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SPRING protocol

Survival Prolongation by Rationale INnovative Genomics (SPRING):

A proof of concept study to explore safety and efficacy of tri-therapy approach in advanced/metastatic NSCLC and retrospectively assess the ability of integrated genomics and transcriptomics to match patients to the combination

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Protocol title:	**Survival Prolongation by Rationale Innovative Genomics (SPRING)** A proof of concept study to explore safety and efficacy of tri-therapy approach in advanced/metastatic NSCLC and retrospectively assess the ability of integrated genomics and transcriptomics to match patients to the combination
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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

PI signature:	
Date: (dd/mm/yyyy)	__ __ / __ __ / 20 __ __

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANC	Absolute neutrophil count
CBC	Complete blood count
CDER	Center for drug evaluation and research
CDK	Cyclin-dependent kinases
CMC	Clinical monitoring committee
CMP	Complete metabolic profile
CNS	Central Nervous System
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DNA	Ribonucleic acid
DSMB	Independent safety and data monitoring committee
ECG	Electrocardiogram
EGFR	Endothelial growth factor receptor
EMA	European medicines agency
FFPE	Formalin-fixed paraffin-embedded
GDPR	General Data Protection Regulation
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
IDE	Investigational device exemption
IEC	Institutional ethics committee
IRB	Institutional review board
irAE	Immune-related adverse event
IV	Intravenous
LD	Longest diameter
MRI	Magnetic resonance imagery

MTD	Maximal tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PFS1	Progression-free survival on the immediate line prior SPRING
PFS2	Progression-free survival on the matched or unmatched SPRING therapy
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable disease
SIMS	Simplified interventional mapping system
SOP	Standard operating procedure
SPRING	Survival Prolongation by Rationale Innovative Genomics
SUSAR	Suspected unexpected serious adverse reaction
TBili	Total bilirubin
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of Normal
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cells
WIN	Worldwide Innovative Network

1. KEYNOTES AND STUDY OVERVIEW

1.1. KEYNOTES - SPRING PROJECT AT A GLANCE

Survival Prolongation by Rationale Innovative Genomics (SPRING) clinical trial is pursuing two goals:

(i) Establish the safety and clinical activity of triple targeted combination therapies following the historical model of this approach in AIDS. SPRING is a proof of concept study that will test only one combination of three targeted agents: avelumab - Bavencio /anti PD-L1 (PFIZER/MERCK), palbociclib – Ibrance / CDK4/6 inhibitor (PFIZER) and axitinib - Inlyta / anti VEGFR (PFIZER):

- Avelumab is a fully human IgG1 monoclonal antibody (mAb) that targets programmed deathligand 1 (PD-L1) with the ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC). It is FDA-approved for the treatment of metastatic Merkel cell carcinoma and locally advanced or metastatic urothelial carcinoma.
- Axitinib is a selective inhibitor of vascular endothelial growth factor receptors (VEGFR-1, -2, and -3) that is FDA-approved for the second-line treatment for advanced renal cell carcinoma (RCC).
- Palbociclib is an oral, small molecule kinase inhibitor which is active against cyclin-dependent kinase (CDK) 4 and 6 which play a critical role in facilitating the gap 1 (G1) to synthesis (S) phase transition. Palbociclib received accelerated approval for use, in combination with letrozole, and for use, in combination with fulvestrant, for the treatment of patients with ER positive, HER2-negative, breast cancer who had not received previous systemic treatment.
- This trial will not evaluate the individual contribution of each of the tested drugs.
- First, the safe dose of the combination of the three agents will be determined in a phase 1 study. It is important to outline that the dual combination avelumab and axitinib was already tested in a phase 1 trial, and the recommended phase 2 dose (RP2D) has been established. This dose for the dual combination avelumab and axitinib is currently used in the study JAVELIN Renal 101, a randomized phase 3 trial referenced at https://clinicaltrials.gov/ct2/show/NCT02684006?term=avelumab+and+axitinib&rank=1.
  For the triple combination, the starting dose of each agent of the dual combination will be reduced in order to add the third agent. Doses will then be progressively increased with, at each dose escalation, 3 new patients being added. Patients will be closely monitored to detect any adverse event until the MTD of the triple combination is determined or reaching the highest dose level of each agent, whichever occurs first. Note that if the MTD is reached, this dose combination is the RP2D.
- Specific safety measures related to administration of avelumab will be implemented in each participating center: specific inclusion/exclusion criteria, safety assessments (pregnancy testing, monitoring of free T4 and TSH), premedication in order to mitigate avelumab infusion-related reactions, administration of avelumab in a facility that enable immediate access to emergency care unit, extended follow up to 90 days following the last administration of avelumab, monitoring of all specific adverse events, and reporting to the Pharmacovigilance Unit of the sponsor, within 24 hours of any serious adverse events. For simultaneous administration with palbociclib and axitinib, other specific safety measures will be implemented (for example careful monitoring of arterial tension, bleeding, assessment of risk of arterial and venous thromboembolic events

relating to administration of axitinib, and careful monitoring of hematologic toxicities relating to administration of palbociclib). These specific measures are presented in a detailed manner in this protocol, at each concerned section/chapter; as well as in a specific appendix 6.

– The study will then be expanded to a phase 2 in order to confirm the safety profile and assess the clinical utility of the tri-therapy approach in the treatment of metastatic NSCLC. All patients included in phase 2 will be receiving the tri-therapy combination at the RP2D, and will be followed up to determine clinical response, duration of the response and overall survival. Patients enrolled in the phase 1 study who receive the RP2D will also be included in the phase 2 efficacy assessment.

(ii) Validate the clinical utility of a new tool/algorithm enabling matching of advanced/metastatic NSCLC patients with the tested combination of three targeted agents. The Simplified Interventional Mapping System (SIMS) algorithm enable a new approach in treating metastatic lung cancers using tri-therapy approach**,** following the historical success in AIDS, and was awarded Success Story of the European Community EUFP7 program.

The tool SIMS (1) is based on integrated genomics and transcriptomics from tumor/metastasis tissue and normal matched tissue and was designed to predict efficacy of any mono, dual or triple therapy. In this study, all patients enrolled will receive the triple therapy combination and the SIMS (1) algorithm will only be used for preplanned retrospective correlations.

To this aim patients will need to have adequate biopsy material to enable investigations of the DNA and RNA:

– Tumor tissue from the primary tumor or from the metastatic lesion. For this purpose patients will have to consent to a biopsy.
– Normal matched tissue, which in this case will be the bronchial mucosa. To this aim, patients will consent to the normal tissue biopsy obtained through bronchoscopy under video guidance, using a minimum of 2.5 mm^3 forceps.

Tumor/metastasis and normal tissue biopsies will be controlled for cellularity content with a threshold at 50% of tumor or 30% to 50% normal epithelial cells respectively, and will be used for genomic and transcriptomic analyses to generate the SIMS scoring. SIMS provides a 1 to 10 score indicating the activation of the targets (interventional points) of each specific drug. The threshold to consider an interventional point activated is >5. This threshold applies for each of the interventional point, including the PDL1. SIMS score for each patient will then be retrospectively correlated with the patients' clinical outcome in order to assess its predictive value and ability to match patient's tumor biology with the tri-therapy combination. SIMS will not be used for treatment decision. All patients will receive the tri-therapy combination.

SPRING trial will aim to enroll patients who are usually offered first line platinum-based chemotherapy. Patients with **documented** targetable driver alterations (EGFR mutations, ALK rearrangements, ROS1 and MET exon 14 skipping mutations) will be excluded. This population currently, without actionable oncogenic driver mutations, envisioned for the enrollment in SPRING trial represents the majority of patients with metastatic NSCLC (~80% in the Caucasian population).

Although the triple combination includes an immunomodulator (avelumab, anti PD-L1), patients will be included regardless of their PD-L1 expression status. Nevertheless, all molecular data available at enrollment will be recorded including PD1 and PD-L1 testing using any of the available IHC tests. Subsequently, the activation status of PD1 or PD-L1 will be assessed through the 1 to 10 SIMS scoring (where 5 is the cut-off), and will be used retrospectively for correlations with clinical outcome and any previous PD1 or PD-L1 tests.

We estimate that overall 85% of the patients treated in the trial will have a profile that is matched to at least one out of the three drugs: 10% matched with three drugs, 36% matched with two drugs and 39% matched with one drug.

SPRING trial phase 2 is intended in first therapeutic line of metastatic NSCLC. Indeed, due to the current extensive use of checkpoint inhibitors (e.g. anti-PD-1, anti-PD-L1) in first line of metastatic NSCLC, any testing of the tri-therapy in subsequent lines would make the enrollment extremely difficult, if not impossible. In addition, following the analogy with AIDS and tuberculosis for which only tri-therapy demonstrated long term efficacy, it would be conceptually difficult to prescribe first an immunomodulator as a monotherapy followed in second line by the tri-therapy, including the immunomodulator. Indeed, we can hypothesize that monotherapy will likely select for resistant clones that would hamper the treatment efficacy and compromise the clinical outcome.

Nevertheless, patients with one to a maximum of 2 prior systemic regimens in the metastatic setting will be accepted for enrollment in phase 1.

SPRING clinical trial is intended to open in a limited number of cancer centers of the WIN Consortium (2 centers in USA, 5 in Europe and 1 in Israel) enabling a rapid enrollment and follow-up of patients. It is expected that 130 patients will be enrolled over an 18-month period (phase 1, 6 to 8 months – phase 2, 8-12 months). With an additional 12/24 months of follow up, the total study duration will be 3 to 4 years.

1.2. STUDY OVERVIEW

1.2.1. The first goal of the SPRING protocol is to test the safety and the activity of the selected tri-therapy in patients with metastatic NSCLC patients in first therapeutic line for the phase 2 portion of the trial (for the phase 1 patients with a maximum of 2 prior lines will be accepted).

The trial will start with a Phase 1 safety study to establish the dose of each of the three agents. This part of the study will require about 30 patients treated (~40 patients enrolled). The Phase 1 will be followed by a first extension Phase 2 to test efficacy on up to 100 patients who will all receive the tri-therapy (100 patients treated/ ~120 patients enrolled (~20 patients screen failures)). All patients will have the necessary biopsies performed to ensure that adequate biopsy material is available before starting treatment. For ethical reasons, patients whose biopsies fail to produce interpretable data will still be treated with the tri-therapy. Pending clinical activity, the study may be extended by an additional 100 patients treated (total = 200 patients on the phase 2 portion) in order to firm up the initial efficacy assessment and identify the potential subgroups of patients with clinically meaningful efficacy.

Patients with specific documented oncogenic aberrations (EGFR mutations, ALK translocations, ROS1 if available and MET exon 14 skipping mutation if available) will be excluded from the trial. The study cohort will aim to include patients who are not generally treated with specific targeted therapeutics. Patients will be included in the study regardless of their PD1 or PD-L1 expression status. In the case of patients already treated on SPRING protocol who are later determined to have EGFR mutation or ALK translocation or ROS1 or MET exon 14 skipping mutations after SIMS analyses, amenable to treatment with an approved therapy, they will be given the option to continue investigational treatment in the SPRING trial after obtaining appropriate re-consent or discontinue treatment.

Early futility stopping rules will be applied in the phase 2 study should the tri-therapy have less than the expected efficacy to guard against patients being enrolled in ineffective treatment.
We estimate that overall 85% of the patients treated in the trial will have a profile that is matched to at least one out of the three drugs: 10% matched with three drugs, 36% matched with two drugs and 39% matched with one drug.

1.2.2. The second goal of the SPRING protocol is to validate retrospectively the SIMS (1) algorithm enabling matching patients to the best therapy (mono, dual or triple).

For this purpose, patients enrolled in each of the selected participating cancer center will undergo a dual biopsy for tissue collection and biomarker analysis, that are part of the study protocol. Adequate material from fresh frozen biopsies from NSCLC metastasis or primary tumor and normal bronchial mucosa tissue (by bronchial bronchoscopy) are necessary to the study. FFPE biopsies from both tumor and normal tissues will also be collected if possible. The samples will be processed for histology quality control and comprehensive omics analyses (including genome sequencing and transcriptomics (mRNA and miRNA)). Tumor/metastasis and matched normal tissue biopsies are necessary for investigations of the transcriptome in order to subtract the noise induced by the genetic variability between individuals. Both biopsies (of the tumor tissue and normal tissue) have proven to be well accepted by patients and safe in the WINTHER study (246 patients biopsied for both normal and tumor tissues) (http://clinicaltrials.gov/show/NCT01856296).

The algorithm (SIMS) (1, Appendix 1 and Appendix 2) will integrate the genomics and transcriptomics data from paired tumor/metastasis and normal tissue performed on fresh frozen biopsies' material from patients. SIMS will identify activated pathways and so-called intervention points that are druggable targets. This information will be used retrospectively to assess how well the algorithm predicted the response to the triple therapy tested (druggable targets anti-PD-L1, CDK 4/6 and anti VEGFR). SIMS will identify for each patient how many intervention points are activated out of the three tested. The hypothesis is that clinical outcome will be correlated to the number of targets activated as predicted by SIMS (1, 2 or 3).
Based on previously published data on SIMS (1) we estimate that PD-L1-positive patients will represent 50% of the enrolled patients with metastatic NSCLC.

In this study, we estimate that we will treat up to 100 patients in the first part of phase 2 (overview in Figure 1) with futility early stopping rules. If the trial is not stopped early after the first 100 patients, the study could be extended to an additional 100 patients treated.

Main outcome variables for the expansion phase will include response rate (RR) by RECIST 1.1, duration of response, progression-free survival (PFS), and overall survival (OS).

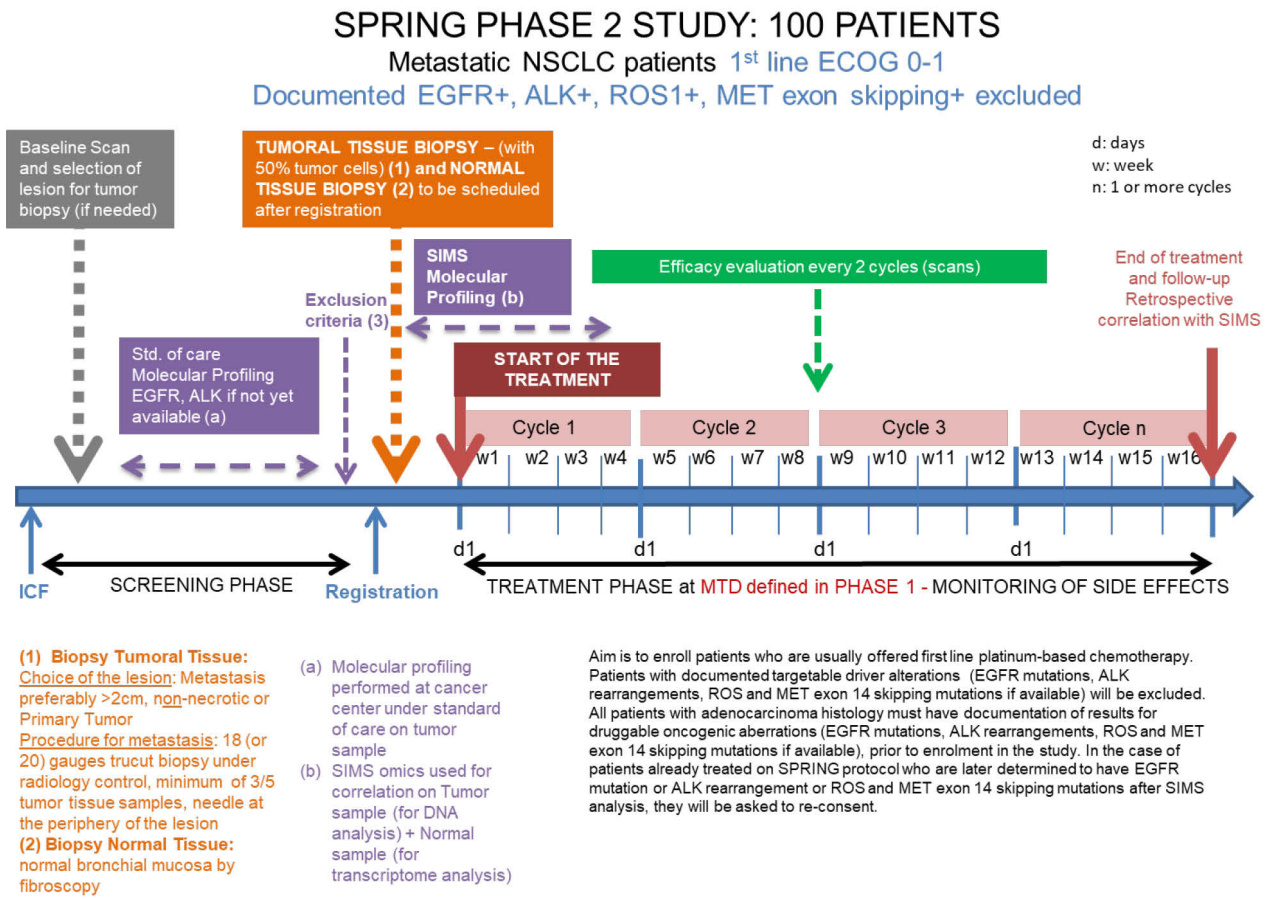

Figure 1: Overview of SPRING Phase 2

1.3. GLOBAL AIMS IN RELATION TO CLINICAL CANCER

1. Safely and significantly improve treatment outcome in patients with advanced/metastatic NSCLC through drug combinations of molecular/immune targeted agents.

2. Explore the clinical utility of SIMS for matching patients with combination therapy in the advanced NSCLC setting.

1.4. SPRING STUDY SCHEMA

Refer to Figure 2 below.

The trial design is a two-part, multiple parallel cohort, dose-finding and activity-estimating study. The study will enroll patients with metastatic NSCLC that have no targetable alterations (EGFR mutations or ALK translocation) and for whom targeted therapies are not recommended. In the first Phase 1 portion of the trial, patients may have received a maximum of two prior therapies for

metastatic NSCLC but in the second portion of the trial, ONLY patients who have not received prior systemic therapy in the metastatic setting will be included. All patients included must be ECOG 0-1. All patients must consent to a dual biopsy of the tumor tissue obtained from a metastatic lesion under radiologic guidance or from the primary tumor, and of normal matched tissue (bronchial mucosa), obtained through bronchoscopy under video guidance. The paired biopsy samples will be processed in a centralized facility for comprehensive analyses including genome sequencing and transcriptomics (mRNA and miRNA).

The primary objectives of the Phase 1 portion of the trial will be to establish the safety, tolerability, dose-limiting toxicities (DLTs), maximum tolerated doses (MTDs), and RP2Ds of the three drugs, administered concurrently, through enrollment in sequential dose-escalating.

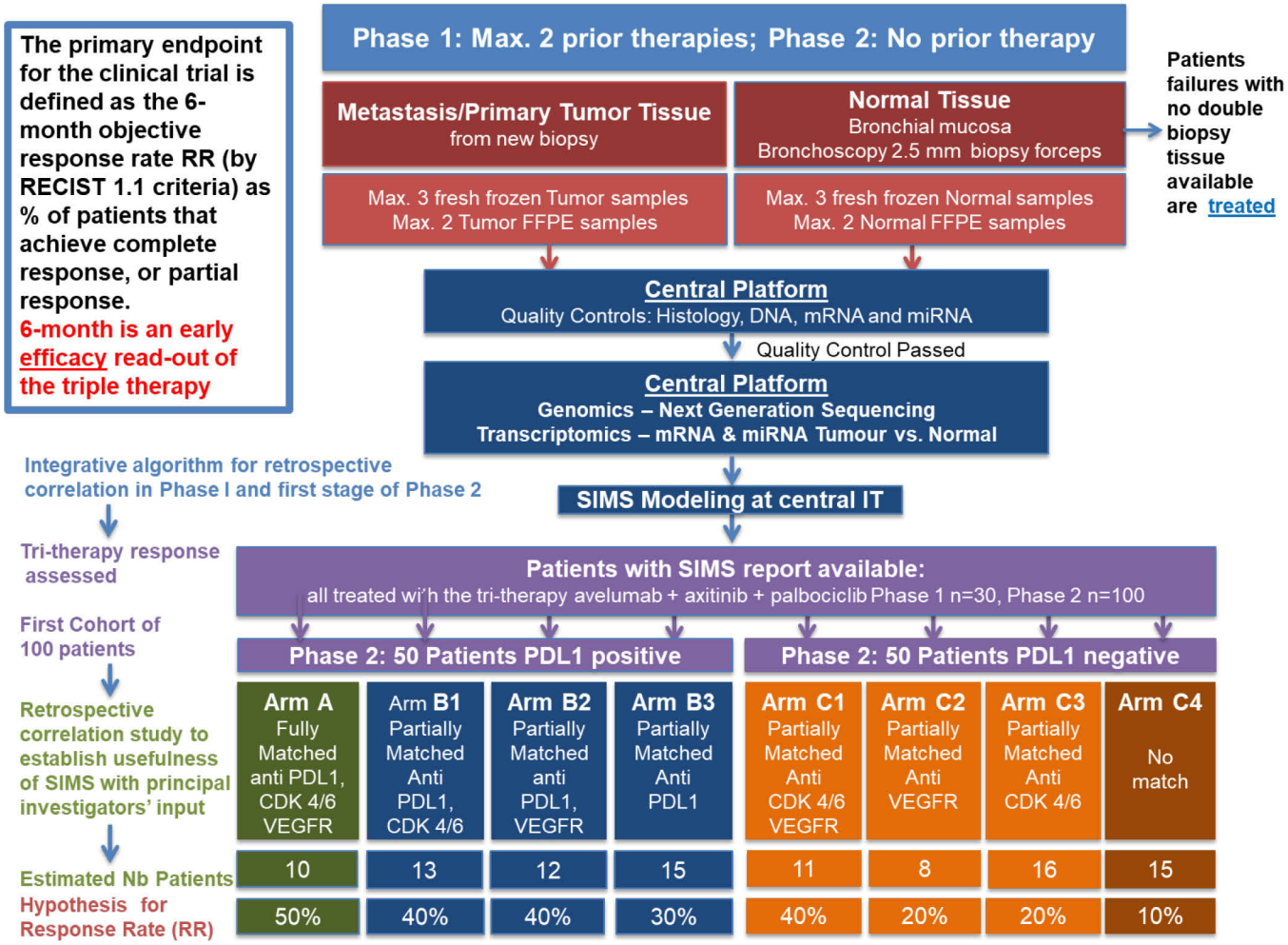

Figure 2: Study design and planned retrospective analysis of the clinical utility of the SIMS algorithm and integrated genomic/transcriptomic analysis.

The statistical design of the trial has been performed by Prof. J. Jack Lee, University of Texas MD Anderson Cancer Center, Adjunct Professor of Statistics, Associate Vice Provost, Adjunct Professor of Biostatistics, Professor of Biostatistics, Biostatistics, Regular Member of the Graduate Faculty.

We estimate that we will treat up to 100 patients in the first part of phase 2 with futility early stopping rules.
For the first cohort of 100 patients it is expected that half of the patients will be PD-L1 positive and half of the patients will be PD-L1 negative. The hypothesized 6-month response rate in Arm A (fully matched) is 50%; in Arms B1, B2, and C1 (partially matched with two targets) is 40%; in Arm B3 (matched with PD-L1 only) is 30%; in Arms C2 and C3 (partially matched with VEGFR or CDK4/6) is 20%; and in Arm C4 (non-matched group) is 10%. The expected 6-month response rate is 30% in the entire group assume the triple therapy works.

- The first futility early stopping rule will be applied after treating 14 patients with the tri-therapy at the RP2D level. If none of the 14 patients has 6-month response (CR or PR), the patient enrollment will be halted and the trial can be stopped for futility.
- The second futility early stopping rule will be evaluated every 10 patients after 20 patients are treated at the RP2D by applying the predictive probability. The trial will be stopped early if we see the following 6-month responses or less: 2 in 20, 3 in 30, 5 in 40, 6 in 50, 7 in 60, 9 in 70, 11 in 80, or 12 in 90 patients.

If the trial is not stopped early after the first 100 patients, the study could be extended to an additional 100 patients treated with an amendment. Two possible scenarios can then be envisioned:

- Repeat identically all investigations for additional 100 patients, (exactly as for the first cohort), with the purpose to have a final cohort of 200 patients, which would give good statistical power for the study. With 5% one- sided type I error, we need to treat 20 patients to demonstrate the usefulness of the tri-therapy approach to achieve and 86% power based on the exact binomial test. With an expected 10% of patients who will be fully matched, we need to enroll 200 patients in the study.
- For the second cohort, use SIMS to stratifying patients and select only the subgroups with the highest efficacy as demonstrated after the study of the first cohort. This statistical model will be much more powerful to demonstrate usefulness of the tri-therapy approach. This scenario is also the most appropriate from an ethical perspective.

It is planned that after collecting data on about 50 patients, a meeting with the FDA will be organized in order to assess which scenario of design is recommended and to ask for a risk determination for need for IDE.

2. BACKGROUND AND RATIONALE

Today, most malignancies (including lung cancer) are detected at a late stage (i.e., metastatic setting), and despite all recent progress in the field of personalized therapy, almost all patients will die of their disease. One reason behind this slow progress is that targeted and immune therapies have been typically tested and used as monotherapies.

2.1. LUNG CANCER

Lung cancer is one of the most prevalent and deadly malignancies, contributing a staggering 1.6 million cases diagnosed per year and about 21% of cancer deaths to the global cancer burden (2, 3). The majority of individuals with non-small cell lung cancer (NSCLC) present at the metastatic stage, and most patients with localized disease will relapse. The standard of care in advanced disease– mainly cytotoxic chemotherapy and targeted agents for selected subsets– has had modest impact on mortality as even responders inevitably develop resistance and succumb to their disease. Only about half of all patients diagnosed (regardless of stage) are alive at one year, and there are dismal one- and five-year survival rates of around 15% and 4%, respectively, for those with metastatic disease (2, 3, 4). For patients who have failed first-line therapy, the median survival is only about seven months.

More importantly, in the majority of patients with Stage IV NSCLC, chemotherapy remains the standard first-line treatment option, despite modest benefit. Targeted monotherapies can produce excellent response rates in small subsets of patients, but responders inevitably develop resistance and succumb to their disease. Combination of drugs may overcome such resistance, but a scientific methodology for determining individualized therapy combinations that can be used to treat lung cancer or other deadly malignancies does currently not exist.

2.2. TARGETED THERAPY IN LUNG CANCER

Targeted therapies implemented in standard care are directed at the activated products of mutated epidermal growth factor receptor (EGFR) (5) or ALK translocation (6). Such therapies have shown high response rates, and improved progression-free survival (PFS). However, these monotherapies apply to only small subsets of oncogene-driven patients, and virtually all develop resistance and succumb to their disease (7). Relapse occurs mostly as a consequence of the Darwinian selection of tumor clones harboring genomic variants that lead to the activation of additional signaling pathways and, hence, resistance. This is perhaps not unexpected, as tumors often exhibit a large variety of molecular abnormalities (7, 8), even at diagnosis. Heterogeneity across tumor clones is amplified in metastases, and in response to therapeutic pressure.

2.3. LIMITATIONS OF CURRENT TARGETED THERAPY APPROCHES

As mentioned, in NSCLC, as well as in many cancer types, molecular characterization of the tumors has resulted in segmentation of nosological classifications, based previously on the organ of origin and histology, into a variety of molecular subtypes, often characterized by one specific driver molecular genetic alteration (5, 9). However, this strategy has several limitations: (i) only a portion

of tumors have an identified driver mutation, and many of these simple models may have been already described (10, 11); (ii) there is no recognized strategy to efficiently pinpoint unrecognized drivers within the complex and multiple genomic alterations observed in most tumors; (iii) targeted treatments are not uniformly efficient even in these selected subgroups; (iv) the majority of tumors are actually driven by multiple aberrant genes (9, 12, 13), making the monotherapy paradigm unsuitable for most metastatic cancers; and (v) resistance uniformly emerges in a Darwinian manner in patients treated with a single targeted therapy.

2.4. COMBINATION THERAPY AND CANCER

Combination of cytotoxic therapies has been demonstrated to be effective where single agents provide only moderate benefits, as illustrated in Hodgkin's lymphoma. Whether this paradigm applies to targeted therapy remains unclear for most diseases. However, recently, combinations targeting the same pathway in BRAF-mutant melanoma (14) (using trametinib (MEK inhibitor) together with dabrafenib (BRAF inhibitor)), or resistance pathways (combining PIK3CA and MEK inhibitors) (15) showed some efficacy, either pre-clinically and/or in the clinic.

With the aim of further enhancing clinical benefit and increasing survival, we intend to explore the efficacy of triple regimen therapy, following the historical success in diseases such as acquired immunodeficiency syndrome. The major challenges for this effort are delineating the scientific rationale for matching agents with patients' tumors, while being cognizant of potential toxicity for multi-drug regimens.

2.5. PREVIOUS EXPERIENCE - WINTHER STUDY

The study workflow and the use of dual biopsies were previously investigated in the WINTHER trial (http://clinicaltrials.gov/show/NCT01856296) of the Worldwide Innovative Networking (WIN) Consortium (www.winconsortium.org) for personalized cancer therapy (PI: JC Soria; Co-PI: R Kurzrock). WINTHER was built as a molecularly driven navigation trial. It was developed on the shoulders of previous trials:

(i) The biomarker-driven trial pioneered by Dr. Von Hoff, which was one of the first to show that using biomarkers was feasible, and that, by using patients as their own controls (looking at PFS2 on matched therapy versus prior PFS), improved outcomes could be demonstrated without randomization (16).

(ii) BATTLE study (17), which proved definitively that molecular profiling on fresh biopsies in lung cancer was feasible and safe.

(iii) PREDICT, a navigation trial that showed that molecular matching (albeit non-randomized) was associated with substantially increased response rates PFS, OS, and PFS2/PFS1 ratio, even in the Phase I setting (18).

(iv) NCI-Match, which started in 2015 and uses a similar molecularly driven, non-randomized strategy (19, 20).

(v) Lung-Map in USA and CR-UK Matrix Lung in UK.

To date, the WINTHER study has been activated in 6 cancer centers (Gustave Roussy, Centre Léon Bérard, Chaim Sheba Medical Center, Val d'Hebron, MD Anderson Cancer Center and McGill Segal Cancer Center) across 5 countries (France, Spain, Israel, Canada, USA). The study has accrued

more than 300 patients (study ongoing). The WINTHER study includes dual biopsies from both normal and tumor tissues and stratifies patients in different arms, i.e. Arm A (genomics, Next Generation Sequencing, Foundation Medicine) and Arm B (transcriptomic data, which uses the dual biopsies to compare the transcript levels in tumor to corresponding normal tissue) has been used to direct matched therapy. Specifically, patients who harbor a targetable genomic alteration are stratified to Arm A; patients with no targetable genomic alteration are stratified to Arm B and the choice of therapy is based on mRNA expression profiling analyzed by an algorithm. In the WINTHER trial, weekly Clinical Monitoring Committees (CMC) were successfully established (with calls occurring each Monday evening and allowing patients presentation, review of -omics data, and therapy suggestions by the participating physicians from the five countries). There have been no serious safety signals to date, and the dual biopsies have proven safe and feasible.

The following elements have been established for WINTHER and will be used by the SPRING trial:

- Dual biopsies of tumor and normal matched tissue in solid tumors (including lung) patients. No significant safety issue encountered, with 246 patients having undergone dual biopsies.
- Use of both genomics and transcriptomics in the clinical setting was possible, under stringent quality control.
- Multi-country trial across 6 centers and 5 countries (France, Spain, Israel, Canada and USA) - approved by IRB and regulatory authorities.
- Information technology structure with web portal to support principal investigators (PIs) to make their therapeutic choice.
- Weekly clinical monitoring committee with investigators from multiple countries convening to present and discuss patients, and assist with decision-making, was immensely successful.
- Trial funded by a highly competitive peer-review European EU-FP7 grant of 3 million euros (funding only 2% of submitted grants) and also by philanthropy (2 million euros) and industry (1.5 million euros).

2.6. THE SPRING STRATEGY

The SPRING trial will build on the established infrastructure from the WINTHER trial. It will, however, be a strategic second-generation trial, incorporating the following additional approaches:

- Tri-therapy combinations instead of monotherapy will be tested
- Immunotherapy will be incorporated
- Genomics and transcriptomics will be integrated for correlation purposes at the end of the study
- The SIMS algorithm will be incorporated (1) for **correlation purposes at the end of the study.**

The simplified interventional mapping system (SIMS) algorithm will be applied to integrate genomic and transcriptomic data (1). SIMS merges knowledge about existent drugs and their impact on the hallmarks of cancer. Our integrative approach and new mathematical modeling converts thousands of genomic and other "omics" measurements into a simple result that enables selection of individualized rational therapies including combinations of targeted therapies (1).

More specifically, the use of SIMS can allow identification and scoring (from 1 to 10) of specific interventional points/nodes for drugs based on the pathways deregulated in each patient's cancer. This approach for prioritizing intervention points for a patient is simple and easy to interpret.

The basic premise is that, when the genes associated with an intervention point are more disturbed (in terms of sequence and/or expression level), the intervention point is assigned a higher score and thus is more likely to be crucial to the tumor. From this, it follows that the more disturbed the genes of an intervention point are, the more likely it is that therapeutics targeting that point will benefit the patient. This new therapeutic approach of combination therapies aims to simultaneously block different biologic pathways and reduce the chance of developing secondary resistance. SIMS identifies within the hallmarks of cancer (11) only signaling and regulatory pathways that can be targeted with available therapeutic agents.
Our work suggests that using the SIMS algorithm to orient therapeutic decision would benefit from several major assets: The interrogation of dual biopsies of tumor/metastasis and its normal counterpart, combined with a comprehensive systems biology investigation and innovative bioinformatics and scoring systems, may enable matching each individual patient with the most appropriate treatment. One of the cornerstones of this new methodology is use of dual matched tumor tissue and normal tissue biopsies from the same patient, enabling the subtraction of transcriptomic background noise in each patient (9, 21).

We propose to test this novel SIMS algorithm **retrospectively** on the cohort of patients who will be treated with the tested tri-therapy. The concept of SIMS was published in a peer-reviewed journal (1 and appendix 1). SIMS enabled to estimate the frequency of occurrence of the activation of each target of the three drugs used in the combination.

2.7. CONSIDERATIONS CONCERNING THE BIOPSIES IN SPRING TRIAL

A cornerstone of the SPRING strategy is the interrogation of tumor tissue (from metastatic tissue or primary tumor) and matched normal tissue (namely bronchial mucosa) by bronchoscopy in order to investigate DNA and RNA and run the SIMS algorithm. In doing so, our utmost concern will be the safety of the procedures.

In a majority of cases, percutaneous core needle biopsy is a standard part of initial work-up. In order to perform standard molecular testing (EGFR, ALK) more than one biopsy (bronchoscopic and percutaneous) is often required in clinical practice and is supported by NCCN (Diag-A 1 of 2). A second biopsy at time of progression is also supported by NCCN in select cases for further molecular characterization (NSCL 16-17). Repeat biopsies for cancer progressing after initial treatment is a common practice.

In the SPRING trial, the additional biopsy of normal tissue is integral to the SIMS algorithm and the hypothesis is that it will improve precision oncologic therapy selection.

In our previous experience in the WINTHER study where 303 patients were registered, 246 underwent a dual biopsy of the tumor tissue and normal matched tissue of which 55 were dual biopsies in lung cancer patients. From the 55 lung cancer dual biopsied patients, 45 had CT-guided lung tumor core needle biopsies. 4 patients were observed in the hospital for 24 hours because they developed a small pneumothorax that resolved rapidly (among which 2 required chest tubes). There were no life-threatening complications.

Research biopsies are a frequent component of current clinical trials. In MD Anderson's experience in Oncologist 2011, a total of 281 research biopsies on 155 distinct patients and 42 lung biopsies had been done and 2 patients had a pneumothorax for rate of 4.8% (22).

Furthermore, a meta-analysis performed in April 2016 reported 8,133 CT-guided core needle biopsy procedures. The pooled rate of pneumothorax requiring intervention was 5.6% (23) (e.g., clinically relevant pneumothorax requiring placement of chest tube). The published complication rate of endobronchial forceps biopsy is 4% rate of minor bleeding with endobronchial forceps biopsy (24) and 1.5% rate of pneumothorax (25).

The following measures implemented in WINTHER will be applied to SPRING in order to mitigate any risk:

- Biopsy of lowest risk lesion performed by experienced interventional radiologist,
- As often as possible, biopsy of a liver lesion or lymph node (very low risk) to be chosen.

An Independent safety and data monitoring committee (DSMB) will review the overall patient safety during the trial.

In addition, the Informed Consent will be very detailed and clear about the risks of biopsy and the rationale for the dual biopsy approach. The interventional risk will be discussed with the patients in the context of the overall risk of their disease, the mortality risk of which is extremely high in lung cancer and will be juxtaposed to the potential benefits: Biopsies are a crucial component of the SIMS algorithm.

2.8. SUMMARY OF RATIONALE BACKGROUND AND STRATEGY

The standard of care in advanced disease—mainly cytototoxics or matched targeted monotherapies—has had modest impact on mortality as even responders inevitably develop resistance and succumb to their disease (7). Indeed, the fact that tumors are driven by multiple aberrant genes (9, 12, 13), and that resistance uniformly emerges in a Darwinian manner in patients treated with a single targeted therapy render the monotherapy paradigm unsuitable for most metastatic cancers.

With the aim of further enhancing clinical benefit and increasing survival, we propose to test a triple therapy combination of novel targeted drugs in NSCLC. This mirrors the approach that has been so successful in treating AIDS and select cancer types, such as certain leukemias and malignant lymphomas.

In the SPRING proof of concept trial, we selected three agents based on multiple criteria:

- To limit the toxicity profile of the combination, we selected a modulator of immune check point (anti PD-L1) in association with two small molecule tyrosine kinase inhibitors (TKI): anti CDK 4/6 (selective dual inhibitor of CDK 4/6) and an anti – VEGFR. The anti PD-L1 selected is avelumab, co-developed by MERCK and PFIZER. It demonstrated, so far, a good safety profile and is currently tested in various phase 3 programs (see Appendix 3).
- The selected TKIs, palbociclib and axitinib (PFIZER), are approved in other indications and have individually also a safe toxicity profile (see Appendix 3).
- Our data suggests a strong activation of these targets in a significant proportion of advanced NSCLC (see Appendix 4).

- We estimate that overall 85% of the patients treated in the trial will have a profile that is matched to at least one out of the three drugs: 10% matched with three drugs, 36% matched with two drugs and 39% matched with one drug.
- The three agents were made available for combination by PFIZER.
- Specific safety measures related to the administration of avelumab will be implemented in each participation center.

3. SPRING OBJECTIVES AND DESIGN

3.1. PRIMARY OBJECTIVES

- To determine the safety of the tested 3-drug combination therapy based on NCI CTCAE v4.03; June 14, 2010.

- To assess activity parameters, including response rate (RR) by RECIST 1.1, duration of response, progression-free survival (PFS), overall survival (OS),

- To correlate clinical outcome with the predicted SIMS matching through a retrospective study.

Criteria of success:

- We will document best response in all patients. Patients shall be followed for at least six months on treatment (providing their tumors do not progress earlier) in order to document best response: The trial will be considered as meeting its primary endpoint if a 6-month response rate (% of patients achieving RECIST 1.1 complete or partial response within 6 months of treatment start) of 50% is achieved for patients who are fully matched according to the SIMS retrospective analysis and is superior to the partially matched arms. With a type I error of 10% and a power of 94%, 20 patients fully matched will be enough to demonstrate the usefulness of the approach assuming a null response rate of 20% based on the one-sided Fisher's exact test. This would require a cohort of 200 patients treated. Nevertheless, we intend to treat an initial cohort of 100 patients as an exploratory observational study. Pending clinical activity, the study could be extended to an additional 100 patients treated in order to attain sufficient statistical power to support the validity of the approach.

- SIMS will show clinical utility:
  - If the proportion of patients fully matched to the combination versus partially matched estimated using SIMS (20/80) is similar to the observed proportion in the SPRING cohort (maximum coefficient variability allowed 20%),
  - If fully matched patients show significantly better clinical outcomes than the partially matched ones and the fully or partially matched ones show significantly better clinical outcomes than the non-matched ones.

3.2. SECONDARY OBJECTIVES

- Describe any safety issues related to biopsy acquisition or drug combinations,

- Describe genomic/transcriptomic aberrations seen in NSCLC.

3.3. SPRING STUDY DESIGN

For the triple combination tested, we will conduct a seamless Phase 1/2 trial to establish the safety of the regimen and to identify the recommended Phase 2 dose.

3.3.1. The Phase 1

A Phase 1 study will be conducted to assess the safety of the triple combination and establish concentration of each of the agents:

All patients enrolled in the Phase 1 of the study will be treated with the tested combination until progression unless toxicity occurs earlier. Eligible patients will be those with advanced/metastatic disease NSCLC with a maximum of two prior lines of treatment. Patients with already documented druggable oncogenic aberrations (EGFR mutations, ALK rearrangements, ROS1 or MET exon 14 skipping mutations if available) will be excluded from the trial. All patients with adenocarcinoma histology must have documentation of results for druggable oncogenic aberrations (EGFR mutations, ALK rearrangements, and ROS1 when available) prior to enrollment on the study.
In the case of patients already treated on SPRING protocol who are later determined to have EGFR mutation or ALK translocation or ROS1 or MET exon 14 skipping mutations after SIMS analyses, they will be asked to re-consent.
Patients enrolled in the phase 1 study who receive the RP2D will also be included in the phase 2 efficacy assessment. All patients will undergo a tumor and normal tissue biopsy in order to obtain correlative genomic and transcriptomic data.

Safety assessments for administration of avelumab in combination with palbociclib and axitinib

- **Blood chemistry and hematology assessments:** must be performed at baseline, every week during the first cycle and then prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up (+/- 3 days).
- Monitor carefully proteinuria
- **Urine or blood pregnancy test** for women of childbearing potential must be performed at baseline and at least every month during treatment.
- **Free T4 and TSH** must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks). Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.
- **Blood pressure should** be carefully monitored prior to initiating axitinib and after onset of the treatment, in particular after 4 days.
- Monitor carefully all risk to arterial or venous thromboembolic event.
- Monitor carefully active gastrointestinal bleeding. If any bleeding requires medical intervention, temporarily interrupt axitinib.
- Monitor symptoms of gastrointestinal perforation or fistula periodically throughout treatment with axitinib.
- **ECG** will be performed at the beginning of each treatment cycle (+/- 3 days).

During the phase 1, patients will be closely monitored as follows:

- Within one week before day 1 of administration of the drugs, a full clinical examination will be performed,
- During the first month, patients will be seen about every week,
- Afterwards about every two weeks,
- **Extended safety follow-up:** Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration. The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

Treatment Plan:

	1 cycle of treatment																										
	Week 1							Week 2							Week 3							Week 4						
Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Avelumab	X														X													
Axitinib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palbociclib	off	off	off	off	off	off	off	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Avelumab is administered at the study center via an intravenous perfusion
Axitinib (Inlyta®) and palbociclib (Ibrance®) are taken orally at home

The phase 1 of the dual combination avelumab and axitinib has been done and RP2D of the combination has already been assessed (avelumab (10 mg/kg IV every two weeks -1/+3 days) and axitinib (5 mg po bid). These doses are used in the study JAVELIN Renal 101, a randomized phase 3 trial, referenced at US Clinical Trials website:
https://clinicaltrials.gov/ct2/show/NCT02684006?term=avelumab+and+axitinib&rank=1
In order to add the third agent palbociclib, the dual drug combination dose will be reduced and the third drug will be added: **n ~ 30 patients.**

Dose level -1	3 patients receiving avelumab (10 mg/kg IV every two weeks -1/+3 days) and axitinib (2 mg po bid) and palbociclib at 75 mg po daily (7 days off; 21 days on)
Dose level 1	3 patients receiving avelumab (10 mg/kg IV every two weeks -1/+3 days) and axitinib (3 mg po bid) and palbociclib at 75 mg po daily (7 days off; 21 days on)
Dose level 2	3 patients receiving avelumab (10 mg/kg IV every two weeks -1/+3 days) and axitinib (5 mg po bid) and palbociclib at 75 mg po daily (7 days off; 21 days on)
Dose level 3	3 patients receiving avelumab (10 mg/kg IV every two weeks -1/+3 days) and axitinib (5 mg po bid) and palbociclib at 100 mg po daily (7 days off; 21 days on)
Dose level 4	3 patients receiving avelumab (10 mg/kg IV every two weeks -1/+3 days) and axitinib (5 mg po bid) and palbociclib at 125 mg po daily (7 days off; 21 days on)

Important note (1)	A new escalation will be performed after 4 weeks of observation of at least three patients at the previous level if no dose-limiting toxicity (DLT) is observed. If there is DLT at a dose level (clinically relevant, grade 3 or 4 toxicity or inability to complete 50% of treatment administration due to AEs) in the first four weeks, three new patients will be included at the same level. If a second patient has dose limiting toxicity at that dose level, the dose level will be declared above the MTD and the next lower dose level will be expanded to six patients from three patients. The next lower dose level will be declared the MTD providing that no more than 1 patient of six has dose limiting toxicity (or < one third of patients have DLTs). Once the presumed MTD is found, this dose will be set as the RP2D and the first part of the phase 2 study begins. Bayesian toxicity monitoring will be performed throughout the phase 2 study to ensure that the DLT for the tri-therapy is no more than 33% with high confidence. If greater than or equal to one third of patients have DLT, then next lower dose is MTD and that dose will be expanded in the same way.
Important note (2)	The Clinical Monitoring Committee (CMC) constituted by all principal investigators will meet at least monthly by teleconference to discuss the patients included in the study, with the purpose of monitoring and managing any toxicity related issue.
Important note (3)	A key point will be to understand the contribution of each of the drugs in generating toxicities. To this purpose, the CMC will specifically investigate whether observed toxicities relate to overlapping effects (such as fatigue, nausea diarrhea) or specific toxicities (such as febrile neutropenia – palbociclib) or low platelets level (axitinib). Appendix 8 describes all observed toxicities and outlines common or specific toxicities. Main toxicities specific to each drug are summarized in Important note (5). **Rules in case of toxicity/dose modifications:** For any Grade 3 dose-limiting toxicity (see page 32 for dose-limiting toxicity definitions) that is deemed to be drug specific, that drug will be held until resolution to <Grade 1. The drug will then be restarted with the dose at the next lowest level. If Grade 3 or greater toxicity recurs, the drug will be permanently stopped. Exception is hematologic toxicity which may be handled as in Important note (5), palbociclib section or Important note (6). If a toxicity has been deemed to be due to a single drug, but persists at ≥ grade 3 level after stopping the drug, all drugs will be stopped. If it is unclear as to the drug that is causing a toxicity, all three drugs will be held.

	Toxicities that may be clearly attributable to avelumab include immune toxicities such as immune mediated pneumonitis, hepatitis, colitis and nephritis, and infusion related reactions. Toxicities clearly attributable to axitinib include hypertension and proteinuria. Toxicities clearly attributable to palbociclib include lowering of white blood cells (WBC) or platelet counts. For Grade 4 dose limiting toxicities, the drug to which it is attributable will be permanently stopped. If it is not clear as to which drug is associated with the toxicity, all drugs will be permanently stopped. A Clinical Monitoring Committee (that includes site PIs) may be convened to help decide to which drug the toxicity is attributable.
Important note (4)	For dose interruption and reduction events, accurate medical administration records will be maintained to capture changes in dosing regimens, including concomitant medications.

Important note (5):
Below are the AEs specific to each drug, warnings/precautions and guidance for dose modifications/interruption of drugs.

Palbociclib (IBRANCE): *(reference USPI- IBRANCE)*

1. Capsules should be taken with food. Patients should be encouraged to take their dose of palbociclib at approximately the same time each day.
2. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Palbociclib capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.
3. It is known there is a potential for palbociclib to increase the exposure of axitinib through a time-dependent CYP3A4 mediated drug-drug interaction. As a weak time-dependent CYP3A4 inhibitor, palbociclib may reduce the clearance of axitinib, which may increase its exposure-related toxicities. Therefore, it is advised to: Exclude patients currently taking strong CYP3A4 inducers and inhibitors if an alternative concomitant medication cannot be used because they will increase the variability in PK for both axitinib and palbociclib, See Appendix 9.
4. Exclude patients with moderate hepatic impairment from the dose escalation phase of the study or until the MTD for the combination regimen has been determined. The combined effect of CYP3A4 inhibition by palbociclib along with the reduced clearance observed in patients with moderate hepatic impairment on the PK of axitinib is unknown. See US package insert (PI) for axitinib for further details,
5. Exclude patients currently taking proton pump inhibitors from the study due to their impact on the disposition of palbociclib during the dose escalation phase. Patients taking H2-receptor blockers and local antacids can be included in the dose escalation portion of the study as these classes of agents do not alter the PK of palbociclib.
6. Grapefruit or grapefruit juice intake during the whole duration of the treatment should be avoided as it may increase concentration of the drug in blood.

Toxicity management

The most common (≥2%) Grade ≥3 adverse reactions of palbociclib were neutropenia, leukopenia, anaemia, fatigue, and infections

1. Monitor complete blood counts prior to starting palbociclib therapy and at the beginning of each cycle, as well as on Day 14 of the first 2 cycles, and as clinically indicated
2. Dose interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia
3. Special warning is febrile neutropenia has been reported in about 1% of patients exposed to palbociclib.
4. Guidelines for dose adjustments for hematologic toxicities attributable to palbociclib
    - Grade 3: No dose adjustment is required. Consider repeating complete blood count monitoring one week later. Withhold initiation of next cycle until recovery to Grade ≤ 2.
    - Grade 3 ANC (<1000 to 500 mm^3) + Fever ≥ 38.5°C and/or infection: Withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2 (≥ 1000/mm^3). Resume at next lower dose.
    - Grade 4: Withhold palbociclib and initiation of next cycle until recovery to Grade ≤ 2. Resume at next lower dose

Axitinib (INLYTA) *(reference USPI-INLYTA)*

1. Administer axitinib doses approximately 12 hours apart with or without food. Axitinib should be swallowed whole with a glass of water.
2. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.
3. It is known there is a potential for palbociclib to increase the exposure of axitinib through a time-dependent CYP3A4 mediated drug-drug interaction. As a weak time-dependent CYP3A4 inhibitor, palbociclib may reduce the clearance of axitinib, which may increase its exposure-related toxicities. Therefore, it is advised to: Exclude patients currently taking strong CYP3A4 inducers and inhibitors if an alternative concomitant medication cannot be used because they will increase the variability in PK for both axitinib and palbociclib, see Appendix 9.
4. Exclude patients with moderate hepatic impairment from the dose escalation phase of the study or until the MTD for the combination regimen has been determined. The combined effect of CYP3A4 inhibition by palbociclib along with the reduced clearance observed in patients with moderate hepatic impairment on the PK of axitinib is unknown
5. Grapefruit or grapefruit juice intake during the whole duration of the treatment should be avoided as it may increase concentration of the drug in blood.

Toxicity management

The most common (≥20%) adverse reactions are diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

1. Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100

mmHg) was within the first month of the start of axitinib treatment and blood pressure increases have been observed as early as 4 days after starting. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the axitinib dose. Discontinue axitinib if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of axitinib, and discontinuation should be considered if there is evidence of hypertensive crisis. If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension

2. Use axitinib with caution in patients who are at risk for, or who have a history of, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion). Axitinib has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.
3. Use axitinib with caution in patients who are at risk for, or who have a history of venous thromboembolic events. Axitinib has not been studied in patients who had a venous thromboembolic event within the previous 6 months.
4. Axitinib should not be used in patients with recent active gastrointestinal bleeding. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.
5. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with axitinib.
6. Monitor thyroid function before initiation of, and periodically throughout, treatment with axitinib. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.
7. Discontinue axitinib in patients developing Reversible Posterior Leukoencephalopathy Syndrome RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. The safety of reinitiating axitinib therapy in patients previously experiencing RPLS is not known.
8. Monitoring for proteinuria before initiation of, and periodically throughout, treatment with axitinib is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt axitinib treatment.
9. Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with axitinib.
10. Monitor for cavitation apparition throughout the treatment with axitinib.

Avelumab (BAVENCIO)

Premedication: Premedication for the first four doses of avelumab is mandatory. An antihistamine and paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 doses of avelumab is preferred (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). Equivalents of these drugs can be used in case of allergy or other contraindication. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

Premedication may be modified based on local treatment standards and guidelines, as appropriate. Examples of premedication options include but are not limited to nonsteroidal anti-inflammatory drugs as well as non-sedating anti-histamines like Zyrtec (cetirizine hydrochloride).

Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to

implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Instructions for Storage: Avelumab drug product must be stored at 2 °C to 8 °C until use and protected from light. Avelumab stored at higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

Instruction for Preparation: Avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag; alternatively a 0.45% saline solution can be used if needed. The diluted solution is stable 8h at room temperature and up to 24h at 2–8 °C.

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

Avelumab should be administered as an approximately 90 to 120 minutes infusion for the first administration to avoid infusion-related reactions. For subsequent doses, it can be administered as a 60 min or longer infusion.

Toxicity Management (see Table 2, Table 3 and Table 4, in appendix 6):

Adverse Drug Reactions requiring avelumab discontinuation or modification (Table 2)

Treatment Modification for Symptoms of Infusion-Related Reactions (Table 3)

Management of immune-mediated adverse reactions (Table 4)

Understanding contribution of each of the three drugs in observed toxicities, and manage dose reductions.

Observation period*:* Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

ADVERSE DRUG REACTIONS REQUIRING AVELUMAB DISCONTINUATION OR MODIFICATION

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability (refer to Appendix 6). Resume avelumab in patients whose adverse reactions recover to Grade 1 or resolved.

Any Grade 4 ADRs require permanent treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management and endocrinopathies controlled with hormone replacement.

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that does resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Recurrent Grade 3 ADRs and Grade 3 infusion-related reaction require permanent discontinuation.

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, it should be treated as a Grade 3 or 4 (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

Important note (6):	**<u>Specific protocol dose modification for toxicity management related to palbociclib:</u>** - In case of recurrent grade 3 hematologic toxicities, palbociclib may be reduced to 75 mg po daily one week off and one week on. - In case of other severe (≥ grade 3) toxicity related to palbociclib, consider holding palbociclib until toxicity is grade 1 or less, then resume at the alternate schedule of 2 weeks OFF / 2 weeks ON.

- **DLT will be defined as:**
  Any of the following events that are considered to be clinically significant and meaningful as per evaluation of the attending physicians and confirmed by CMC and at least possibly related to drug. DLTs for the purposes of dose-escalation will be evaluated during the 28-day period following the first dose of study treatment. Each treatment cycle is four weeks. Toxicities will be graded and documented according the NCI CTCAE (v4.03).

- **Non-hematological dose-limiting toxicity is defined as:**
  - Persistent Grade 3 or 4 hypertension despite treatment with anti-hypertensive drugs.
  - Grade 3 or 4 Gastrointestinal bleeding.
  - Grade 3 or 4 Gastrointestinal perforation or fistula.
  - Development of Reversible Posterior Leukoencephalopathy Syndrome.
  - Persistent Grade 3 or 4 proteinuria.
  - Grade 3 or 4 arterial or venous thromboembolic events.
  - Any other Grade 3 or Grade 4 non-hematological toxicity that are considered at least possibly related to a study drug and clinically significant after discussion at CMC with exceptions listed below:
    grade 3 nausea, vomiting, diarrhea, that responds to maximal supportive treatment(s) within 3 days, grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to Grade ≤1 or baseline prior to the time for the next treatment cycle.
  - Allergic reactions that necessitate discontinuation of the study drug responsible for the reaction.
  - Any Grade ≥ 2 pneumonitis of any duration.

- **Hematological dose-limiting toxicity is defined as:**
  - Grade 4 neutropenia (absolute neutrophil count, ANC) for > 7 days
  - Platelet count <10.000/mm3 one time or bleeding requiring transfusion
  - Toxicity that causes a delay of >14 days between treatment cycles
  - Febrile neutropenia despite G-CSF secondary prophylaxis
  - Either isolated or recurrent (i.e., cardiac, renal, neurologic) toxicity that is judged by the Investigator to be a DLT.

- **Further evaluation of the combination's toxicity at a dose level:**
  Up to 3 additional patients could be added at a dose level to explore the toxicity on an occasional basis after discussion with the CMC. All additional patients will be included in the study's assessment.

- **To decide for dose-escalation cohort at a higher dose level**, the CMC that includes the study investigators and the sponsor clinical study team, will review available data (e.g. safety profile). Subsequent safety reviews by the CMC will be conducted prior to enrollment of patients in a new cohort and to establish the RP2D.

- **Intra-patient dose escalation**:
  Patients will be permitted to have a dose escalation to the highest dose shown to be safe at the time of escalation, provided they have no clinically relevant drug-related toxicity > Grade 1 at the dose

level they are on and that both they and their physician deem a dose escalation to be in their interest. For a dose level to be considered proven safe, there must be at least three patients treated at that dose level for at least four weeks, and the clinical monitoring committee must have deemed that dose level to be at or below the MTD.

- **Dose reduction**
  Patients who have a dose limiting toxicity and it is unclear as to which drug may have caused the toxicity, may restart drugs at the next lower dose level once toxicity returns to $\leq$ Grade I. If the investigator deems the toxicity to be due to one of the drugs in the regimen, only that drug may need to be reduced to the next lower dose level. A second dose reduction of this type may occur if toxicity recurs. For a patient who is responding (PR or CR) the investigator may continue to reduce the dose to the lowest dose level tolerable; for these responding patients, if one drug is deemed responsible for recurring serious toxicity, it may be stopped and the other two drugs continued after review by the clinical monitoring committee.

3.3.2. The Phase 2

When the recommended Phase 2 dose is reached, there will be a first expansion of the study to explore efficacy of the tested triple combination. In the expansion, only patients with unresectable or metastatic NSCLC with no prior treatment line will be treated. Up to 100 patients will be treated with the combination (~120 patients enrolled*) until progression. For ethical reasons, even patients who failed biopsy(ies) will be treated with the triple-therapy. Pending clinical activity, the study may be extended (with a study amendment) to an additional 100 patients treated in phase 2 in order to attain sufficient statistical power to support the validity of the approach.

Study participation will be offered to patients with locally advanced or metastatic disease.
Patients with documented oncogenic aberrations (EGFR, ALK, ROS1 if available, MET exon 14 skipping if available) at enrollment will be excluded from the trial. In the case of patients already treated on SPRING protocol who are later determined to have EGFR mutation or ALK translocation or ROS1 or MET exon 14 skipping mutations after SIMS analyses, they will be asked to re-consent.
Patients will be included in the study regardless of their PD1 or PD-L1 expression status.
Main outcome variables will include response rate (RR), progression-free survival (PFS), and overall survival (OS).

4. ENROLLMENT OF PATIENTS

Patients will be identified as potential candidates for the SPRING trial and may consent to enrollment in SPRING and to related study procedures including biopsies from the tumor tissue (metastatic lesion or primary tumor), and from its histologically matched normal tissue (bronchial mucosa).
Biopsies will be processed and investigations performed (i) to detect genomic alterations (in the case that this information is not already available from the patient's file) in order to exclude the patient from the tested tri-therapy trial if such aberrations are detected, (ii) to generate the SIMS scoring. However, the scoring will not be used other than to establish correlations retrospectively between biological data and clinical outcome. All eligible patients will receive the triple combination.

4.1. ELIGIBILITY CRITERIA

Note: Eligibility criteria should be verified between consent and registration (28 days maximum window).

For phase 1 and phase 2:

- Age: Men and women aged ≥18 years,
- Signed written informed consent,
- Any histologic type of locally advanced or metastatic NSCLC,
- Life expectancy of ≥ 12 weeks,
- Measurable or evaluable (cytologically or radiologically detectable disease such as ascites, peritoneal deposits, or lesions which do not fulfill RECIST 1.1 criteria for measurable disease) lesions according to RECIST 1.1 criteria for phase 1 portion. For phase 2, all patients must have RECIST 1.1 measurable disease,
- PHYSIOLOGIC FUNCTION:
  - ✓ Hematologic: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused),
  - ✓ Hepatic: Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN,
  - ✓ Renal: Estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method).
- PREGNANCY AND CONTRACEPTION:
  - ✓ Pregnancy test: Negative serum or urine pregnancy test at screening for women of childbearing potential.
  - ✓ Contraception: Highly effective contraception for both male and female subjects throughout the study and for at least 90 days after last treatment administration if the risk of conception exists.
- Ability to comply with protocol requirements,
- Willingness to consent and ability to undergo a trucut biopsy to obtain a fresh metastasis or primary tumor biopsy, and to undergo bronchoscopy to obtain a biopsy from normal bronchial mucosa,

- No serious or medically uncontrolled concomitant conditions that are likely to make the patient unfit for SPRING combination therapy, as per investigator assessment,
- ECOG performance status of 0 to 1.

4.2. EXCLUSION CRITERIA

Note: Exclusion criteria should be verified between consent and registration (28 days maximum window).

- Patients with documented oncogenic aberrations at enrollment: EGFR, ALK, ROS1 when available, MET exon 14 skipping when available. For squamous undifferentiated cell carcinoma, documentation of these aberrations is not mandatory.
  Note: For Phase 1 portion, all patients with adenocarcinoma histology must have documentation of results for druggable oncogenic aberrations (EGFR mutations, ALK rearrangements, and ROS1 when available) prior to enrollment on the study.
- For Phase 1 portion, >2 lines of prior therapy in the metastatic setting.
- For the dose escalation phase of the study or until the MTD for the combination regimen has been determined, patients with moderate hepatic impairment defined as AST, ALT, ALP >5 times ULN, which would be grade 3 or higher. However, patients with liver metastases with AST/ALT ≤ 5 x ULN can be included in the study.
- For Phase 2 portion, any prior therapy in the metastatic setting.

Clinical criteria for phase 1 and phase 2 studies:

- Patients with treated brain metastases are eligible as are patients with new, active untreated brain metastasis.
- Participants with a history of myocardial infarction within the last 2 years or with significant cardiac arrhythmias uncontrolled by medication or pacemaker,
- Participants with any history of interstitial lung disease,
- Prior clinically significant toxicities from anticancer agents or radiotherapy which have not regressed to Grade ≤ 1 severity (NCI-CTCAE version 4.03) apart from peripheral neuropathy and alopecia,
- History of any second malignancy in the last two years; patients with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible. Patients with a history of other malignancies are eligible if they have been continuously disease-free for at least two years,
- Autoimmune condition requiring medical intervention,
- Uncontrolled concomitant illness, active infection requiring i.v. antibiotics,
- Patients who have had a thromboembolic event within six months are excluded, as are patients on anticoagulants, except for low dose aspirin (<100 mg/day) and low doses of anticoagulants meant to keep line access open;
- Patients with Grade 3 or 4 (serious) gastrointestinal bleeding within the last six months are excluded.
- Prior ≥ G3 hemoptysis, major blood vessel involvement (specifically including aorta, superior and inferior vena cave, main pulmonary arteries and veins, subclavian arteries and veins and other

large blood vessels that in the investigator's opinion places the patients at high risk for major bleeding), and/or central cavitations,

- Known or suspected drug hypersensitivity to any drug used in the combination,
- Difficulty swallowing, malabsorption or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the oral drugs,
- Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location, etc.) that, in the judgment of the investigator may affect the patient's ability to sign the informed consent and undergo study procedures,
- Taking another experimental drug within 28 days prior to day 1 of the protocol medications in this study,
- Pregnant or breast-feeding women,
- Both male and female patients of reproductive potential must agree to use highly effective contraception, during the study and for 3 months following the last dose of study drug,
- Patients currently taking strong CYP3A4 inducers and inhibitors, See Appendix 9.
- Patients currently taking proton pump inhibitors due to their impact on the disposition of palbociclib during the phase 1.
- Patients taking other anticancer agents with the exception of denosumab or equivalent medication for bone metastases.
- A time period of at least three weeks (including radiotherapy) or five drug half-lives, whichever is shorter must have elapsed from last non-investigational therapy before first day of treatment on this study,
- A time period of at least 10 days must have elapsed from last palliative radiotherapy before the first day of treatment on this study,
- Specific exclusion criteria for administration of avelumab, in combination:
  - ✓ IMMUNOSUPRESSANTS: Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
  - ✓ AUTOIMMUNE DISEASE: Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.
  - ✓ ORGAN TRANSPLANTATION: Prior organ transplantation including allogenic stem-cell transplantation.
  - ✓ INFECTIONS: Active infection requiring IV (Intra venous) therapy.
  - ✓ HIV/AIDS: Known history of testing positive for HIV or known acquired immunodeficiency syndrome.
  - ✓ HEPATITIS: Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).
  - ✓ VACCINATION: Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines.
  - ✓ HYPERSENSITIVITY TO STUDY DRUG: Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3).

- ✓ CARDIOVASCULAR DISEASE: Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia inadequately controlled by medication.
- ✓ OTHER PERSISTING TOXICITIES: Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
- ✓ Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

5. STUDY PROCEDURES

5.1. INFORMED CONSENT

Subjects will be asked to provide written consent using an IRB/EC-approved consent form. The investigator or study coordinator will obtain informed consent in a language understood by the prospective participant or their legally authorized representative, using certified translations of study documents and qualified translators, where applicable. Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legal representative, if the subject is unable to provide informed consent) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a Regulatory Authority and/or IRB/IEC. The investigator with assistance from the study coordinator will describe the study, including detailed information about risks, benefits, and voluntary nature of the study, to potential subjects. Subjects will be given ample time to read the consent form at the same visit or may take it with them to read at another time. Potential study subjects will be given the opportunity to ask any questions they may have about the study, including its risks and benefits, or about the consent form itself before signing the consent form. Each subject's signed informed consent form(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The patient or patient's legal representative should receive a copy of the signed and dated written informed consent form(s) and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

Patients who fulfill the eligibility criteria will be offered further participation in this study.

Participants will also be requested to sign a separate authorization for the use of protected health information (i.e., HIPAA or other applicable privacy rules as per provisions of countries in which sites are active). Only patients who have consented and provided HIPAA authorization will have identifiers or linked information (e.g., study numbers, etc.) recorded on the Screening/Enrollment Log.

Patients will be informed of the difference between receiving the combination of avelumab /anti PD-L1 (PFIZER/MERCK), palbociclib – Ibrance / CDK4/6 inhibitor (PFIZER) and axitinib - Inlyta / anti VEGFR (PFIZER) and the standard of care treatments that they could be receiving if they were not electing to participate in this study. Potential risks vs. potential benefits will be clearly presented so that patients can make an informed choice regarding their treatment. In particular, risks relating to any additional intervention (biopsy) than the standard of care will be detailed in the context of the overall risk of their disease.

Patients with specific documented oncogenic aberrations (EGFR mutations, ALK translocations, ROS1 if available and MET exon 14 skipping mutation if available) will be excluded from the trial. Patients with unknown ROS 1 or MET exon 14 skipping mutation status at the time of enrollment who are later determined to have an actionable mutation amenable to treatment with an approved therapy can then be given the option to continue investigational treatment in the SPRING trial after obtaining appropriate re-consent or discontinue treatment.

5.2. MOLECULAR PROFILING OF TUMOR AND NORMAL BIOPSIES AND BLOOD SPECIMENS

5.2.1. Collecting/processing methods of tissue biopsies

Tissue biopsies will be collected and/or processed using WIN Consortium Standard Operating Procedures' Manual. To summarize:

1. The patient shall undergo a new tumor tissue biopsy. A minimum of 3 (but preferably 5) metastasis (or primary tumor) tissue samples from the patient will be obtained using 18 (or 20) gauges trucut biopsies under radiology control. The metastatic lesion chosen for the biopsy must be non-necrotic and preferably with a $\geq$ 2 cm diameter. The needle will be placed at the periphery of the lesion so that the trucut (measuring 1.5 cm) remains within the metastasis in order to maximize tumor content and avoid contamination with surrounding stroma and normal tissues. The appropriate selection of the metastatic lesion biopsied is the most essential criteria to ensure success of the biopsies,
2. A minimum of 3 (but preferably 5) random tissue samples from the patient's normal bronchial mucosa will be obtained using minimum of 2.5 mm^3 forceps under bronchoscopy. The normal bronchial mucosa biopsies can be done on any normal-appearing bronchial mucosa, with the safest location selected at the discretion of the pulmonologist performing the procedure.
3. Up to 3 tumor biopsy specimens will be fresh frozen and if possible up to 2 stored in formalin-fixed paraffin-embedded (FFPE) block.
4. Normal tissue biopsy specimens up to 3 will be fresh frozen and if possible up to 2 stored in FFPE block.
5. The tissue samples obtained from tumor/metastatic tissue and normal tissue will be used for histology control and preparation of nucleic acids (DNA and RNA) either at the cancer center or in the appointed central laboratory(ies) according to Standard Operating Procedures Manual.
   Histological control performed will determine the percentage of tumor cells and characterize the content of other components of the specimen (stroma, immune infiltrate, etc.) Acceptable tumor/metastasis and normal tissue biopsies will reach a threshold of 50% of tumor content and 30% to 50% normal epithelial cells respectively, for performance of the genomic and transcriptomic analyses to generate the SIMS scoring.
   For FFPE specimens, macrodissection can be performed, if necessary, to ensure that tumor/metastatic tissue specimens reach the threshold of 50% tumor cells content.

5.2.2. Control of variability and reduction of noise

- The use of tumor/metastasis and normal matched tissue biopsies from the same patient will attenuate noise related to variability between individuals. The same applies for blood samples obtained from the same patient before and after treatment,
- The use of dual biopsies enables the reduction by 16 folds the variance of micro arrays measuring gene expression in normal and tumor/metastasis tissues,
- Strict control of histological preparations discards/minimizes inter-organ variability,
- As much as possible, biopsies will be investigated in the same conditions. Genomic investigations will be performed by centralized laboratories in order to avoid inter-platform variability,

- Raw genomic data and clinical biological and pathology data will be merged into a single database.

5.2.3. Molecular profiling of tissue biopsies

Central genomics and transcriptomic platform(s) will be used.
The following investigations will be done in the selected central platform(s):
(i) Sequencing: A panel of 270 genes that will at least include the 183 cancer relevant genes of SIMS selected by capture will be sequenced using Illumina technology with a deep reading of at least 1000x, according to Standard Operating Procedures (SOP) of WIN Consortium. The purpose is detection of mutations and all known translocations.
Whilst only the sequencing data obtained on 183 SIMS genes will contribute to the evaluation of the 2nd goal of the study (evaluation of the SIMS scoring), the sequencing will include other genes. This additional information will be used for other correlative studies, including an extensive study to predict efficacy to immunomodulators.

(ii) Differential expression from tumor/metastatic tissue and normal tissue:
Direct comparison of tumor/metastasis and normal mRNA will be performed to determine the differential expression levels between the two tissues for the 183 genes of the SIMS panel. Nevertheless, we will be using a large panel of probes (25,000) enabling the investigation of gene expression for almost all genes.
Similarly, the top interacting 5 microRNA for each of the SIMS 183 genes will be investigated using the same method.

Transcriptomic investigations (mRNA and MIR) for the purpose of validation of SIMS algorithm will be performed on RNA preparations from fresh frozen biopsies. Such investigations will be performed with validated technologies such as microarrays or RNAseq.

FFPE biopsies might be used for ancillary analysis. Transcriptomic investigations might be done on FFPE samples with the objective to explore their correlation with frozen specimens and potentially determine if FFPE biopsies can indeed be used in the clinical setting and replace in the future frozen samples for RNA investigations. Also, will be explored the possibility to do proteomics correlative researches.

5.2.4. Blood specimens for research purpose

Blood specimens will be collected for each patient enrolled at baseline (before starting the treatment at Day 1 Cycle 1), one week after onset of the treatment and about every 8 weeks thereafter (Day 1 before treatment of every odd cycles). Whilst data collected from blood will not be used for the therapeutic decision, they will be essential for further research into specific genomic/transcriptomic/proteomic markers that relate to predicting outcomes.

- 10 ml blood will be collected. Blood specimens will be processed and stored locally in each participating center. Processing will consist in high speed centrifugation (4500g) collection of serum, and generation of 500 µl aliquots that will be stored at -80°C,
- Requisition forms will be kept for record,

- Blood aliquots will be stored for further research,
- Testing performed will be for research purpose only.

5.2.5. Blood specimens for pharmacokinetics (PK) monitoring purpose

The PK profile is known for each of the three drugs separately, as well as for the dual combination avelumab-axitinib.

- The monitoring of PK in SPRING study has three purposes:
    1. Assess the simultaneous PK profile of the three drugs in combination and compare with known PK profiles,
    2. Determine if the PK profile of the three drugs in combination is stable across at least 4 cycles,
    3. Monitor the apparition of auto-antibodies against avelumab (long term survey, after 4 cycles).

- To this aim, the blood collections will be performed on Day 15 visit of each cycle during phase 1, for each dose level and every two cycles during the phase 2. The accurate monitoring will require that at each blood drawn we utilize a specific tube and conditions for processing, storage, shipment. The specific processing conditions and detailed protocols for each type of analyte, are described in appendix 7 and PK manuals. Briefly, monitoring of avelumab will require obtaining serum, whilst monitoring of palbociclib and axitinib will require obtaining plasma. Handling of tubes for axitinib will require protection from light. In addition, it is known that there is a potential for palbociclib to increase the exposure of axitinib through a time-dependent CYP3A4 mediated drug-drug interaction. As a weak time-dependent CYP3A4 inhibitor, palbociclib may reduce the clearance of axitinib, which may increase its exposure-related toxicities. As a direct consequence, it will be mandatory to obtain PK blood samples at +0h45 and +1h15 after intake of palbociblib and axitinib, that is reflected in the PK steps below. Measurement of analytes will be performed in central laboratory(ies), based on suggestion made by Pfizer.

- In order to have a maximal insight, we suggest the following blood draws for the day 15 of each cycle (as detailed in Table1):

    - ✓ **Step 1** Time 0 – in the morning of day 15, obtain blood for baseline PK samples,
    - ✓ **Step 2** Intake of palbociclib and axitinib with meal/food,
    - ✓ **Step 3** Time 0h45 - Obtain PK samples, after intake of axitinib and palbociclib,
    - ✓ **Step 4** Time 1h15 - Obtain PK samples, after intake of axitinib and palbociclib,
    - ✓ **Step 5** Time 2h – Obtain PK samples, after intake of axitinib and palbociclib,
    - ✓ **Step 6** Premedicate 30 to 60 minutes prior the avelumab infusion (in a facility with easy access to intensive care unit)
    - ✓ **Step 7** Obtain PK samples 4h after intake of axitinib and palbociclib and immediately prior to start of the infusion with avelumab
    - ✓ **Step 8** Administer avelumab for one hour,
    - ✓ **Step 9** Obtain PK samples immediately at the end of the avelumab infusion,
    - ✓ **Step 10** Obtain PK Samples 1 h, 2h, 3h, 4h and 5h after infusion with avelumab

Note that PK samplings must be recorded in PK requisition form.

All PK samples are allowed to be drawn with a +/- 5 minutes window.

Table 1: Overview of PK sampling

Step	Time	Action	Time points axitinib	Time points palbociclib	Time points avelumab
1	**0**	PK blood drawn (separate tubes 4 ml: one for each analyte axitinib and palbociclib)	**Baseline (0) (pre-dose)**	**Baseline (0) (pre-dose)**	
2		Oral intake of palbociclib and axitinib with meal			
3	**+ 0h45**	PK blood drawn (separate tubes 4 ml: one for each analyte axitinib and palbociclib)	**+ 0h45**	**+ 0h45**	
4	**+ 1h15**	PK blood drawn (separate tubes 4 ml: one for each analyte axitinib and palbociclib)	**+ 1h15**	**+ 1h15**	
5	**+ 2h**	PK blood drawn (separate tubes 4 ml: one for each analyte axitinib and palbociclib)	**+ 2h**	**+ 2h**	
6		Premedication for avelumab			
7	**+ 4h**	PK blood drawn for all 3 analytes	**+ 4h**	**+ 4h**	**Baseline (0)** before infusion
8		Infusion with avelumab (1h)			
9	**+ 5h**	PK blood drawn Immediately after the end of avelumab infusion for avelumab			**Immediately at the end of the infusion**
10	**+6h**	PK blood drawn for each of the 3 analytes	**+ 6h**	**+ 6h**	**+1h** after the end avelumab infusion
10	**+7h**	PK blood drawn for avelumab			**+2h**
10	**+8h**	PK blood drawn for each of the 3 analytes	**+ 8h**	**+ 8h**	**+3h**
10	**+9h**	PK blood drawn for avelumab			**+4h**
10	**+10h**	PK blood drawn for avelumab			**+5h**

The apparition of auto-antibodies against avelumab will be monitored during the phase 2: 1 blood sample of 4 mL will be collected on Day 15 at baseline every two months.

5.3. BIOINFORMATICS AND DATA MANAGEMENT

A centralized IT structure will be set up to support the data collection and analyses.

(i) Central Bioinformatics platform will collect and will enable analysis of all data related to the study:

- Clinical data through CRF or eCRF generated by each participating cancer center,
- Quality Controls at all steps of the biological workflow generated by local and central laboratories,
- Raw biological data generated by both genomics/transcriptomics and proteomics platforms.

(ii) The bioinformatics platform will also run the SIMS scoring algorithm. The SIMS report including a comprehensive list of co-activated interventional points for the patient will be issued.

IT infrastructure, database and tools/algorithms will be coordinated by IT team coordinator.

5.4. PROCEDURES DURING TREATMENT

Refer to study Flow Chart in Appendix 5 and study assessment manual for further directions at the discretion of the investigator.

As dictated by standard of care, tumor assessments are to be done approximately every 8 weeks (+/- 7 days).

Safety assessments

- **Blood chemistry and hematology assessments:** must be performed at baseline, every week during the first cycle and then prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up (+/- 3 days). Complete Blood Count (CBC), Complete Metabolic Profile (CMP), amylase, lipase, and urine protein by dipstick are recommended.
- Monitor carefully proteinuria. If the patient has 3+ proteinuria on dipstick, this should trigger a 24-hour urine to quantify the proteinuria so that it can be graded.
- **Urine or blood pregnancy test** for women of childbearing potential must be performed at baseline and at least every month during treatment.
- **Free T4 and TSH** must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks). Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.
- **Blood pressure should** be carefully monitored prior to initiating axitinib and after onset of the treatment, in particular after 4 days.
- Monitor carefully all risk to arterial or venous thromboembolic event.
- Monitor carefully active gastrointestinal bleeding. If any bleeding requires medical intervention, temporarily interrupt axitinib.
- Monitor symptoms of gastrointestinal perforation or fistula periodically throughout treatment with axitinib.
- **ECG** will be performed at the beginning of each treatment cycle (+/- 3 days).

Other minor modifications of scheduled visits or medication administration for medical, personal, or logistical reasons may be done after CMC discussion providing that CMC determines that modifications do not impact patient safety.

5.5. FOLLOW-UP PROCEDURES

Extended safety follow-up

- The Clinical Monitoring Committee (CMC) constituted by all principal investigators will meet at least monthly by teleconference to discuss all the patients included in the study, with the purpose of monitoring and managing any toxicity related issue.
- Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration. The last patient 90-day follow-up visit is defined as the last patient last visit.
- The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

After the patient comes off study, follow up to determine survival will be done for 2 years every 6 months. Follow-up will consist of survival contacts via medical record review, telephone call, or review of the Social Security Index.

5.6. SAFETY REPORTING

5.6.1. Adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

5.6.1.1. Definition of adverse events

An adverse event (AE) is any untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject. An AE can therefore be any unfavorable and unintended symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram), whether or not a causal relationship (i.e related/not related) with investigational medicinal products and/or the study procedures is suspected. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

5.6.1.2. Definition of serious adverse events

For detailed definition and example, refer to the Pfizer Safety Report Reference Manual.

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening: An adverse event is life-threatening if the subject was at immediate risk of death from the event as it occurred i.e. does not include a reaction that might have caused death if it had occurred in a more serious form. For instance, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.
- Requires in-patient hospitalization (even if for less than 24 hours) or prolongation of existing hospitalization (any extension beyond the anticipated/required stay for the original reason for admission or beyond the length of stay described in the protocol)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect

  or
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  An important medical event also includes suspected transmission via avelumab, axitinib, palbociclib or another Pfizer product of an infectious agent, pathogenic or non-pathogenic, or development of drug dependency or drug abuse of any product (whether avelumab, axitinib, palbociclib, another Pfizer product or any non-Pfizer product).

The following are not considered to be serious adverse events (SAE):

- A visit to the emergency room or other hospital department for less than 24 hours that does not result in admission
- Outpatient or same-day or ambulatory procedures
- Observation or short-stay units without an AE
- Hospitalization due to diagnostic procedures or standard supportive care (e.g. implant of central venous catheter)
- A pre-planned hospitalization for a condition which existed at the start of study drugs and which is not associated with the development of a new AE or which do not worsen during the course of study drugs treatment
- Social admission (e.g., subject has no place to sleep; hospice facilities)
- Administrative admission (e.g., for yearly physical examinations)

- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the study protocol or for clinical research)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)

5.6.2. Recording of adverse events

5.6.2.1. Time period for collection of adverse events

AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 90 +/-7 days after study treatment is discontinued.

SAEs occurring in the follow-up period should be reported to the sponsor as described on section 5.6.3.

5.6.2.2. Follow-up of unresolved adverse events

AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

Covance pharmacovigilance unit retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

If an investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to axitinib, avelumab and palbociclib, the investigator should notify the pharmacovigilance unit of the sponsor.

5.6.2.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product
- Action taken with regard to investigational product
- Outcome

The grading scales found in the current National Cancer Institute CTCAE version 4.03 will be used for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

5.6.2.4. Causality collection

The causal relationship between the study medication and the AE must be characterized as not related, unlikely, possible/probable, or definitely by the investigator. Drug-related events will be defined as those with a possible/probable or definite classification.

5.6.2.5. Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF.

When collecting AEs, recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

5.6.2.6. Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfill any of the criteria for a SAE, a DLT or are the reason for discontinuation of treatment with the investigational product(s) unless clearly due to progression of disease under study (section 5.6.2.7).

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information.

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

5.6.2.7. Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational products are being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered

as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs/SAEs during the study.

Progression of the disease under the study is reportable only if the patient dies of the disease progression within the study reporting period. Hospitalization due to signs and symptoms of malignancy progression should not be reported.

5.6.2.8. New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

5.6.2.9. Handling of deaths

All deaths that occur during the study, or within the follow-up period after the administration of the last dose of investigational product, should be reported as follows:

- Death, which is unequivocally due to disease progression within the study reporting period should be reported as a SAE.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the sponsor as an SAE immediately upon awareness. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported to the sponsor as a SAE but every effort should be made to establish a cause of death. Include a summary of autopsy findings, if available.

5.6.2.10. Handling of exposure during breastfeeding

An exposure during breastfeeding occurs if an infant or child may have been exposed through breast milk to the Pfizer/Merck product during breastfeeding by a female taking the Pfizer/Merck product. Exposure during breastfeeding is reportable to the pharmacovigilance unit regardless of whether there is an associated SAE in the infant or child.

5.6.2.11. Handling of exposure during pregnancy

Exposure during pregnancy occurs when a fetus (from pre-embryo to birth) may have been exposed at any time during the pregnancy to a Pfizer/Merck product. Exposure during pregnancy is reportable to the pharmacovigilance unit regardless of whether there is an associated SAE.

The specific details that need to be included in the report of an Exposure during Pregnancy depend on whether the exposure was maternal or paternal. The anticipated date of delivery should be included in the report, for both maternal and paternal exposures. The principal investigator must then follow the subject through the pregnancy and is to notify the sponsor and Pfizer/Merck of the outcome as a follow-up to the initial exposure during the pregnancy report.

An Exposure During Pregnancy Occurs Through Either:

- Maternal exposure

A female subject becomes, or is found to be, pregnant either while receiving or having been exposed to a medicinal product, or the female becomes, or is found to be, pregnant after discontinuing or being exposed to the medicinal product

A pregnant woman may have an environmental exposure involving direct contact with a Pfizer/Merck product (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products by inhalation or spillage)

OR

- Paternal exposure

A male subject has been exposed, either due to treatment or environmental exposure, to a medicinal product prior to or around the time of conception of his child or during his partner's pregnancy.

If the **outcome of the pregnancy meets any of the criteria for seriousness, report it to the pharmacovigilance unit** as an SAE.

Examples of pregnancy outcomes that are SAEs:

- Spontaneous abortion (includes miscarriage and missed abortion)
- Stillbirth
- Congenital anomaly (including in an aborted fetus, a stillborn infant, or neonate that dies shortly after birth)
- Neonatal death

In the case of neonatal death:

- Any neonatal death that occurs within 1 month of birth should be reported, without regard to causality, as an SAE

In the case of infant death:

- Any infant death that is assessed as possibly related to the in utero exposure to the Pfizer product or blinded therapy should be reported as an SAE.

5.6.2.12. Occupational exposure

An occupational exposure is an exposure to a Pfizer/Merck product for human use as a result of one's occupation. An occupational exposure is reportable regardless of whether there is an associated SAE.

5.6.2.13. Potential drug-induced liver injury (Hy's law cases)

For Pfizer investigational (non-authorized) medicinal products and Pfizer products that are investigational in the United States (irrespective of being authorized elsewhere), interventional clinical study reports with elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) in addition to and/or preceding total bilirubin (TBili) elevations (>2 x ULN) are considered potential drug-induced liver injury (DILI- assessed per Hy's law criteria) cases and should always be considered important medical events and should be reported as SAEs, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST or ALT values >3 x ULN and a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For subjects with baseline AST or ALT or TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which value(s) are above the ULN at baseline.
- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values and >3 × ULN; or >8 × ULN (whichever is smaller).
- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks are assessed individually based on clinical judgment; any case where uncertainty remains as to whether it might represent a potential DILI case is reviewed with the sponsor. The investigator coordinator is informed if such a situation occurs during the study and she will inform the HIC that will provide the necessary support for an appropriate evaluation.

5.6.3. Reporting of Serious Adverse Events

Any SAE which occurs or comes to the attention of the investigator at any time during the study since consent is given and within 90 days (+/-7 days) after the last dose of study drugs, have to be reported to the sponsor's appointed pharmacovigilance unit without delay and in no circumstances later than 24 hours after first awareness by the investigator, whether or not considered causally related to the investigational product, or to the study procedure(s), by fax/email via a SAE report form according to the study procedure.

Fax number: +1.888.887.8097
Phone: +1.888.724.4908
E-mail: SAEIntake@Covance.com
(9 a.m. - 6 p.m. from Monday to Friday, except on bank holidays)
Pharmacovigilance unit address:
Covance
206 Carnegie Center Blvd
Princeton, NJ 08540, USA

All late Serious Adverse Events (occurring after this period of 90 days) considered to be reasonably related to the IMPs or the protocol must be reported (no time limit).

Information collected in the SAE form is crucial to assess the case. For this reason, diligence in collecting as much verifiable and reliable information is needed: both, quality and timeliness are key factors. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all SAEs: onset, duration, intensity, seriousness, relationship to study drugs and/or to the protocol, action taken and corrective treatment required.

The investigator must also attach the following to the serious adverse event report form, wherever possible:

- ✓ A copy of the summary of hospitalization or prolongation of hospitalization
- ✓ A copy of the post-mortem report (if applicable)
- ✓ A copy of all relevant laboratory examinations and the dates on which these examinations were carried out, including relevant negative results, as well as normal laboratory ranges.
- ✓ All other document that he judges useful and relevant.

All these documents will remain anonymous.
Further information can be requested (by fax, telephone, email or when visiting) by the monitor and/or the safety manager.

Follow-up information

- The investigator is responsible for the appropriate medical follow-up of patients until resolution or stabilization of the adverse event or until the patient's death. This may mean that follow-up should continue once the patient has left the trial.
- Follow up information about a previously reported serious adverse event must be reported by the investigator to the Pharmacovigilance Unit within 24 hours of receiving it (on the serious adverse event report form, by ticking the box marked Follow-up Nr). The investigator also transmits the final report at the time of resolution or stabilization of the SAE.
- The investigator retains the documents concerning the supposed adverse event so that previously transmitted information can be completed if necessary.
  All SAEs will be recorded in the CRF.

The Sponsor is responsible for meeting all local regulatory safety reporting requirements and obligations in all countries participating in this trial. This includes expedited reporting of all serious,

unexpected and possibly study-drug-related SAEs (SUSARs) from the study to the local Regulatory Authority and IEC/IRB, as required and to the EMA pharmacovigilance database (Eudravigilance).

All SAEs information will be transferred to Pfizer.

5.7. REMOVAL OF SUBJECTS FROM STUDY

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient withdraws consent,
- Patient is unable to comply with protocol requirements,
- Treating physician judges continuation on the study would not be in the patient's best interest.

5.8. EFFICACY EVALUATION

Efficacy evaluation will be primarily based on investigator assessment:

- Best Overall Response: Best response is the maximal response recorded from the start of a treatment until the end of treatment taking into account any requirement for confirmation.
- 6-month Response: The primary endpoint of the study is defined as the 6-month response rate (proportion of patients with complete or partial response based on the RECIST 1.1 criteria) from the start of treatment.
- Progression-Free Survival: Progression-free survival (PFS) is defined as the duration of time from the start of treatment until tumor progression or death,
- Overall Survival: Overall survival (OS) is defined as the duration of time from the start of treatment to death.

PFS may include review of CT images. CT or MRI scans will be performed as per routine institutional practice. Patients will be considered evaluable if they received at least one cycle of treatment and had their baseline scan within 28 days of the start of therapy and follow-up scans about every 8 weeks (+/- 7 days) thereafter. The same imaging technology (i.e., CT or MRI as preferred by the physician) as used at baseline will be required at all follow up examinations. Since previous studies suggest that early radiographic response assessment of patients receiving immunotherapy may initially meet RECIST criteria for progressive disease only to demonstrate response or stable disease on a subsequent scan, the investigator may consider performing a confirmatory scan 4 weeks after progression to confirm this finding if clinically indicated. If the disease is confirmed to meet RECIST criteria for progression, the patient will no longer be treated on the study. However, if criteria are not met for progression, the patient may continue on the study, and radiographic assessment will continue on 8 week intervals thereafter.

Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical

assessment). Target lesions at screening/baseline must have a unilateral tumor measurement of at least 2 times the size of the CT/MRI scan interval cut. The longest diameters for all target lesions will be recorded and a sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. At baseline, all measurable lesions up to a maximum of 5 lesions per organ systems and 10 lesions in total should be identified as target lesions, ideally representative of all involved organs.

5.9. DATA COLLECTION

This study will require analysis of all data generated on all patients for whom the biomarker molecular analysis was performed. Data will include, but will not be limited to, information about side effects, efficacy and patient demographics as well as any biological monitoring performed during the treatment.

5.10. ETHICAL AND REGULATORY REGULATIONS

5.10.1. Rules and regulation

This study will be conducted in accordance with applicable laws and regulations including, but not limited to:

- The US Code of Federal Regulations, Title 21, 50, 54, 56, 201 and 312.
- The French Public Healthcare Law (n° 2004-806) of August 9, 2004, a partial adaptation of the European Directive (2001/20/EC) and Jardé law (n° 2012-300) of March, 5th 2012 on the conduct of clinical trials, modified by the ordinance No. 2016-800 of June 16 2016 and its implemented decree n° 2016-1537 of November 16th 2016.
- The European Directive (2001/20/EC and 2005/28/EC).
- The Informatics and Liberties Law (n° 78-17) of January 6, 1978, modified by Law n° 2004-801 of August 6, 2004, the EU regulation 2016/679 (General Data Protection Regulation – "GDPR") repealing the EU Directive 95/46 CE and the HIPAA 1996 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- Law n° 2002-303 of March 4, 2002 relative to patients' rights and to the quality of the healthcare system.
- Annex 13 of the E. U. Guide to Good Manufacturing Practices (revised and adopted in January 2010 by the European Commission).
- The Good Clinical Practices guidelines (International Conference on Harmonization (ICH E6) and Statistical Principles for Clinical Trials (ICH E9).

5.10.2. Ethic Committee – Competent Authorities

The institutional review board (IRB)/independent ethics committee (IEC) must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-

required procedures are performed, the subject must sign and date the IRB/IEC-approved informed consent form.

This protocol was submitted to the Ethic Committee/IRB/CPP which gave its approval on the ***dd/mmm/yyyy***.
This protocol has also been approved by the Competent Authority on the ***dd/mmm/yyyy***.
The sponsor(s) has taken out a legal liability insurance policy (Nr. ***xxxxxx***).
A final report on the trial will be written at the latest, 1 year after the end of the trial and sent to the competent authority and to the Ethic Committee/IRB/CPP.
The sponsor(s) will maintain records of essential trial documentation in the Sponsor file for a minimum duration of 15 years after the end of the trial.

5.10.3. Withdrawal of consent for continued study participation

Study data are protected by the use of a subject identification number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying in written the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

5.10.4. Data handling and record keeping

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number and age. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Studies records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the informed consent form(s) (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, GDPR 2016/679). Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured in accordance with the specific data retention periods that are described in the clinical study site agreement and based upon local requirements. Study documents must not be destroyed without prior written approval of the sponsor.

6. QUALITY CONTROL AND QUALITY ASSURANCE

Direct Access to Source Documents

The study will be monitored by the sponsor on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, ICFs, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated ICFs, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to subjects, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, may be collected, as available, for all subjects who provide written informed consent. For subjects who provided informed consent and were not entered into the study, the reason the subject was not entered, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), may also be collected.

Study Monitoring

In order to guarantee the authenticity and the credibility of the data in conformity with good clinical practices, the sponsor has installed a quality assurance system which includes:

- Trial management in accordance with the procedures at WIN,
- Quality control of data at the investigating site,
- Possible auditing of investigating centers,

Quality control includes verification that the investigator's file exists and that it is updated, verification of the consent forms, that subjects fulfill eligibility criteria, the validity of evaluation criteria and treatment toxicity with the help of source documents (and others to be specified and adapted according to the study),

Drug accountability will also be checked and the drug accountability forms will need to be validated and signed by the in-house pharmacist before any request for destruction.

Audit and Inspection of the Study

During and after the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a

reasonable manner. Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received

7. STATISTICAL CONSIDERATIONS

The statistical design of the trial has been performed by Prof. J.Jack Lee, University of Texas MD Anderson Cancer Center Adjunct Professor of Statistics, Associate Vice Provost, Adjunct Professor of Biostatistics, Professor of Biostatistics, Biostatistics, Regular Member of the Graduate Faculty.

The proposed study is a proof of concept protocol to evaluate the outcome of patients who receive triple therapy and to evaluate through a retrospective analysis, the clinical utility of the SIMS algorithm and integrated genomic/transcriptomic analysis. For the selected triple combination therapy, we will incorporate a seamless Phase 1/2 design with a limited Phase 1 run-in to determine the recommended Phase 2 dose for the regimen. Patients enrolled in the phase 1 study who receive the RP2D will also be included in the phase 2 efficacy assessment. In the first part of the phase 2 study, up to 100 patients will receive the triple combination therapy and all will have dual biopsies in order to obtain the full set of genomic and transcriptomics data resulting from the investigation of matched tumor and normal biopsies. The population for analysis of response (evaluable patients) will be those that received at least one cycle of treatment. The SIMS algorithm will not be used prospectively to assign patients to treatment. However, it is expected that the SIMS score for each patient will be available within 3 months after the treatment start date. SIMS algorithm will be used retrospectively for defining patient subgroups and correlation correlating with treatment outcome. Patients will be stratified into the fully matched group (Arm A) with all three interventional points activated, or partially matched group, with one or two interventional points activated (Arms B1-B3, C1-C3) or the non-matched group (Arm C4) (see study schema). In addition, after completion of the clinical trial, a correlation study will be performed between patients' clinical outcomes and the predicted match determined by SIMS and all potential prognostic and predictive variables. The primary endpoint for this study is defined as the 6-month objective response rate (by RECIST 1.1 criteria as percent of patients achieve complete response, or partial response). We choose the 6-month response rate for an early efficacy read of the triple therapy. Other efficacy endpoints may include best overall response rate, progression-free survival (PFS), overall survival (OS). The expected result is a better clinical outcome in the fully matched patients arm (arm A) as compared to the partially matched or the non-matched patients' arms.

Also we will compare the estimated numbers of patients in each of the arms as predicted by SIMS versus the observed distribution in the patients treated. Based on previous data published (1), the estimated match in PD-L1 positive (50 patients) is:

- Arm A: Fully matched group, with all three activated targets, will be seen in 10 patients.
- Arms B1 or B2: Partially matched group, with two activated targets (anti PD-L1 + CDK4/6 or anti PD-L1 + anti VEGFR), will be seen in 13 patients and 12 patients respectively.
- Arm B3: Remaining 15 patients will only be matched to anti PD-L1.

For the PD-L1 negative patients (50 Patients), they are further grouped into the following 4 subgroups:

- Arm C1: Partially matched group with two activated targets (CDK4/6 and VEGFR), will be seen in 11 patients.

- Arm C2 or C3: Partially matched group with one activated targets (VEGFR or CDK4/6), will be seen in 8 and 16 patients, respectively.
- Arm C4: Non-matched group, with none of the three activated target matched, will be seen in 15 of patients.

It is expected that half of the patients will be PD-L1 positive and half of the patients will be PD-L1 negative. The hypothesized 6-month response rate in Arm A (fully matched) is 50%; in Arms B1, B2, and C1 (partially matched with two targets) is 40%; in Arm B3 (matched with PD-L1 only) is 30%; in Arms C2 and C3 (partially matched with VEGFR or CDK4/6) is 20%; and in Arm C4 (non-matched group) is 10%. The expected 6-month response rate is 30% in the entire group assuming the triple therapy works.

7.1. SEAMLESS PHASE 1/ 2 TRIALS FOR THE TRIPLE COMBINATION THERAPY

For the triple combination therapy we will conduct a seamless Phase 1/2 trial to establish the safety of the regimen and to identify the recommended Phase II dose. Efficacy and safety will be assessed throughout both Phase 1 and 2. The starting dose for phase 2 will depend on the drugs administered. The target toxicity level is no more than one-third (33%) of patients experiencing dose DLT defined as Grade 3 non-hematological or Grade 4 hematological toxicities under the NCI CTCAE version 4.03.

7.2. PHASE 2 EFFICACY EVALUATION

The Phase 2 study will be conducted in two parts. In the first part of the Phase 2 study, we expect to enroll approximately 120 patients in order to obtain 100 patients eligible for the study treatment. Futility early stopping rule will be implemented to ensure that the treatment has met the minimum efficacy requirements. If not meeting the minimum efficacy requirement, the trial will be stopped early. If the trial is not stopped early after the first 100 patients, the study could be extended, (with an amendment) to the second part of the Phase 2 study in order to reach a total of 200 patients treated.

7.2.1. Statistical analysis of the primary efficacy end point

The primary efficacy evaluation for measuring a clinical meaningful improvement is defined as demonstrating an improvement of the primary efficacy endpoint of 6-month objective response rate from 20% (under the null hypothesis) to 50% (under the alternative hypothesis) in the fully matched arm. With 5% one-sided type I error, we need to treat 20 patients to demonstrate the usefulness of the tri-therapy approach to achieve and 86% power based on the exact binomial test. With an expected 10% of patients who will be fully matched, we need to enroll 200 patients in the study. All inevaluable patients will be replaced. **To ensure that patients will not receive ineffective treatments after sufficient evidence, two efficacy futility early stopping rules** will be implemented.

- The first futility early stopping rule will be applied after treating 14 patients with the tri-therapy at the RP2D level. If none of the 14 patients has 6-month response (CR or PR), the patient enrollment will be halted and the trial can be stopped for futility. This futility early stopping rule coincides with the first stage of the Gehan's design targeting 20% response rate with 95% confidence (26).

- The second futility early stopping rule will be evaluated every 10 patients after 20 patients are treated at the RP2D by applying the predictive probability (27). The trial can be stopped early if we see the following 6-month responses or less: 2 in 20, 3 in 30, 5 in 40, 6 in 50, 7 in 60, 9 in 70, 11 in 80, or 12 in 90 patients. The design has 5% type I error rate and 95% power with a null response rate of 10% and a target response rate of 30% at 6 months in the whole group. The probability of early stopping is 0.95, 0.31, and 0.04 if the response rate in the whole group is 10%, 20%, and 30%, respectively.

- In addition to the futility analysis for early stopping of the trial if the triple therapy does not show minimum efficacy in the whole group, we will also look for efficacy signal in the subgroups. The triple therapy will be considered potentially effective if the posterior probability of response rate greater than 0.3 is larger than 60% in any of the predefined subgroups (Arm A, Arms B1-B3, Arms C1-C3, or any of the combined groups). Assuming a weak prior of Beta (0.1, 0.9), the treatment will be considered potentially efficacious if we see 4 responses in 10 patients, 7 responses in 20 patients, or 10 responses in 30 patients.

- In rare occasions that the early futility stopping criterion is met but the treatment shows potential efficacy in predefined subgroups, further discussions will be conducted among study PIs, sponsors, and regulatory agencies to determine whether study will be terminated or extended in specific subgroups.

These cohort size estimates are based on *in silico* data generated by SIMS using an independent set of data obtained from investigation of tumor and matched normal biopsies from the same patient. SIMS model will be considered clinically meaningful if the observed matches are similar to estimated matches, with a maximal tolerated coefficient of variability of 20%, and if fully matched group shows better outcome than partially matched groups.

7.2.2. Statistical analysis of the secondary efficacy end point and other endpoints

In addition to analyze response rate (RR), and PFS, we will measure other efficacy endpoints including best overall response rate, and overall survival (OS), etc. Kaplan-Meier estimate and Cox proportional hazards model will be applied to analyze time-to-event data such as PFS and OS. Our goal is to achieve OS $\geq$ 60% at 1.5 years for the matched patients.

7.3. SAFETY AND TOXICITY EVALUATIONS

The toxicity profile of each patient and each treatment regimen will be documented using the NCI CTCAE version 4.03. Severe adverse events will be reported to the study IRB and regulatory agencies. To ensure the safety of study patients, we will also implement the Bayesian toxicity

monitoring to alert the study investigators when the probability of unacceptable toxicity (DLT rate ≥ 33%) is higher than 50%. The corresponding toxicity stopping boundaries is to stop the trial if we see DLT in number of patients as follows: at least 4 in 10, 7 in 20, 10 in 30, 14 in 40, 17 in 50, 20 in 60, 24 in 70, 27 in 80, and 30 in 90 patients.

7.4. STATISTICAL ANALYSES OF THE SECONDARY OBJECTIVES

Descriptive statistics will be generated, standard statistical methods will be applied, and exploratory data analysis will be performed to achieve the goals for the secondary objectives. For example, the success rate of biopsy acquisition and the frequency and severity of biopsy related adverse incidence will be recorded and analyzed. The frequency and distribution of genomic/transcriptomic aberrations including DNA mutations/amplifications, RNA gene expression, and microRNA profiling in NSCLC will be estimated and analyzed. In addition, we will fine tune the SIMS algorithm using cumulative data and updated knowledge with the goal of enhance the overall performance of the predictive method. For example, available data both inside and outside the trial will be acquired to correlate genomic scores with treatments and the efficacy outcomes to improve the predictive algorithm. The institution variation will be estimated and efforts will be made to reduce the institution-to-institution variation.

7.5. INTERIM ANALYSIS

As described earlier toxicity and efficacy monitoring will be conducted throughout the first 100 patients. A descriptive interim analysis will be performed for this study after enrollment, treatment, and follow up of the first 50 patients, during which enrollment will continue. The PFS ratio will be estimated in all groups. No hypothesis testing will be performed and no early stopping rules will be implemented. The sample size re-estimation may be carried out should the observed improvements rates be much different from the estimated rates. This analysis will be share with FDA CDER in order to assess whether SIMS will be used prospectively or retrospectively in the second part of the phase 2 (=100) and if applicable there is need for an IDE application.

7.6. FINAL ANALYSIS

It is expected that 130 patients will be enrolled over an 18-month period (phase 1, 6 to 8 months – phase 2, 8-12 months). With an additional 12/24 months of follow up, the total study duration will be 3 to 4 years. Final analysis will be performed after enrollment, treatment, and follow-up of all patients enrolled in the study. Both intent-to-treat and per-treatment analyses will be performed. Due to the nature of the Phase 2 study, no multiplicity adjustment will be made. All study findings will need to be validated by future studies.

8. DATA OWNERSHIP / PUBLICATION POLICIES

The investigator promises, on his/her behalf as well as that of all the persons involved in the conduct of the trial, to guarantee the confidentiality of all the information related to the SPRING trial until the publication of the results of the trial.
All publications, abstracts or presentations including the results of the trial require prior approval of the investigators and sponsor. All oral presentations, manuscripts must include a rubric mentioning the sponsor, the investigators / institutions and all other institutions or companies that participated or contributed to the conduct of the trial and the bodies which funded the research.

9. REFERENCES

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10. APPENDIXES

10.1. APPENDIX 1: The Simplified Interventional Mapping System (SIMS) Paper Reference

A simplified interventional mapping system (SIMS) for the selection of combinations of targeted treatments in non-small cell lung cancer

Lazar, V., Rubin, E., Depil, S., Pawitan, Y., Martini, J., Gomez-Navarro, J., Yver, A., Kan, Z., Dry, J., Kehren, J., Validire, P., Rodon, J., Vielh, P., Ducreux, M., Galbraith, S., Lehnert, M., Onn, A., Berger, R., Pierotti, M., Porgador, A., Pramesh, C., Ye, D., Carvalho, A., Batist, G., Chevalier, T., Morice, P., Besse, B., Vassal, G., Mortlock, A., Hansson, J., Berindan-Neagoe, I., Dann, R., Haspel, J., Irimie A, A., Laderman, S., Nechushtan, H., Al Omari, A., Haywood, T., Bresson, C., Soo, K., Palmer, G., Lacroix, L., Koscielny, S., Eterovic, K., Blay, J., Buller, R., Eggermont, A., Schilsky, R., Mendelsohn, J., Soria, J., Rothenberg, M., Scoazec, J., Hong, W., & Kurzrock, R.

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ABSTRACT

Non-small cell lung cancer (NSCLC) is a leading cause of death worldwide. Targeted monotherapies produce high regression rates, albeit for limited patient subgroups, who inevitably succumb. We present a novel strategy for identifying customized combinations of triplets of targeted agents, utilizing a simplified interventional mapping system (SIMS) that merges knowledge about existent drugs and their impact on the hallmarks of cancer. Based on interrogation of matched lung tumor and normal tissue using targeted genomic sequencing, copy number variation, transcriptomics, and miRNA expression, the activation status of 24 interventional nodes was elucidated. An algorithm was developed to create a scoring system that enables ranking of the activated interventional nodes for each patient. Based on the trends of co-activation at interventional points, combinations of drug triplets were defined in order to overcome resistance. This methodology will inform a prospective trial to be conducted by the WIN consortium, aiming to significantly impact survival in metastatic NSCLC and other malignancies.

10.2. APPENDIX 2: SIMS Explained

Table 1. Summary of the interventional points or nodes (N=24) defined by the genes involved (N = 183) and examples of drugs that can impact these nodes

Interventional points are defined by (genes/group of genes) that, when activated, could be blocked by a customized therapy combination.

Nodes	Components of the inteventional points	Examples of drugs acting on interventional points
HER	EGF, TGFA, AREG, EREG, HBEGF, BTC, NRG1, NRG2, NRG4, EGFR, ,ERBB2 , ERBB3, ERBB4	Afatinib Dacomitinib-(Pan-Her inhibitor)
CDK4, 6	CDK4, CDK6, CCND1, CCND2, CCND3, CDKN2A, CDKN2B, CCNE1, CCNE2, CCNE3, RB1	Palbociclib (CDK4,6 inhibitor)
PLK/ AURK	PLK1, AURKA, BORA, ILK, KIF11	Aurora A kin inhib
Angio genes	VEGFA, VEGFB, VEGFC, VEGFD, VEGFR1, VEGFR2, VEGFR3, PDGFA, PDGFB, PDG-FRA, PDGFRB, Kit	Axitinib Motesanib
Angio poietins	THBS1, TGFB1, ANGPT1, ANGPT2, ANGP-TL1, ANGPT4, TIE1, TEK	-
Immune modulator	PD1L, PDCD1LG2, PDCD1, CTLA4, LAG3	Ipilimumab (CTLA4); Tremelimumab (CTLA4), Nivolumab (PD1); AMP514 (PD1), Pidilizumab (PD-1); MED14736 (PD-L1) PF-05082566 (4-1 BB)
PI3K	PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3C2B, PRKCB, PRKCA, PRKCB, PIK3R1, PIK3R2, PIK3R3	PF-384 (PI3K/mTOR-inhibitor) AZD8186 (PI3Kb) PI3Kalpha inhibitor
MET	HGF, MET, AXL, MST1R	Crizotinib, Cabozantinib, Volitinib (cMet)
MEK	MAP2K1, MAP2K2, MAP2K3, MAP2K4, MAP3K1, MAP3K2, MAP3K3, MAP3K4	Trametanib Selumetinib (MEK)
ERK	MAPK3, MAPK1, KSR1, MAPK11	-
Anti-apoptosis	BCL2, BCLXL, BIRC5, XIAP, BAk, TP53	ABT-199 (BCL-2) MK-1775 (Wee-1 inhibitor; p53)
FGF	FGF1 to FGF18, FGFR1, FGFR2, FGFR3, FGFR4	Lenvatinib , Lucitanib AZD4547 (FGFR1, 2, 3)
mTOR	mTor, AKT1, AKT2, PTEN, TSC1, TSC2, STK11, PIM1, PIM2, PIM3	Everolimus, Temsirolimus PF-384 (PI3K/mTOR inhibitor) AZD2014 (TOR kinase) ; AZD5363 (AKT1, 2 ,3) AZD1208 (PIM1, 2) ; TORC1/TORC2 inhibitor
Ras/Raf	KRAS, NRAS, HRAS, RAF1, BRAF, CRAF	Trametinib,Vemurafenib, Dabrafenib Pan-RAF inhibitor
Telomerase	TERT, TERC, TEP1, HSP90AA1, DKC1, PTGES3	-
IGF	IGF1,IGF2,IGF1R,IGF2R,INSR,IRS1,PKM	Cixitumumab Medi-573 (IGF)
Wnt	CDH1, CTNNA1, CTNNB1, WNT 1, FZD1, WNT5A, B, FZD5, WIF1, DKK1	PRI-274
PARP	PARP1, BRCA1, XRCC1, RAD54L, RAD54B, ATM, ATR, CHEK1, CHEK2, WEE1	Olaparib (PARP) AZD1775 (Wee1) AZD6738 (ATR)
HDAC	HDAC1, HDAC2, HDAC3, HDAC4, HDAC5	Vorinostat
JAK-STAT	JAK1, JAK2, STAT1, STAT2, STAT3, SOCS1	Riluxitinib; AZD9150
Hedgehog	SHH, PTCH1, SMO, STK36, PRKACA, SUFU,	Vismodegib
NOTCH	NOTCH1, Adam17, PSEN1, NCSTN, JAG1, SRRT, APH1A	LY3039478
DNA Repair	ERCC1, RAD52, XRCC4, RAD51, BRCA1, NEDD8, NAE1	NEDD8 activating enzyme inhibitor
Others	RET, ALK, ROS1, UB1	Crizotinib, Ceritinib,Sorafenib, Cabozantinib

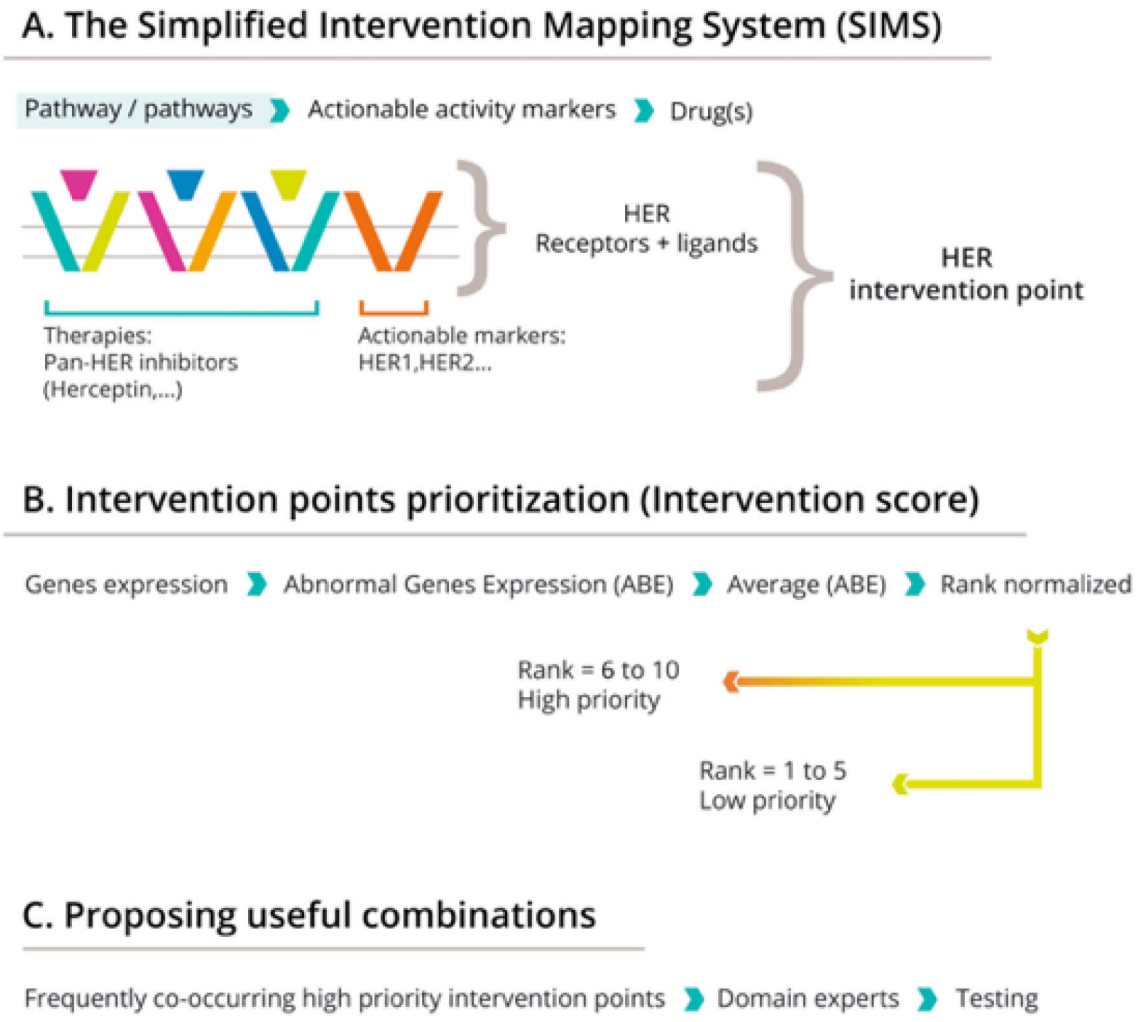


Figure 1. The framework for combinatorial personalized cancer medicine. The SIMS strategy has three steps:

A: Mapping therapeutic efficacy to cellular components and identification of interventional nodes. The example outlines the HER interventional point, constituted by four receptors (EGFR, Her2, Her3 and Her4) and their major ligands (EGF, TGFA, NRG1, NRG2, NRG4 and NRG4). Activation of this node can be induced by receptor mutations or overexpression of receptors and or ligands in tumor as compared with the normal counterpart, and this activation can be efficiently blocked by a panHer inhibitor, such as afatinib; **B**: Scoring the status of specific nodes in the interventional maps defined and predicting combination efficacy. Interventional points scored over 5 (6 to 10) are high priority. **C.** Finding the most frequent co-existing interventional nodes and hence suggesting combinations. Frequently co-occurring, high priority interventional points are determined, and cognate drugs are identified based on literature reviews.

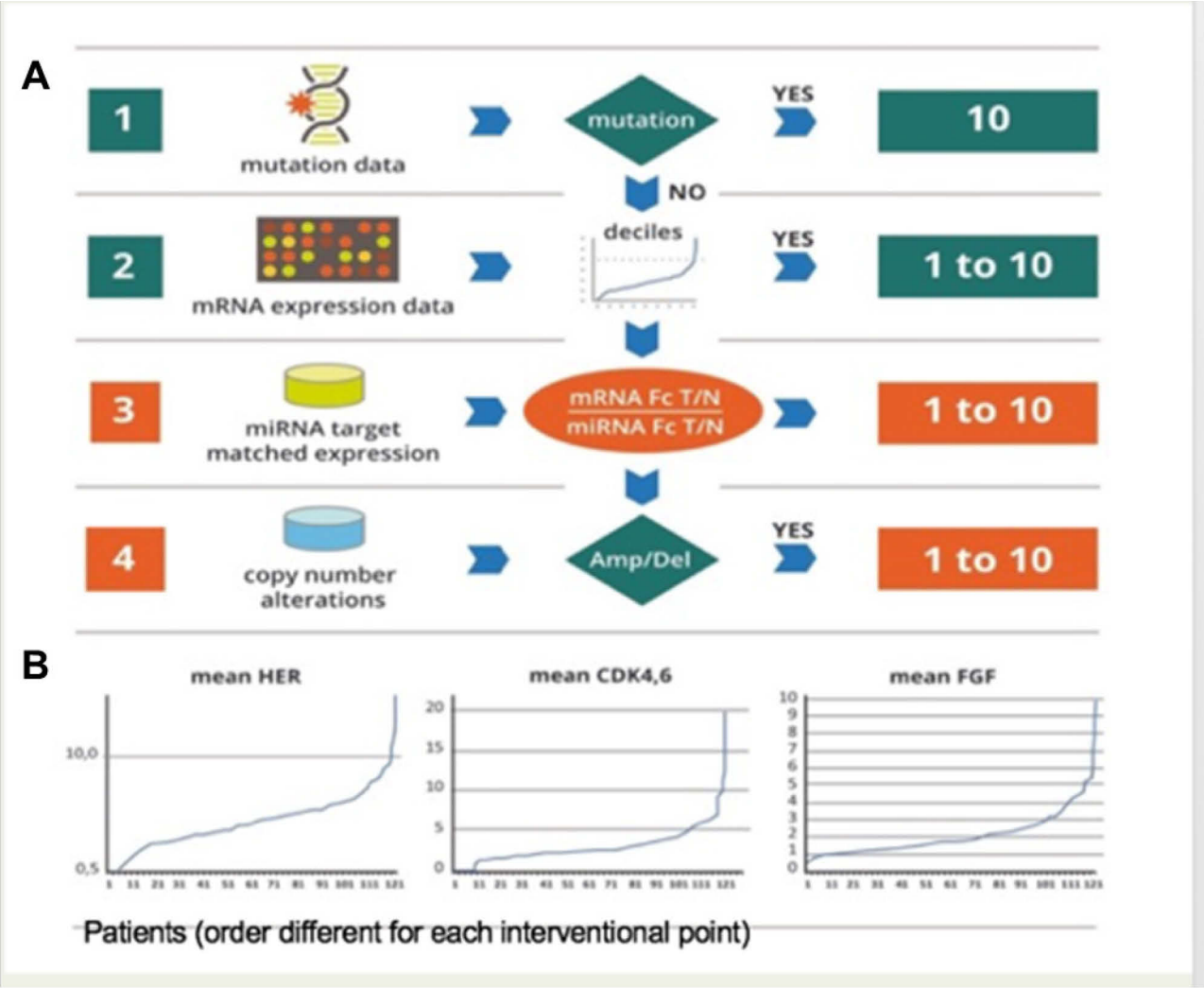


Figure 2: **A:** Flowchart of the scoring system: The principles of the score are the followings: A Score is designed to correlate with the likelihood that an interventional node is abnormally active in the tumor. It ranges from 1 to 10. The score combines evidence from 3 data sources: mutations, meanfold change in gene over expression (mRNA and miRNA) in the tumor versus normal and copy number variation. Different data sources will trigger different weights in the score: i) activating mutations (e.g. *KRAS* in the RAS path) have decisive weight. The maximal score of 10 is given to every node with an activating mutation; ii) in the absence of a mutation, the score is based on weighted sum of the mRNA meanfold changes corrected by an adjustment based on miRNAs and to a lesser extent on CNV abnormalities. **B:** Principle of the calibrator: In Y: Fold change (Fc) of differential gene expression between tumor (T) and normal (N) in each patient. In X: number of patients (NB): for each graph, the order of patients is different. This series serve as a calibrator for calculation of deciles. For every new measurement in each patient, the meanfold change for mRNA is plotted against the calibrator curve, and the deciles partition of the curve enables assignment of a score from 1 to 10. The score obtained based on the mRNA is corrected by miRNA, and is considered in the absence of mutations.

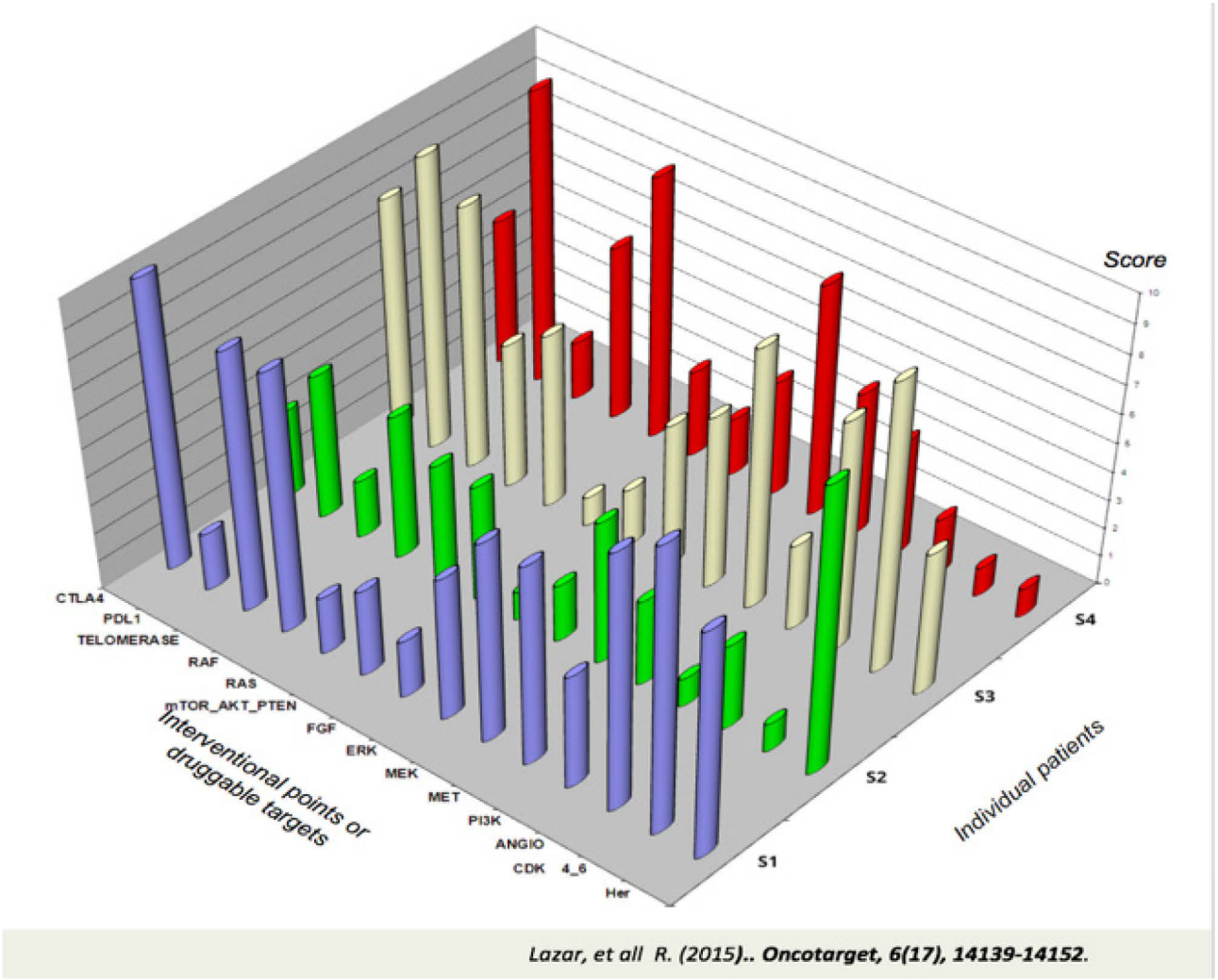


Figure 4. 3D representation of the scoring system. Axis Z shows score from 1 to 10 of each interventional point. Axis X represents examples of interventional points. Axis Y represents each patient. Four subjects are shown to demonstrate the complexity of co-activation of interventional points. Abbreviations used to designate interventional points are described in Table 1. Each patient's tumor shows numerous activations, suggesting multiple possibilities for combinations. S1, S2, S3, and S4 each represent an individual patient.

10.3. APPENDIX 3: Drug Information

- **Bavencio - avelumab:** has been approved in March 2017 for the treatment of metastatic Merkel Cell Carcinoma and in May 2017 for the treatment of locally advanced or metastatic urothelial carcinoma. Avelumab is an immune checkpoint inhibitor, directed against programmed cell death ligand 1 (PD-L1). Signals from PD-L1 help tumors avoid detection by the immune system. Avelumab blocks these signals, countering the tumor's immune-evading tactics. As an anti–PD-L1 antibody, avelumab binds to PD-L1, allowing T-cells to recognize and kill tumor cells. It exhibits no immunogenicity that impacts pharmacokinetics or pharmacodynamics at 10 mg/kg**.** The most common any-grade Adverse events (Aes) in patients receiving all doses of avelumab were fatigue (7%), nausea (5%), vomiting (5%), arthralgia (4%), and rash (4%).

- **Ibrance - palbociclib**: Approved in February 2015 for the treatment of ER positive HER2 negative breast cancers. Palbociclib is an orally available pyridopyrimidine derived cyclin dependent kinase inhibitor. Palbociclib is a very selective dual inhibitor of cyclin-dependent kinase (CDK) 4 and 6. It blocks progression of cells from G1 into S phase. In particular, it shows activity in presence of high levels of Cyclin A. MTD is 125 mg orally daily for 21 consecutive days, followed by 7 days off treatment. If the patient vomits or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Ibrance capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact. **Palbociclib capsules should be taken with food.** Grapefruit or grapefruit juice intake during the whole duration of the treatment should be avoided as it may increase concentration of the drug in blood. Most common adverse reactions (greater than or equal to 10%) is neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse event were pulmonary embolism (4%) and severe diarrhea (2%). Avoid concomitant use of strong and moderate CYP3A inducers.).

- **Inlyta - axitinib**: approved in January 2012 for the treatment of advanced renal carcinoma Inlyta is a kinase inhibitor. It has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. Inlyta is supplied as a tablet for oral administration. The recommended starting dose of Inlyta is 5 mg twice daily. Doses should be administered approximately 12 hours apart with or without food. The tablet should be swallowed whole with a glass of water. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Side effects include: diarrhea, fatigue, decreased appetite, nausea, hypertension, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, constipation.

The Dual combination avelumab + axitinib is currently referenced in two clinical trials:

- **A Study Of Avelumab In Combination With Axitinib In Advanced Renal Cell Cancer (JAVELIN Renal 100).** This is a Phase 1b, open-label, multi-center, multiple-dose trial designed to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 dose (RP2D) of **avelumab** (MSB0010718C) in combination with **axitinib** (**AG-013736**). Once the MTD of **avelumab** administered in combination with **axitinib** is estimated (dose finding portion), the dose expansion phase will be opened to further characterize the combination in term of safety profile, anti-tumor activity, pharmacokinetics, pharmacodynamics and biomarker modulation.
  https://clinicaltrials.gov/ct2/show/NCT02493751?term=avelumab+and+axitinib&rank=2

- **A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer (JAVELIN Renal 101).** This is a phase 3 randomized trial evaluating the anti-tumor activity and safety of **avelumab** in combination with **axitinib** and of sunitinib monotherapy, administered as first-line treatment, in patients with advanced renal cell carcinoma.
  https://clinicaltrials.gov/ct2/show/NCT02684006?term=avelumab+and+axitinib&rank=1

The doses for avelumab in combination with axitinib used in the study JAVELIN Renal A01 are:

Assigned Interventions

Drug: **Avelumab** (MSB0010718C)

IV treatment **Avelumab** administered at 10 mg/kg IV every two weeks

Drug: **Axitinib** (**AG-013736**)

Oral treatment **Axitinib** given 5 mg PO BID

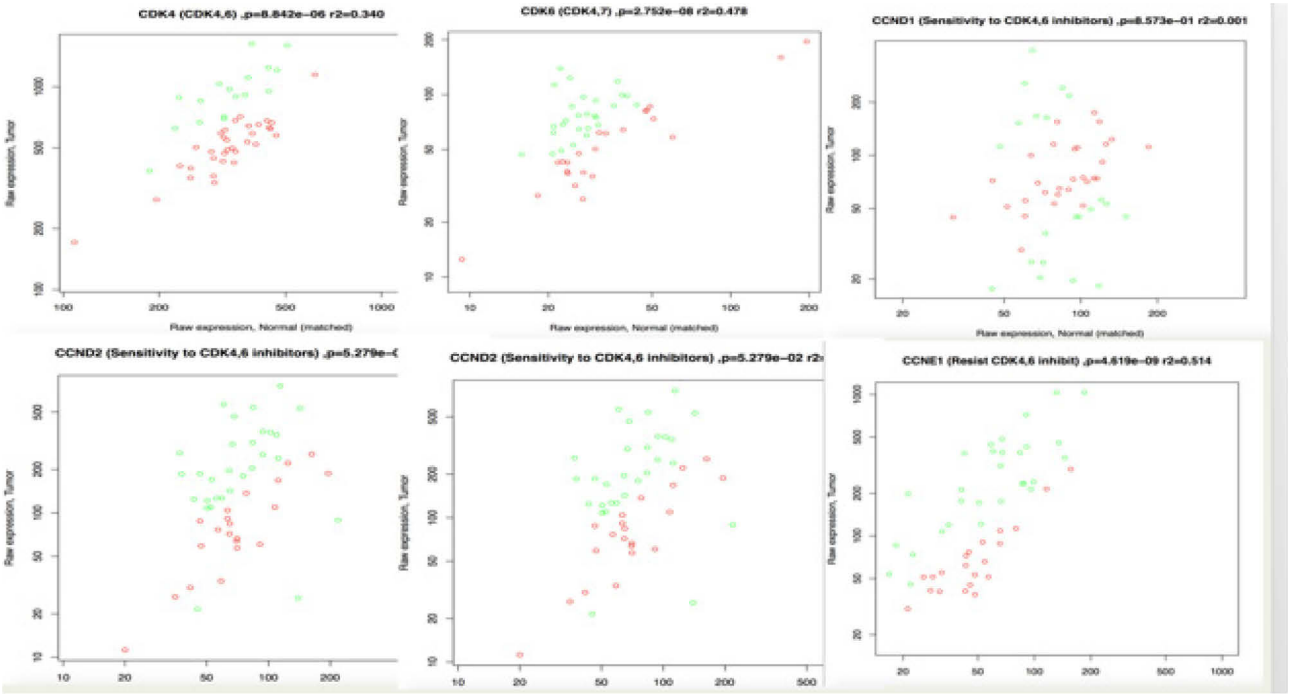
Other Name: **Inlyta**

10.4. APPENDIX 4: Gene Expression Tumor vs. Normal

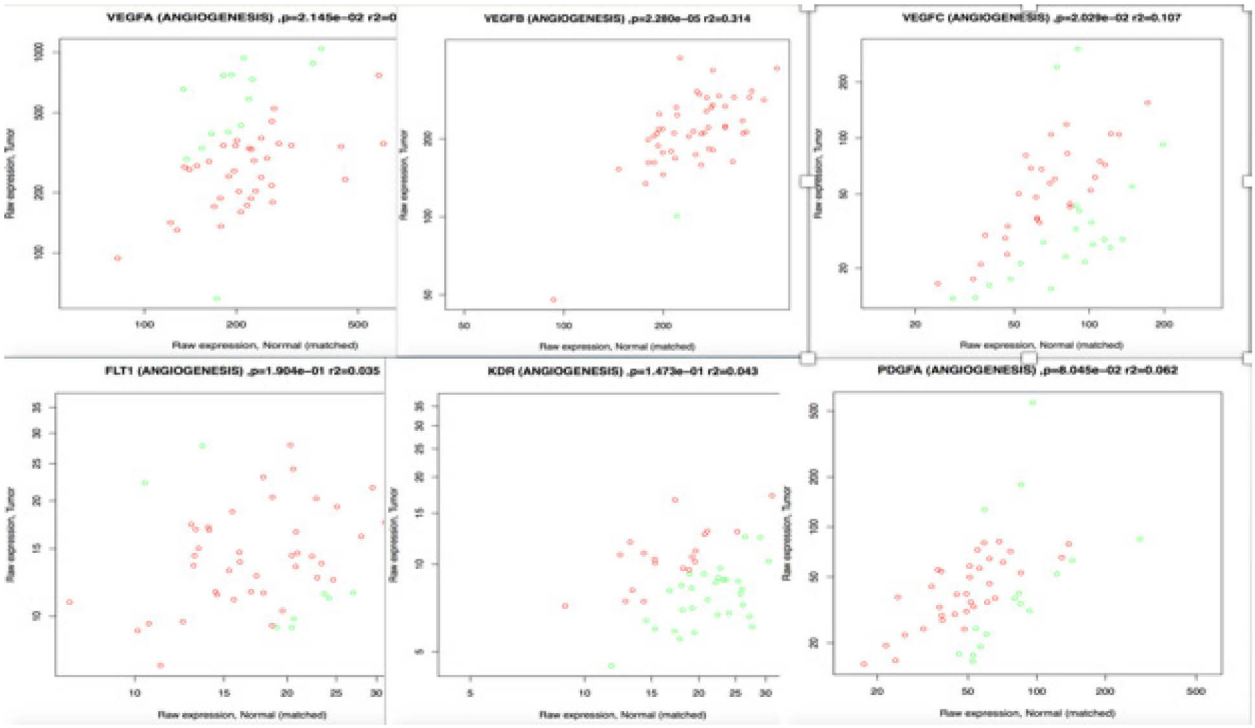
GENE EXPRESSION TUMOR vs. NORMAL SUPPORTING THE CHOICE OF INDIVIDUAL AGENTS

Gene Expression intensities of Tumor tissue (Y axis) and Normal (X axis) tissue for relevant genes targeted by the selected agents were obtained from the retrospective data from Chemores cohort. Red circles represent patients with **no** differential expression T/N (cut off of the Fold change is 2). Green circles represent patients with differential T/N expression. Correlation of intensities demonstrates the necessity of using dual biopsies.

Expression data Tumor vs. Normal supporting the use of palbociclib in NSCLC



Gene Expression data Tumor vs. Normal supporting the use of axitinib in NSCLC and showing that the main contributor to neoangiogenesis is VEGFA



The frequencies of activation of actionable interventional points in three groups of NSCLC patients:

Group 1	NSCLC patients with activated PD1L - 63 out of 121 NSCLC (52%)																
Nb Patients	36	63	35	30	28	27	25	28	28	31	32	23	21	51	27	29	42
% group 1	30	100	56	48	44	43	40	44	44	49	51	37	33	81	43	46	67
Group 2	NSCLC with activated CTLA4 -58 out of 121 NSCLC (48%)																
Nb Patients	58	34	32	28	32	22	33	30	34	37	32	20	25	45	17	32	40
% group 2	100	59	55	48	55	38	57	52	59	64	55	34	43	78	29	55	69
Group3	NSCLC without activated PD1L and activated CTLA4 - 36 out of 121 NSCLC (30%)																
Nb Patients	0	0	8	19	15	17	10	18	17	20	12	14	18	19	10	17	24
% group 3	0	0	22	53	42	47	28	50	47	56	33	39	50	53	28	47	67
Activated Nodes	CTLA4	PD1L	MEK	mTOR	PI3K	ERK	MET	AURKA	CDK 4,6	HER	Angio	FGF	PARP	Ras/ RAF	IGF	DNA REPAIR	mTOR /PI3K

10.5. APPENDIX 5: Clinical Flowchart

	Screening / Baseline	Biopsies	Cycle 1[12]				Cycle 2				Cycle n		Discontinuation (for progression or toxicity, etc.)	Follow-up	
	D-28 to registration		D1	D8	D15	D22	D1	D8	D15	D22	D1	D15		D30 after last treatment administration	D90 after last treatment administration[11]
WRITTEN INFORMED CONSENT	X														
INCLUSION/EXCLUSION CRITERIA VERIFICATION[1]	X														
ASSIGNMENT OF STUDY IDENTIFICATION NUMBER	X														
DEMOGRAPHIC DATA	X														
PREVIOUS MEDICAL HISTORY	X														
CONCOMITANT MEDICATION	X		CONTINUOUS MONITORING												
PHYSICAL EXAMINATION	X		X	X	X	X	X		X		X	X	X	X	X
HEIGHT	X														
WEIGHT	X		X	X	X	X	X		X		X	X	X		
ECOG PERFORMANCE STATUS	X		X	X	X	X	X		X		X	X	X	X	X
VITAL SIGN	X		X	X	X	X	X		X		X	X	X	X	X
ELECTROCARDIOGRAM	X		X				X				X				
BLOOD TEST FOR VIRAL INFECTION (HEPATITIS A, B, AND C)	X														
PREGNANCY TEST[2]	X		X				X				X		X		
THYROID FUNCTION TESTS (FREE T4 AND TSH)[3]	X		X								X		X	X	

Study Assessments	Screening / Baseline	Biopsies	Cycle 1[12]				Cycle 2				Cycle n		Discontinuation (for progression or toxicity, etc.)	Follow-up	
	D-28 to registration		D1	D8	D15	D22	D1	D8	D15	D22	D1	D15		D30 after last treatment administration	D90 after last treatment administration[11]
HEMATOLOGY, CHEMISTRY AND URINE TESTS [4]	X		X	X	X	X	X		X		X	X	X	X	
COAGULATION PROFILE (PROTHROMBIN TIME)	X		X	X	X	X	X		X		X	X	X	X	
RADIOLOGIC TUMOR ASSESSMENT AS PREFERRED BY THE PHYSICIAN - USUALLY CT (BUT COULD BE PET/CT OR MRI OR OTHER IMAGING AS CLINICALLY APPROPRIATE) RECIST 1.1[5]	X										X		X		
TUMOR AND NORMAL BIOPSIES		X													
AVELUMAB ADMINISTRATION[6]			X		X		X		X		X	X			
AXITINIB ADMINISTRATION[7]			X	X	X	X	X	X	X	X	X	X			
PALBOCICLIB ADMINISTRATION[8]			off	X	X	X	off	X	X	X	off	X			
AES/SAES	X		CONTINUOUS MONITORING												
BLOOD SAMPLE COLLECTION FOR TUMOR MARKERS[9]			X	X							X				
PK BLOOD SAMPLE COLLECTION[10]					X				X			X			
MUTATION STATUS (EGFR, ALK) IF NOT ALREADY DOCUMENTED.	X														

[1] Eligibility criteria should be verified between consent and registration (28 days maximum window).
[2]Urine or blood pregnancy test for women of childbearing potential must be performed at baseline and every month during treatment.
[3]Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).
[4]Hematology and Chemistry tests and urinalysis (see section 5.4) should be performed every week +/- 3 days during the first cycle and then every 2 weeks +/- 3 days prior the avelumab infusion.
[5] Baseline scan within 28 days of the start of therapy and follow-up scans about every 8 weeks (+/- 7 days): end of C2, C4, C6, etc.
[6] Avelumab is administered at the study site at D1 (-1/+3 days) and D15 (-1/+3 days) of each cycle. Premedication in order to mitigate infusion-related reactions, with an antihistamine and with paracetamol (acetaminophen) should be given 30 to 60 minutes prior to avelumab infusion for at least the 4 first doses. Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.
[7] Axitinib is taken every day orally at home. Treatment diary should be provided to the patient to record treatment intake and side effects.
[8] Palbociclib is taken orally from day 8 to day 28 every cycle at home. Treatment diary should be provided to the patient to record treatment intake and side effects.
[9] Blood specimens will be collected for each patient enrolled at base line, before starting the treatment, one week after onset of the treatment and about every 8 weeks thereafter.
[10] PK Blood specimens will be collected for each patient at day 15 of each cycle (-1/+3 days according to the 2nd avelumab injection) at the following time +/- 5 minutes: before intake of axitinib and palbociclib, after 0h45, 1h15 and 2h of axitinib and palbociclib intake, 4h after axitinib and palbociclib intake and before avelumab IV, at the end of avelumab infusion, after 1h, 2h, 3h and 5h of avelumab infusion.
[11] The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.
[12] 1 cycle = 28 days

Other minor modifications of scheduled visits or medication administration for medical, personal, or logistical reasons may be done after CMC discussion providing that CMC determines that modifications do not impact patient safety.

10.6. APPENDIX 6: Safety Related Items for Avelumab

1. Safety relevant inclusion and exclusion criteria (see Table 1):

Minimum required safety-related inclusion and exclusion criteria for avelumab are described in Table 1. Additional inclusion and exclusion criteria should be considered based on requirements related to other drugs used in combination treatments, target population or study objectives as well as based on Sponsor (investigator) judgment.

2. Safety assessments

- **Blood chemistry and hematology assessments:** must be performed at baseline, prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up.
- **Urine pregnancy test** for women of childbearing potential must be performed at baseline and at least every month during treatment.
- **Free T4 and TSH** must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).

3. Extended safety follow-up

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.

The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

4. Special Precautions for Administration:

- **Premedication:** In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the avelumab infusion is mandatory for at least the first 4 infusions (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.

- **Setting:** Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

– **Observation period:** Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

5. Toxicity Management (see Table 2, Table 3 and Table 4):

– Adverse Drug Reactions requiring avelumab discontinuation or modification (Table 2)
– Treatment Modification for Symptoms of Infusion-Related Reactions (Table 3)
– Management of immune-mediated adverse reactions (Table 4)

TABLE 1. SAFETY RELATED INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA
1. AGE: Male or female subjects aged ≥ 18 years. **2. PHYSIOLOGIC FUNCTION**: **Hematologic:** Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and hemoglobin ≥ 9 g/dL (may have been transfused) *(Applicable for solid tumors.* **Hepatic:** Total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver). **Renal:** Estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method). **3. PREGNANCY AND CONTRACEPTION:** **Pregnancy test:** Negative serum or urine pregnancy test at screening for women of childbearing potential. **Contraception:** Highly effective contraception for both male and female subjects throughout the study and for at least 60 days after last avelumab treatment administration if the risk of conception exists.
EXCLUSION CRITERIA
1. IMMUNOSUPRESSANTS: "Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)." 2. AUTOIMMUNE DISEASE: "Active autoimmune disease that might deteriorate when receiving an immuno-stimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible." 3. ORGAN TRANSPLANTATION: "Prior organ transplantation including allogenic stem-cell transplantation." 4. INFECTIONS: "Active infection requiring systemic therapy. " 5. HIV/AIDS: "Known history of testing positive for HIV or known acquired immunodeficiency syndrome."

6. HEPATITIS: “Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)”
7. VACCINATION: “Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines “
8. HYPERSENSITIIVTY TO STUDY DRUG: “Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)”
9. CARDIOVASCULAR DISEASE: “Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.”
10. OTHER PERSISTING TOXICITIES: “Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator’s judgment are acceptable.”
11. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

TABLE 2. ADVERSE DRUG REACTIONS REQUIRING AVELUMAB DISCONTINUATION OR MODIFICATION

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability (refer to Appendix 6). Resume avelumab in patients whose adverse reactions recover to Grade 1 or resolved.

Any Grade 4 ADRs require permanent treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management and endocrinopathies controlled with hormone replacement.

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1
- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Recurrent Grade 3 ADRs and Grade 3 infusion-related reaction require permanent discontinuation.

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, it should be treated as a Grade 3 or 4 (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

TABLE 3. TREATMENT MODIFICATION FOR SYMPTOMS OF INFUSION-RELATED REACTIONS

NCI-CTCAE Grade	Treatment Modification for avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the study drug infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

TABLE 4. MANAGEMENT OF IMMUNE-MEDIATED ADVERSE REACTIONS

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE version 4.03 grade) Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4) Grade 3 to 4: treat with high dose corticosteroids Treatment of gastrointestinal, dermatological, pulmonary, hepatic, renal, cardiac, endocrine or other irAEs should follow guidelines set forth in the table below.		
Gastrointestinal irAEs		
Severity of Diarrhea / Colitis	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤1: Resume avelumab therapy. If persists > 5 to 7 days or recur: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisolone IV or equivalent	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement:

Grade 4: life-threatening, perforation	Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisolone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisolone or equivalent Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3)
Pulmonary irAEs		
Grade of Pneumonitis	**Initial Management**	**Follow-up Management**
Grade 1	Consider withholding avelumab therapy	Re-assess at least every 3 weeks If worsens:

Radiographic changes only	Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day prednisolone or equivalent followed by a corticosteroid taper. Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	Permanently discontinue avelumab therapy Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisolone or equivalent followed by a corticosteroid taper Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month. If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2	Withhold avelumab therapy	If returns to Grade ≤ 1:

AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Increase frequency of monitoring to every 3 days	Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisolone or equivalent, followed by a corticosteroid taper Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal irAEs		
Grade of Creatinine Increased	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If resumes to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor Creatinine daily.	If resumes to Grade ≤ 1: Taper steroids over at least 1 month.

	1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephology consult.	
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult. Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled-out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)

Endocrine irAEs		
Endocrine disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression) Continue hormone replacement/ suppression and monitoring of endocrine function as appropriate.

Hypopituitarism / hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.E. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of others hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated. If hypophysitis confirmed: • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI on 1 month. • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add appropriate antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement) In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/ suppression therapy as appropriate.

Other irAES		
Grade of other irAEs	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs of symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation.	If irAE is rled-out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy. If irAE is conforme, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤ 1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAE	Permanently discontinue avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy. 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency.	Permanently discontinue avelumab therapy. Specialty consult.	

Persistent Grade 2 or 3 irAE lasting 12 weeks or longer.		

ACTH = adrenocorticotropic hormone; ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; CK-MB = creatine kinase MB; CT = computed tomography; FSH = follicule-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor 1; irAE = immune-related adverse event; IV=intravenous; LH = luteinizing hormone; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; PRL = prolactin; T4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

10.7. APPENDIX 7: Protocols for PK

Avelumab PK serum and ADA/Nab serum sampling, processing and storage instructions:

PK Avelumab: MSB0010718C
Use Yellow-Gold Top, Plastic, SST, 3.5mL and Cryovial, 2mL, screw cap w/o-ring sterile

1. The entire blood processing to serum and placing the samples in the freezer described below should be completed within 90 minutes of blood collection.
2. Collect a minimum of 3.5mL of whole blood per PK time point into an appropriately labeled yellow-gold top SST tubes.
3. It is important to thoroughly mix the blood with the clotting activation agent by gently inverting the tube for at least five times (do not shake).
4. Place the blood collection tube in the upright position and keep the tube at room temperature for at least 30 mins but no longer than 60 mins (tube standing upright) to allow for clotting the blood to serum.
5. Centrifuge at approximately 1700 x g for 10 min or until serum is clearly separated from the clot. A refrigerated centrifuge is preferred but not essential. If a refrigerated centrifuge is not available, samples may be pre-chilled by refrigerating for 30 minutes prior to centrifuging and/or centrifuged in pre-chilled rotors.
6. Using a separate clean disposable pipette or a tip for each blood collection tube, transfer serum in to the 1 appropriately labeled PK sample storage cryo vials.
7. Store the sample cryo vials at approximately -70°C until shipment. If -70°C is not available, samples may be stored at -20°C. Once frozen, samples should not be allowed to thaw.
8. Ship the serum samples on dry ice to Central Lab using sufficient dry ice to ensure that samples remain frozen for at least 72 hours. It is contemplated that shipment be performed by clinical site in one single batch with all phase 1 patients' samples at a date that will be instructed by the sponsor for the analysis. Performance of the analysis on a single batch will avoid variability between assays done on different batches.

Monitoring of Immunogenicity
ADA: ANTI- MSB0010718C: Nab: NEUTRALIZING ANTI-MSB0010718C

1. The entire blood processing to serum and placing the samples in the freezer described below should be completed within 90 minutes of blood collection.
2. Collect a minimum of 3.5mL of whole blood per ADA/NAB time point into an appropriately labeled yellow-gold top SST tubes.
3. It is important to thoroughly mix the blood with the clotting activation agent by gently inverting the tube for at least five times (do not shake).
4. Place the blood collection tube in the upright position and keep the tube at room temperature for at least 30 mins but no longer than 60 mins (tube standing upright) to allow for clotting the blood to serum.
5. Centrifuge at approximately 1700 x g for 10 min or until serum is clearly separated from the

clot. A refrigerated centrifuge is preferred but not essential. If a refrigerated centrifuge is not available, samples may be pre-chilled by refrigerating for 30 minutes prior to centrifuging and/or centrifuged in pre-chilled rotors.

6. Using a separate clean disposable pipette or a tip for each blood collection tube, transfer serum in to the 2 appropriately labeled ADA/NAB sample storage cryo vials.
7. Store the sample cryo vials at approximately -70°C until shipment. If -70°C is not available, samples may be stored at -20°C. Once frozen, samples should not be allowed to thaw.
8. Ship the serum samples on dry ice to Central Lab using sufficient dry ice to ensure that samples remain frozen for at least 72 hours. It is contemplated that shipment be performed by clinical site in one single batch with all phase 1 patients' samples at a date that will be instructed by the sponsor for the analysis. Performance of the analysis on a single batch will avoid variability between assays done on different batches.

Axitinib PK plasma sampling, processing, and storage instructions:

Special precautions should be taken throughout sample collection, processing, storage, and shipment to minimize exposure to visible light, which will cause rapid degradation of Axitinib.

1. Using a separate tube per timepoint, collect 3 mL blood per PK sampling timepoint into a commercially available 3-mL collection tube containing K3-EDTA anticoagulant. Samples should be processed as soon as possible after collection. Harvested plasma should be frozen preferably within 1 hour of collection.
2. Each filled blood collection tube should be gently inverted at least 8-10 times to thoroughly mix the blood with the anticoagulant.
3. Blood collection tubes should be protected from light (covered completely in aluminum foil or in black protection tubes) and placed at 2°C to 8°C (e.g., ice bath or under refrigerated conditions) during the interval between collection and centrifugation to harvest plasma.
4. Centrifuge blood samples for at least 10 minutes at 1700 x *g* at 4°C or lower. Following centrifugation, the resulting plasma should be transferred to labeled amber cryovials using a different pipette for each timepoint to avoid cross-contamination.
5. Plasma samples should be transferred to an opaque box to protect from light exposure and stored at - 20°C or lower in a **non-defrosting** freezer within 1 hour of collection. If a sample is inadvertently exposed to light (for 5 minutes or more), the sponsor should be notified so that the sample can be flagged for potentially spurious results.
6. Once frozen, plasma samples should not be allowed to thaw, including during shipment.
7. Frozen plasma samples should be shipped with a completed sample inventory form and sufficient dry ice to last for at least 2 to 3 days. Shipping schedule will be determined by the sponsor. It is contemplated that shipment be performed by clinical site in one single batch with all phase 1 patients' samples at a date that will be instructed by the sponsor for the analysis. Performance of the analysis on a single batch will avoid variability between assays done on different batches.

Sample Handling, Processing and Storage Instructions for Palbociclib (PD- 0332991): Pharmacokinetics of Palbociclib

1. Blood samples (3 or 4 mL, depending on the availability of the blood collection tube) to provide a minimum of 1.0 mL of plasma for pharmacokinetic analysis of Palbociclib will be collected into appropriately labeledtubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) per time point.
2. Upon collection of the blood PK samples, keep the samples on wet ice at all times prior to processing to plasma.
3. The blood samples have to be processed to plasma and placed in a freezer at -20°C within 1 hour of collection.
4. To process the blood samples to plasma, centrifuge the blood samples in a refrigerated centrifuge at approximately 4°C at about 1700 x g for approximately 10 minutes.
5. Using a clean separate pipette for each time point, transfer the plasma samples into pre-labeled 4 or 5 mL polypropylene cryovials and store in the freezer at approximately –20°C until shipment. If a -20°C freezer is not available at the site the samples may be stored at - 80°C. Palbociclib is stable at -20°C and - 80°C for 439 days in frozen K_2EDTA plasma.
6. Ship the frozen samples on dry ice to the contract bioanalytical laboratory. It is contemplated that shipment be performed by clinical site in one single batch with all phase 1 patients' samples at a date that will be instructed by the sponsor for the analysis. Performance of the analysis on a single batch will avoid variability between assays done on different batches.

All information added to the labels should be written with an indelible marker; water-based inks will smear during thawing, making the label unreadable rendering the written information useless. Labels should be affixed only to DRY surfaces. Labels should contain, at a minimum, the following information: -Protocol # or Pfizer IIR Tracking #-Investigator Name-Subject ID-Sample Matrix (e.g. plasma) -Analyte (e.g. palbociclib)-Visit (e.g. C1D14)-Nominal Sampling Time (e.g. 1Hr).

10.8. APPENDIX 8: Global View on Toxicity Profiles

GLOBAL VIEW ON TOXICITY PROFILES (specific and overlapping) and SAE reported by Pfizer/Merck to date.

The tables below show the most common and the most serious adverse events known about the 3 drugs. There might be other side effects that researchers do not yet know about. If important new adverse events are found, the study investigator will discuss these with the patient.

The frequency described in the following table must be understood as follow:

1. Any event listed with a frequency of more than 10% are adverse events considered very common, some may be serious (in 100 people receiving at least one of the drug, more than 10 and up to 100 may have the corresponding side effect)
2. Any event listed with a frequency comprised between 1% and 10% are adverse events considered common, some may be serious (in 100 people receiving at least one of the drug, from 1 to 10 or less may have the corresponding side effect)
3. Any event listed with a frequency comprised below 1% are adverse events considered uncommon, some may be serious (in 1000 people receiving at least one of the drug, from 1 to 10 or less may have the corresponding side effect)

The table indicates also if the adverse events listed is specific to one drug or common to 2 or all.

Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity	Frequency
Infusion-related reaction	X	-	-	Specific	More than 10%
Dysphonia (hoarse voice)	-	X	-	Specific	More than 10%
Hypertension	-	X	-	Specific	More than 10%
Haemorrhage	-	X	-	Specific	More than 10%
Palmar-plantar erythrodysaesthesia syndrome (Hand and Foot Syndrome)	-	X	-	Specific	More than 10%
Proteinuria	-	X		Specific	More than 10%
Infection	-	-	X	Specific	More than 10%
Insomnia	-	-	X	Specific	More than 10%
Malaise	-	-	X	Specific	More than 10%
Ascites	X	-	-	Specific	1% to 10%
Autoimmune disorder	X	-	-	Specific	1% to 10%
Hypoxia	X	-	-	Specific	1% to 10%
Lymphocyte count decrease	X	-	-	Specific	1% to 10%
Pleural effusion	X	-	-	Specific	1% to 10%
Pneumonia, Pneumonitis	X	-	-	Specific	1% to 10%
Respiratory failure	X	-	-	Specific	1% to 10%
Pruritus	X	-	-	Specific	1% to 10%
Rash maculo-papular	X	-	-	Specific	1% to 10%
Sepsis	X	-	-	Specific	1% to 10%
Small intestinal obstruction	X	-	-	Specific	1% to 10%
Cardiac failure events	-	X	-	Specific	1% to 10%
Dehydration	-	X	-	Specific	1% to 10%
Erythema	-	X	-	Specific	1% to 10%

Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity	Frequency
Gastrointestinal perforation and fistula	-	X	-	Specific	1% to 10%
Glossodynia (burning mouth sensation)	-	X	-	Specific	1% to 10%
Haemorrhoids	-	X	-	Specific	1% to 10%
Hyperbilirubinemia	-	X	-	Specific	1% to 10%
Hypercalcaemia		X	-	Specific	1% to 10%
Polycythaemia	-	X	-	Specific	1% to 10%
Potassium and sodium increase	-	X	-	Specific	1% to 10%
Renal failure	-	X	-	Specific	1% to 10%
Tinnitus	-	X	-	Specific	1% to 10%
Venous embolic and thrombotic events and arterial embolic and thrombotic events	-	X	-	Specific	1% to 10%
Abdominal distension and discomfort	-	-	X	Specific	1% to 10%
Blurred vision, Lacrimation increase, Eye dryness	-	-	X	Specific	1% to 10%
Dry mouth	-	-	X	Specific	1% to 10%
Epistaxis (nose bleeding)	-	-	X	Specific	1% to 10%
Febrile neutropenia	-	-	X	Specific	1% to 10%
Hypoaesthesia (reduced sense of touch or sensation)	-	-	X	Specific	1% to 10%
Hypotension	-	-	X	Specific	1% to 10%
Muscle spasms	-	-	X	Specific	1% to 10%
Muscular weakness	-	-	X	Specific	1% to 10%
Night sweats	-	-	X	Specific	1% to 10%
Pain and flank pain	-	-	X	Specific	1% to 10%
Palpitations	-	-	X	Specific	1% to 10%
Rhinorrhoea	-	-	X	Specific	1% to 10%
Adrenocortical insufficiency acute	X	-	-	Specific	0.1% to 0.99%
Acute hepatic failure, hepatic failure, hepatitis	X	-	-	Specific	0.1% to 0.99%
Anaphylactic reaction	X	-	-	Specific	0.1% to 0.99%
Autoimmune hepatitis	X	-	-	Specific	0.1% to 0.99%
Autoimmune hypothyroidism	X	-	-	Specific	0.1% to 0.99%
Blood creatinine phosphokinase increased	X	-	-	Specific	0.1% to 0.99%
Colitis (inflammation of the colon), autoimmune colitis and enterocolitis	X	-	-	Specific	0.1% to 0.99%
Dermatitis exfoliative	X	-	-	Specific	0.1% to 0.99%
Diabetes mellitus, type I diabetes mellitus	X	-	-	Specific	0.1% to 0.99%
Drug hypersensitivity, hypersensitivity and type I hypersensitivity	X	-	-	Specific	0.1% to 0.99%
Erythema multiforme	X	-	-	Specific	0.1% to 0.99%
Guillian-Barré syndrome	X	-	-	Specific	0.1% to 0.99%
Hypopituitarism	X	-	-	Specific	0.1% to 0.99%

Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity	Frequency
Myositis (muscle inflammation)	X	-	-	Specific	0.1% to 0.99%
Pemphigoid	X	-	-	Specific	0.1% to 0.99%
Pruritus generalised	X	-	-	Specific	0.1% to 0.99%
Rash generalised, pruritic, erythematous, macular and popular	X	-	-	Specific	0.1% to 0.99%
Thyroiditis and autoimmune thyroiditis	X	-	-	Specific	0.1% to 0.99%
Tubulointerstitial nephritis	X	-	-	Specific	0.1% to 0.99%
Transaminase increased	X	-	-	Specific	0.1% to 0.99%
Uveitis	X	-	-	Specific	0.1% to 0.99%
Posterior reversible encephalopathy syndrome	-	X	-	Specific	0.1% to 0.99%
Dry skin	-	X	X	Common to 2	More than 10%
Dyspepsia (indigestion)	-	X	X	Common to 2	More than 10%
Stomatitis (inflammation of the mouth)	-	X	X	Common to 2	More than 10%
Pyrexia (fever)	X	-	X	Common to 2	More than 10% for Avelumab, 1% to 10% for Palbociclib
Back pain	X	-	X	Common to 2	More than 10% for Avelumab, 1% to 10% for Palbociclib
Oedema peripheral	X	-	X	Common to 2	More than 10% for Avelumab, 1% to 10% for Palbociclib
Dysgeusia (change of sense of taste)	-	X	X	Common to 2	More than 10% for Axitinib, 1% to 10% for Palbociclib
Mucosal inflammation		X	X	Common to 2	More than 10% for Axitinib, 1% to 10% for Palbociclib
Pain in extremity	-	X	X	Common to 2	More than 10% for Axitinib, 1% to 10% for Palbociclib
Chills	X	-	X	Common to 2	1% to 10% for Palbociclib and Avelumab
Blood creatinine increased	-	X	X	Common to 2	1% to 10% for Axitinib, more than 10% for Palbocyclib
Hypothyroidism	X	X	-	Common to 2	1% to 10% for Avelumab, more than 10% for Axitinib
Neutropenia	-	X	X	Common to 2	0.1% to 0.99% for Axitinib, more than 10% for Palbocyclib
Alanine aminotransferase increased	X	X	-	Common to 2	0.1% to 0.99% for avelumab, 1% to 10% for axitinib
Hyperthyroidism	X	X	-	Common to 2	1% to 10% for axitinib, 0.1% to 0.99% for avelumab
Hypokalaemia	X	X	-	Common to 2	1% to 10%

Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity	Frequency
Lipase and amylase increased	X	X	-	Common to 2	1% to 10%
Alopecia (hair loss)	-	X	X	Common to 2	1% to 10%
Dizziness	-	X	X	Common to 2	1% to 10%
Flatulence	-	X	X	Common to 2	1% to 10%
Oropharyngeal pain	-	X	X	Common to 2	1% to 10%
Constipation	X	X	X	Common to 3	More than 10%
Diarrhoea	X	X	X	Common to 3	More than 10%
Decreased appetite	X	X	X	Common to 3	More than 10%
Fatigue	X	X	X	Common to 3	More than 10%
Nausea	X	X	X	Common to 3	More than 10%
Vomiting	X	X	X	Common to 3	More than 10%
Weight decreased	X	X	X	Common to 3	More than 10% for Avelumab, 1% to 10% for Axitinib and Palbociclib
Anaemia	X	X	X	Common to 3	More than 10% for Avelumab and Palbociclib, 1% to 10% for Axitinib
Abdominal pain	X	X	X	Common to 3	More than 10% for Avelumab and Axitinib, 1% to 10% for Palbociclib
Cough	X	X	X	Common to 3	More than 10% for Avelumab and Axitinib, 1% to 10% for Palbociclib
Dyspnoea (shortness of breath)	X	X	X	Common to 3	More than 10% for Avelumab and Axitinib, 1% to 10% for Palbociclib
Arthralgia (join pain)	X	X	X	Common to 3	More than 10% for Axitinib and for Avelumab, 1% to 10% for Palbociclib,
Headache	X	X	X	Common to 3	1% to 10% for Avelumab and Palbociclib, more than 10% for Axitinib
Rash	X	X	X	Common to 3	1% to 10% for Avelumab and Palbociclib, more than 10% for Axitinib
Weakness	X	X	X	Common to 3	1% to 10% for Avelumab and Palbociclib, more than 10% for Axitinib
Aspartate aminotransferase increased	X	X	X	Common to 3	0.1% to 0.99% Avelumab, 1% to 10% for Axitinib, more than 10% for Palbociclib

Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity	Frequency
Blood alkaline phosphatase increased	X	X	X	Common to 3	1% to 10% for Avelumab and Axitinib, more than 10% for Palbociclib
Itching	X	X	X	Common to 3	1% to 10%
Myalgia (muscle pain)	X	X	X	Common to 3	1% to 10%

The following table lists serious adverse events (SAE) that may require hospitalization or may be irreversible, long-term, or life-threatening. This list contains also fatal events related to single drug treatment axitinib (total of 27 to date), palbociclib (total of 7 to date), avelumab (total of 5 to date).

Adverse events and Serious adverse events are reported from trials with the drug administered as a single drug for all types of cancer and all origins, for treatment-related only (not all-causality) and all clinical phases.

Serious Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity
Acute liver failure, hepatitis and autoimmune hepatitis	X	-	-	Specific
Adrenal insufficiency	X	-	-	Specific
Anaemia	X	-	-	Specific
Anaphylactic reaction	X	-	-	Specific
Arthralgia	X	-	-	Specific
Ascites	X	-	-	Specific
Aspartate aminotransferase (AST) increased	X	-	-	Specific
Blood creatinine phosphokinase increased	X	-	-	Specific
Colitis (inflammation of the colon)	X	-	-	Specific
Constipation	X	-	-	Specific
Cougth	X	-	-	Specific
Diabetes mellitus and Type 1 diabetes mellitus	X	-	-	Specific
Dyspnea	X	-	-	Specific
Edema peripheral	X	-	-	Specific
Guillian-Barré syndrome	X	-	-	Specific
hyponatramia	X	-	-	Specific
Hypothyroidism / hyperthyroidism / Thyroiditis	X	-	-	Specific
Infusion-related reaction	X	-	-	Specific
Myositis (muscle inflammation)	X	-	-	Specific
Non-cardiac chest pain	X	-	-	Specific
Pleural effusion	X	-	-	Specific
Rash generalised	X	-	-	Specific
Respiratory distress	X	-	-	Specific
Small intestinal obstruction	X	-	-	Specific
Transaminase increased	X	-	-	Specific
Tubulointerstitial nephritis	X	-	-	Specific
Type I hypersensitivity	X	-	-	Specific

Serious Adverse Events	Avelumab	Axitinib	Palbociclib	Specificity
Weight decrease	X	-	-	Specific
Aorto-duodenal fistula	-	X	-	Specific
Arterial embolic and thrombotic events	-	X	-	Specific
Cerebrovascular accident	-	X	-	Specific
Circulatory collapse	-	X	-	Specific
General health degradation	-	X	-	Specific
Haemorrhage	-	X	-	Specific
Hepatic cancer	-	X	-	Specific
Hyperosmolar hyperglycaemic state	-	X	-	Specific
Hypertension	-	X	-	Specific
Metastatic renal cell carcinoma	-	X	-	Specific
Myocardial infarction	-	X	-	Specific
Pulmonary embolism	-	X	-	Specific
Venous embolic and thrombotic events	-	X	-	Specific
Weakness	-	X	-	Specific
Alveolitis allergic	-	-	X	Specific
Lung infection	-	-	X	Specific
Abdominal pain	X	X	-	Common to 2
Back pain	X	X	-	Common to 2
Decrease appetite	X	X	-	Common to 2
Dehydration	-	X	X	Common to 2
Dyspnoea (shortness of breath)	X	X	-	Common to 2
Fatigue	X	X	-	Common to 2
Haemoptysis (coughing up blood)	-	X	X	Common to 2
Hepatic failure	X	X	-	Common to 2
Intestinal perforation	-	X	X	Common to 2
Nausea	X	X	-	Common to 2
Pneumonia / Pneumonitis	X	-	X	Common to 2
Pyrexia (Fever)	X	X	-	Common to 2
Respiratory failure	X	-	X	Common to 2
Sepsis (general infection)	X	X	-	Common to 2
Syncope	-	X	X	Common to 2
Vomiting	X	X	-	Common to 2
Cardiac arrest	X	X	X	Common to 3
Diarrhoea	X	X	X	Common to 3

10.9. APPENDIX 9: Modulators of CYP3A4

Relevant strong inhibitors and inducers of CYP3A4 list.

Strong CYP3A4 inhibitors or inducers are prohibited while on this protocol per Important Note (5). Moderate CYP3A4 inhibitors or inducers should be used with caution.

***Note:** This list is not exhaustive. It is expected that the patient's medications' list is reviewed by pharmacy to determine each medication potential effect on the CYP3A4 metabolism system. Medications that are used in disease states that are excluded by the SPRING protocol were specifically excluded from this list (HIV, hepatitis, etc.).

Modulators of CYP3A4	
Strong Inhibitors	**Strong Inducers**
Clarithromycin	Carbamazepine
Itraconazole	Fosphenytoin
Ketoconazole	Phenobarbital
Mifepristone	Phenytoin
Nefazodone	Primidone
Posaconazole	Rifampin
Suboxone	St John's wort
Telaprevir	
Telithromycin	
Voriconazole	

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