg
- 1	400 mg – 200 mg	- 200 mg
0	400 mg BID	0
+ 1	600 mg – 400 mg	+ 200 mg
+ 2	600 mg BID	+ 400 mg
+ 3	800 mg – 600 mg	+ 600 mg
+ 4	800 mg BID	+ 800 mg

Sorafenib dose will not be further increased than 800 mg twice daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions

Sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water. The interval between the doses should be approximately 12 hours.

Interactions

- Concomitant use of proton pump inhibitors, H2-antagonists or antacids is permitted.(6)
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.

Dose adjustments

Dose modifications based on treatment-associated toxicity and trough levels of sorafenib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 3750 ng/mL: increase one dose level	TL < 3750 ng/mL: increase one dose level	TL < 3750 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 3750 ng/mL: continue at the same dose level	TL ≥ 3750 ng/mL: continue at the same dose level	TL ≥ 3750 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level sorafenib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of sorafenib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

20. Sunitinib (Sutent)

Intermittent dosing schedule has different PK-schedule!

Start dose:

- 50 mg OD, 4-weeks on 2-weeks off
- 37.5 mg OD, continuous dosing

Target: (calculated) combined sunitinib and N-desethyl sunitinib (metabolite) trough level ≥ 50 ng/mL when 50 mg OD dosing or ≥ 37.5 ng/mL when 37.5 mg OD continuous dosing, based on Faivre *et al* and Yu *et al*.(5,44)

Indications:

- Gastrointestinal stromal tumour (GIST)
- Metastatic renal cell carcinoma (mRCC)
- Pancreatic neuroendocrine tumours (pNET)

Dose levels:

50 mg OD 4 weeks on and 2 weeks off dosing schedule

Dose level	Sunitinib dose	Change from start dose
-3	12.5 mg OD	- 37.5 mg
-2	25 mg OD	- 25 mg
-1	37.5 mg OD	- 12.5 mg
0	50 mg OD	0
+1	62.5 mg OD	+ 12.5 mg
+2	75 mg OD	+ 25 mg

37.5 mg OD continuous dosing schedule

Dose level	Sunitinib dose	Change from start dose
-2	12.5 mg OD	- 25 mg
-1	25 mg OD	- 12.5 mg
0	37.5 mg OD	0
+1	50 mg OD	+ 12.5 mg
+2	62.5 mg OD	+ 25 mg
+3	75 mg OD	+ 37.5 mg

Sunitinib dose will not be further increased than 75 mg daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions

Sunitinib may be taken with or without food.

Interactions

- Concomitant use of (strong) CYP3A4- or CYP2C8-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4- or CYP2C8-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

Dose adjustments

Dose modifications based on treatment-associated toxicity and total trough levels of sunitinib and SU12662 (N-desethyl sunitinib):
50 mg OD 4 weeks-on, 2-weeks off dosing schedule

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TTL < 50.0 ng/mL: increase one dose level	TTL < 50.0 ng/mL: increase one dose level	TTL < 50.0 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TTL ≥ 50.0 ng/mL: continue at the same dose level	TTL ≥ 50.0 ng/mL: continue at the same dose level	TTL ≥ 50.0 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TTL = total trough level of sunitinib and SU12662 (N-desethyl sunitinib)
* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

37.5 mg OD continuous dosing schedule

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TTL < 37.5 ng/mL: increase one dose level	TTL < 37.5 ng/mL: increase one dose level	TTL < 37.5 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TTL ≥ 37.5 ng/mL: continue at the same dose level	TTL ≥ 37.5 ng/mL: continue at the same dose level	TTL ≥ 37.5 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TTL = total trough level of sunitinib and SU12662 (N-desethyl sunitinib)

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on total through levels for sunitinib and SU12662 (N-desethyl sunitinib):

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

50 mg OD 4 weeks on and 2 weeks off dosing schedule:

- 4, 10 and 16 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

37.5 mg OD continuous dosing schedule:

- 4, 8 and 12 weeks after treatment initiation
- 4 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

21. Tamoxifen

Different PK-schedule!

Indication: hormone receptor positive breast cancer

Start dose: 20 mg OD

Target: (calculated) trough level ≥ 5.97 ng/mL, based on Madlensky *et al.*(45)

Dose levels:

Dose level	Tamoxifen dose	Change from start dose
- 1	10 mg OD	- 10 mg
0	20 mg OD	0
+ 1	30 mg OD	+ 10 mg
+ 2	40 mg OD	+ 20 mg
+ 3	50 mg OD	+ 30 mg
+ 4	60 mg OD	+ 40 mg

Tamoxifen dose will not be further increased than 60 mg once daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Tamoxifen should be administered with a glass of water, with or without food.

Interactions:

- Concomitant use of (strong) CYP2D6-inhibitors (including (but not limited to) (nor)fluoxetine, paroxetine, duloxetine, sertraline, amiodarone, bupropion, cimetidine, cinacalcet, kini(di)ne, propafenone, ritonavir and terbinafine) should be avoided.
- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of endoxifen:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 3.0 ng/mL: increase two dose levels TL 3.0 – 5.9 ng/mL: increase one dose level	TL < 3.0 ng/mL: increase two dose levels TL 3.0 – 5.9 ng/mL: increase one dose level	TL < 3.0 ng/mL: increase one dose level TL 3.0 – 5.9 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL > 5.9 ng/mL: continue at the same dose level	TL > 5.9 ng/mL: continue at the same dose level	TL > 5.9 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level endoxifen

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of endoxifen:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- every 12 weeks until treatment discontinuation

22. Vemurafenib/cobimetinib (Zelboraf/Cotellic)

Different PK-schedule!

Indication:
BRAF V600 mutation-positive unresectable or metastatic melanoma

Start dose:
- **Vemurafenib**: 960 mg BID
- **Cobimetinib**: 60 mg OD, 3-weeks on 1-week off

Target:
- **Vemurafenib**: (calculated) trough level ≥ 42 mg/L, based on Kramkimel *et al* and Goldwirt *et al*.(46)(47)
- **Cobimetinib**: (calculated) trough level ≥ 127 ng/mL, no PK target is reported in the literature, therefore based on Yu et al the mean C_{min} of the approved dose is used.(5)(48)

Dose levels:
Vemurafenib

Dose level	Vemurafenib dose	Change from start dose
-2	480 mg BID	- 960 mg
-1	720 mg BID	- 480 mg
0	960 mg BID	0
+1	1200 mg BID	+ 480 mg
+2	1440 mg BID	+ 960 mg

Cobimetinib

Dose level	Cobimetinib dose	Change from start dose
-2	20 mg OD	- 40 mg
-1	40 mg OD	- 20 mg
0	60 mg OD	0
+1	80 mg OD	+ 20 mg
+2	100 mg OD	+ 40 mg

Vemurafenib dose will not be further increased than 1440 mg twice daily.

Cobimetinib dose will not be further increased than 100 mg once daily.

No dose increments are allowed after a previous dose reduction for toxicity.

Intake instructions:
Vemurafenib can be administered with or without food. However, it should not be taken consequently without food.

Cobimetinib should be administered with a glass of water, with or without food.

Interactions:

- Concomitant use of (strong) CYP3A4-inducers (including (but not limited to) carbamazepine, phenytoin, phenobarbital, rifampicin, dexamethasone and Hypericum perforatum also known as St. John's wort) should be avoided.
- Concomitant use of (strong) CYP3A4-inhibitors (including (but not limited to) aprepitant, clarithromycin, erythromycin, ketoconazole, itraconazole, diltiazem, verapamil, hiv-protease inhibitors, fluoxetine and grapefruit juice) should be avoided.
- Concomitant use of P-glycoprotein-inhibitors (including (but not limited to) ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) should be avoided.
- Concomitant use of proton pump inhibitors, H2-antagonists or antacids is permitted. (6)

Dose adjustments:

- If both vemurafenib and cobimetinib are below target first increase vemurafenib until adequate exposure.
- If side effects not tolerable: decrease one dose level of vemurafenib and cobimetinib, unless stated otherwise in the specific dose modification guidelines.

Dose modifications based on treatment-associated toxicity and trough levels of vemurafenib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 42 mg/L: increase one dose level	TL < 42 mg/L: increase one dose level	TL < 42 mg/L: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by two dose levels and resume treatment**
TL ≥ 42 mg/L: continue at the same dose level	TL ≥ 42 mg/L: continue at the same dose level	TL ≥ 42 mg/L: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by two dose levels and resume treatment**

TL = trough level vemurafenib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding QTc prolongation, LVEF reduction, liver enzyme test disorders, creatine phosphokinase (CPK) elevations, cutaneous squamous cell carcinoma or new primary melanoma, photosensitivity, rash and diarrhea see below.

Dose modifications based on treatment-associated toxicity and trough levels of cobimetinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
TL < 127 ng/mL: increase one dose level	TL < 127 ng/mL: increase one dose level	TL < 127 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
TL ≥ 127 ng/mL: continue at the same dose level	TL ≥ 127 ng/mL: continue at the same dose level	TL ≥ 127 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

TL = trough level cobimetinib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding QTc prolongation, LVEF reduction, liver enzyme test disorders, creatine phosphokinase (CPK) elevations, cutaneous squamous cell carcinoma or new primary melanoma, photosensitivity, rash and diarrhea see below.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of vemurafenib and cobimetinib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption. For specific dose modification guidelines regarding QTc prolongation, LVEF reduction, liver enzyme test disorders, creatine phosphokinase (CPK) elevations, cutaneous squamous cell carcinoma or new primary melanoma, photosensitivity, rash and diarrhea see below.

Specific dose modification guidelines

If treatment-related toxicities occur when vemurafenib is used in combination with cobimetinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued, unless stated otherwise.

Prolongation of the QT interval

Dose modifications below are for vemurafenib, cobimetinib can be continued at the same dose level. After each dose modification an ECG should be made.

QTc value	**Recommended dose modifications of vemurafenib**
QTc >500 ms at baseline	Treatment not recommended
QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values	Discontinue treatment with vemurafenib permanently
1st occurrence of QTc >500 ms during treatment and change from pre-treatment value remains < 60 ms	Withhold dosing until QTc decreases below 500 ms, reduce dose of vemurafenib with one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
2nd occurrence of QTc >500 ms during treatment and change from pre-treatment value remains < 60 ms	Withhold dosing until QTc decreases below 500 ms, reduce dose of vemurafenib with one dose level or to the previous dose level in case of previous dose escalation and resume treatment.
3rd occurrence of QTc >500 ms during treatment and change from pre-treatment value remains < 60 ms	Discontinue treatment with vemurafenib permanently

Left ventricular ejection fraction (LVEF) decrease

Dose modifications below are for cobimetinib, vemurafenib can be continued at the same dose level. After each dose reduction LVEF should be measured after 2, 4, 10 and 16 weeks.

Patient	**LVEF value**	**Recommended dose modification of cobimetinib**	**LVEF value following treatment break**	**Recommended dose modification of cobimetinib**
Asymptomatic	≥ 50% (or 40-49% and < 10% absolute decrease from baseline)	Continue at the same dose level	N/A	N/A
	< 40% (or 40-49% and ≥ 10% absolute decrease from baseline)	Interrupt treatment for 2 weeks	< 10% absolute decrease from baseline	1st and 2nd occurrence: reduce one dose level or to the previous dose level in case of previous dose escalation
				3rd occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
Symptomatic	N/A	Interrupt treatment for 4 weeks	Asymptomatic and < 10% absolute decrease from baseline	1st and 2nd occurrence: reduce one dose level or to the previous dose level in case of previous dose escalation
				3rd occurrence: permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from baseline)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

Liver enzyme test disorders
Grade 1/2: continue treatment at the same dose level
Grade 3: only adjust dose of vemurafenib, continue treatment with cobimetinib at the same dose level
Grade 4: withhold dosing of both vermurafenib and cobimetinib until ≤ grade 1, reduce dose of cobimetinib with one dose level and resume treatment, reduce dose of vemurafenib by judgement of the treating physician. If no improvement within 4 weeks or recurrent grade 4 liver enzyme test disorder: discontinue treatment with vemurafenib and cobimetinib permanently

Creatine phosphokinase (CPK) elevations
Cobimetinib dosing does not need to be modified or interrupted to manage asymptomatic CPK elevations.

Photosensitivity
Grade 1-2 (tolerable): supportive care, no dose modifications.
Grade 2 (intolerable) or ≥ grade 3: both cobimetinib and vemurafenib should be interrupted until ≤ grade 1. Treatment can be restarted with no change in cobimetinib dose. Vemurafenib dosing should be reduced as clinically appropriate.

Rash
Grade 1-2 (tolerable): supportive care, no dose modifications.
Grade 2 (intolerable) or ≥ grade 3:

- Acneiform rash: general dose modification recommendations for cobimetinib should be followed. Vemurafenib dosing can be continued when cobimetinib treatment is modified (if clinically indicated).
- Non-acneiform or maculopapular rash: cobimetinib dosing can be continued without modification if clinically indicated. Vemurafenib dosing may be either temporarily interrupted and/or reduced.

Cutaneous squamous cell carcinoma or new primary melanoma
Continue at the same dose level.

Diarrhea
Grade 1: no intervention or dose reduction.
Grade 2: loperamide (4 mg at first onset, followed by 2 mg after every loose stool, until diarrhea free for 12 hours, max. 16 mg a day). No dose reduction, but if unacceptable to patient or medically concerning, then hold until recovery to ≤ grade 1.
Grade 3-4: (despite optimal use of loperamide): hold until recovery to ≤ grade 1 and resume treatment, if grade 3-4 diarrhea recurs, reduce dose of vemurafenib and cobimetinib by one dose level or to previous dose level in case of previous dose escalation and resume treatment.

PK samples

- 3, 7 and 11 weeks after treatment initiation (in the week before treatment interruption)
- 3 weeks after every dose adjustment
- every 12 weeks until treatment discontinuation

23. Vismodegib (Erivedge)

Different PK-schedule!

Indication: basal cell carcinoma
- symptomatic metastatic
- locally advanced, inappropriate for surgery or radiotherapy

Start dose: 150 mg OD

Target: (calculated) steady state level ≥ 11.4 ng/mL, no PK target is reported in the literature, therefore the mean steady state level is used.(49)

Dose levels:

Dose level	Vismodegib dose	Change from start dose
-2	150 mg twice weekly	- 107 mg
-1	150 mg QAD	- 75 mg
0	150 mg OD	0
+1	300 mg OD	+ 150 mg
+2	450 mg OD	+ 300 mg

Vismodegib dose will not be further increased than 450 mg daily.

After a previous dose reduction for toxicity, re-escalation can be considered if clinically appropriate.

Intake instructions:
Vismodegib should be administered with a glass of water, with or without food.

Interactions:
- No clinical significant interactions with drugs that increase the pH in the stomach are reported.
- No clinical significant interactions with CYP-enzymes and Pgp-modulators are reported.

Dose adjustments:

Dose modifications based on treatment-associated toxicity and trough levels of vismodegib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
SSL < 11.4 ng/mL: increase one dose level	SSL < 11.4 ng/mL: increase one dose level	SSL < 11.4 ng/mL: increase one dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**
SSL ≥ 11.4 ng/mL: continue at the same dose level	SSL ≥ 11.4 ng/mL: continue at the same dose level	SSL ≥ 11.4 ng/mL: continue at the same dose level	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**	Withhold dose until toxicity is ≤ grade 1 (or ≤ grade 2 in case of hematologic toxicity). For treatment related toxicity: reduce dose by one dose level and resume treatment**

SSL = steady state level vismodegib

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.

** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

Dose modifications based on treatment-associated toxicity in weeks without potential dose modifications based on trough levels of vismodegib:

Toxicity				
No toxicity	**Grade 1**	**Grade 2***	**Grade 3**	**Grade 4**
Continue at the same dose level	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**	Withhold dose until toxicity is ≤ grade 1. For treatment related toxicity: reduce dose by one dose level or to previous dose level in case of previous dose escalation and resume treatment**

* If grade 2 toxicities are persistent or unbearable, consider treating them as grade 3.
** Patients who develop grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at grade 3 or 4 despite maximal medical therapy. Patients who develop grade 3 or 4 lymphopenia without other dose-limiting events (e.g. opportunistic infection) may continue treatment without interruption.

PK samples

- every 12 weeks until treatment discontinuation