A phase I-II randomized trial of a combination of Nintedanib/placebo in combination with induction chemotherapy for patients with refractory or first relapse acute myeloid leukemia

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Protocol Version	Protocol Date
Nintedanib AML version 7	05.21.2019

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1.1 Trial summary

Title	A phase I-II trial of a combination of Nintedanib, an oral VEGF inhibitor, in combination with induction chemotherapy for patients with refractory or first relapse acute myeloid leukemia
Indication	Treatment of patients with relapsed/refractory AML as defined by the WHO
Design	Phase I- randomized II study
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Products	**Nintedanib/ placebo, idarubicin, cytarabine**
Summary of Rationale	Nintedanib is an oral VEGF inhibitor with a good tolerance profile. There is evidence of a potential clinical impact of VEGF inhibition in AML and some in vitro evidence of activity of Nintedanib against AML blasts. Given that outcome of relapse/refractory AML patient is poor and that no standard option is available for this group of patients, we anticipate that a combination of nintedanib+ induction chemotherapy may be an effective strategy for this group of patients.
Treatment plan	**Phase** I: Patients who meet eligibility criteria and sign informed consent will receive the following during an inpatient hospital stay; Idarubicin 12mg/m2/d IV Push over 10-15 minutes days 1 to 3, cytarabine 0.667g/m2/d (24 hr.) IV infusion day 1 to 3 and Nintedanib 200mg BID PO day 8-28. There will be no drug administered on days 4-7. Length of inpatient hospital stay is based on local site SOP. **Phase II:** Patients who meet eligibility criteria and sign informed consent will receive the following during an inpatient hospital stay; Idarubicin 12mg/m2/d IV Push over 10-15 minutes days 1 to 3, cytarabine 0.667g/m2/d (24 hr.) IV infusion day 1 to 3 and Nintedanib 200mg BID PO on day 8-28 OR placebo. There will be no drug administered on days 4-7. Length of inpatient hospital stay is based on local site SOP. For both Phase I and II, a maximum of 2 induction and 2 consolidation cycles may be given, cycles are 28 days. During Phase II, all Patients failing to achieve response based on IWG 2003 AML response criteria after cycle 1 will be unblinded, and all those who had been receiving placebo will be offered Nintedanib+ chemotherapy (cross over) for cycle 2. Patients in the Nintedanib arm can be given a second cycle of Nintedanib. Nintedanib maintenance treatment will be given to responding pts not eligible for Hematopoietic stem cell transplantation (HCT) for up to two years or until disease progression. Patients eligible for HSCT will be taken off study prior to HSCT.

Primary objective	Phase I: To determine the safety and tolerability of a combination of Nintedanib + induction chemotherapy. Phase II: To determine the efficacy (rate of CR/CRp/CRi) of Nintedanib+ induction chemotherapy vs. Placebo+ induction chemotherapy
Secondary objectives	• Overall response rate according to IWG AML 2003 criteria • Toxicity profile and safety of the combination • Percentage of patients bridging to transplantation • Overall survival, leukemia free survival including analysis with censoring at HSCT • Rates of haematological improvement according to IWG MDS 2006 criteria • Correlative studies
Inclusion criteria	Patient must meet all of the following inclusion criteria to be eligible for the study 1/ Patient aged 18y or older 2/ Diagnosis of AML according to WHO 2008 criteria. Therapy related to AML may be included if off treatment for their prior malignancy for more than 2 years and in complete remission. AML arising after documented Myeloproliferative Disorder (MPD) is excluded. 3/ Patient must meet <u>one</u> of the following 2 criteria: • Patient refractory (not responsive) to one or two standard induction regimens • Patients with a first untreated relapse within 2 years of documentation of complete remission. Patients relapsing after allogeneic stem cell transplantation are eligible if more than 6 months after transplantation and without signs of active Graft vs Host Disease (GVHD). 4/ Patient may have been pre treated with intermediate to high dose cytarabine (More than 1000mg/m2/d over 5d) if the day of the last infusion was at least 90 days before inclusion in the study. 5/ ECOG performance status of 2 or less 6/ Patient is willing to participate to the study, has the ability to adhere to the study visit schedule and other protocol procedures, and has the ability to understand and signs an informed consent form. 7/ Women of childbearing potential must agree to use effective contraception without interruption through the study and for 3 months after the end of treatment; 8/ Men must agree to not conceive during the treatment and to use effective contraception during the treatment period (including periods of dose reduction or temporary suspension) and for 3 months after the of treatment if their partner is of childbearing potential.

Exclusion criteria	Any of the following criteria excludes the patient from participating to the study. 1/ Patient with documented acute promyelocytic leukemia and/or PML-RAR transcript. 2/ Patient relapsing more than 2 years after initial remission. 3/ Use of any active treatment for relapse/refractory AML including but not restricted to chemotherapy, targeted agents, hypomethylating agents or investigational drugs. Use of hydroxyurea up to 6g per day for cytoreduction is allowed for a maximum of 30 days prior treatment. 4/ Patients with clinical evidence of active Central Nervous System (CNS) disease at enrollment 5/ LVEF below 45% or lifetime exposure to anthracyclines over 350mg/m2 of daunorubicin equivalent 6/ Liver function tests: AST ALT above 2.5 ULN, total bilirubin above 2.5 ULN in the absence of Hemolysis or diagnosis of Gilbert's syndrome 7/ Serum creatinine above 2.0mg/dl 8/ Any sign of active uncontrolled disease including but not restricted to cardiac disease, infections, hepatitis. Any severe chronic disease potentially interfering with the protocol including HIV infection, active hepatitis B or C. It includes major injuries and/or surgery within the past 4 weeks prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period. 9/ Documented platelet refractoriness 10/ Patient has a history of GI surgical procedures, non-surgical procedures or conditions that might interfere with t absorption or swallowing of the study drugs. 11/ Women who are or pregnant, or who are currently breastfeeding 12/ Prior treatment with nintedanib or any other VEGFR inhibitor. With the exception for treatment of prior malignancies with a VEGFR inhibitor. 13/ Known hypersensitivity to nintedanib, any other trial drug, or their excipients 14/ Persistence of any clinically relevant (CTCAE grade 2 or above) non -haematological toxicities from previous AML therapy 15/ Active alcohol or drug abuse 16/ Any other condition that, according to the investigator, may forbid the administration of the idarubicin+cytarabine regimen 17/ Therapeutic anticoagulation with INR modifying drug or use of antiplatelet therapy (with the exception of low dose aspirin<325mg/d) 18/ Any malignancies requiring active treatment within the past year other than basal cell skin cancer or carcinoma in si of the cervix. Patients actively treated with hormone therapy for prostate cancer or breast cancer are eligible.

Planned of duration of the study	2 years of accrual, 2 years of follow-up
Number of patients	22 to 60 patients according to the evaluation (see below statistical methods)
Safety Analysis	An independent safety review committee (SRC) assembled by the PI and comprised of one Investigator from both Yale, and Vanderbilt, two external AML experts and a statistician will meet, when required by the sponsor of the trial, and at least once after the inclusion of the first 6 patients, to analyze tolerance and adverse events and decide on any action to be taken.
Statistical methods	Phase I will use a classical 6+6 design. A n-1 dose level is schedule if DLTs are observed at initial dose level Phase II will use an adaptive randomized design. A minimum of 8 patients will be included in each arm and continuous reassessment method will be used after each patient to evaluate futility or success of each specific arm of treatment.
Patient follow-up	Phase I patients will be followed up to 60 days after the last study drug administration in order to determine if any DLTs are attributable to Nintedanib. Patients will then be followed every 3 months +/- 7 days for 24 months or until the patient begins receiving subsequent anti-cancer therapy or death, whichever comes first. Phase II patients will be followed every 3 months +/- 7 days 24 months or until the patient begins receiving subsequent anti-cancer therapy or death, whichever comes first.

1.2 Rational

1.2.1 Outcome of Acute Myeloid Leukemias after failure of frontline treatment

Acute Myeloid Leukemia (AML) is an aggressive malignant disorder of the bone marrow, characterized by the accumulation of immature white cell precursors in the marrow and blood, ultimately resulting in bone marrow failure with infections and bleeding. Treatment with standard induction including an anthracycline and cytarabine results in complete response rate of 35% to 55% in patients with newly diagnosed AML 60 years old and older[1] and 50% to 90% in younger patients. Despite the high rate of CR, most patients will eventually relapse.

In first relapse, there is no single approach considered standard and treatment is selected based on the age of the patient and the duration of first CR. In patients 60 years old or older, intermediate dose cytarabine alone or in association with another cytotoxic agent (idarubicin, daunorubicin, mitoxantrone or etoposide) is commonly used. Despite substantial variability, the second CR rate generally exceeds 30%[2,3]. However the median overall survival is ≤ 6 months. The prognosis of relapsed AML remains poor, especially in elderly patients. Several investigational agents such as cloretazine, clofarabine, vosaroxin, and elacytarabine have been tested prospectively tested in randomized trial in the settings of patients with AML experiencing early relapse or refractoriness to induction. To date, none of them demonstrated a clear benefit on overall survival and there is no registered drug approved for this indication. Thus there is a strong unmet medical need for this situation

1.2.2 Rational for targeting VEGF/VEGF-R pathway in AML

While multiple cytokines promote AML proliferation and survival, vascular endothelial growth factor (VEGF) likely plays an important role as a paracrine and/or autocrine mediator. Greater than 85% of bone marrow biopsies from patients with AML express VEGF significantly higher than normal bone marrows [reviewed in (Kampen, Ter Elst et al. 2013[4]]. VEGF receptors are also commonly expressed on leukemic blasts from patients with AML[4]. In particular, VEGFR-2 protein levels are consistently higher than in normal bone marrow[5,6]. VEGF isoforms can be detected in the cytoplasm of AML blasts and can be secreted[7,8].

Elevated plasma concentrations of VEGF-A have been associated with lower complete remission

rates and inferior survival in AML patients[9-11]. High VEGF-C expression has been associated with inferior ex vivo sensitivity to cytotoxic chemotherapy in AML blasts[12]. VEGF-C plasma concentrations have been demonstrated to have negative prognostic significance in pediatric and adult AML[13].

Both VEGF-A and VEGF-C stimulate AML blast proliferation and survival in vitro[10,14,15]. VEGF signaling in AML leads to activation of Bcl-2, HSP, MAPK and PI3K[15]. AML bone marrow biopsies often demonstrate increased micro-vessel density compared to normal bone marrow and AML in remission[16-18]. VEGF stimulates osteoblasts and osteoclasts and may lead to remodeling of the stem cell niche[19-21]; to what extent this impacts leukemia stem cells (LSC) is not clear.

VEGF antagonists have demonstrated little clinical activity as monotherapy in relapsed or refractory AML[16,22,23] or MDS[24-26]. However, VEGF antagonists may contribute significantly to outcomes in combination with cytotoxic drugs[27-30]. In timed sequential chemotherapy, AML patients receive a planned second exposure to chemotherapy shortly after their first exposure at a time point planned to coincide with the peak of cytokine-stimulated regrowth of residual leukemia cells. This approach led to superior leukemia-free survival in a pediatric population[31] as well as in an adult population[32] (French). However, timed sequential therapy has led to longer aplasia duration than a single cycle of "seven plus three" (cytarabine plus anthracycline) and has not been widely adopted. Building on this model, Karp and colleagues[30] studied a three day infusion of cytarabine in combination with mitoxantrone in patients with relapsed and refractory AML. Historical experience with this combination indicated that remissions were not likely with these drugs alone.

The VEGF inhibitor bevacizumab was administered on day 8, in lieu of the second drug exposure in the timed sequence (Figure 1):

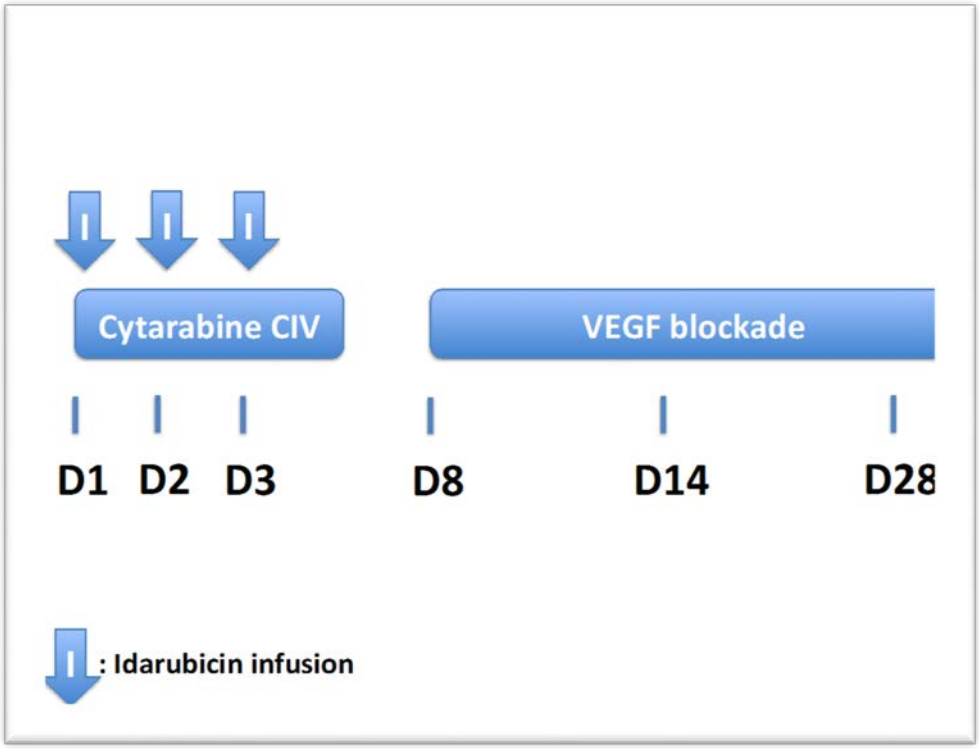

Figure 1. VEGF inhibition in a timed sequential chemotherapy model of AML9 (Attached)

Of 49 patients treated, 15 had primarily refractory disease, 12 were refractory to at least two induction regimens, or to reinduction after first relapse; 18 were in first relapse. Toxicities were as expected with intensive reinduction therapy; additional AEs attributed to the known toxicity profile of bevacizumab were observed. 7 patients experienced induction death.

Importantly, residual leukemia was morphologically detectable in 38/48 patients on day 8 prior to bevacizumab. On Day 15 (one week following bevacizumab), 28/48 patients had cleared morphologic leukemia. 16 patients achieved complete remission, including 2/3 newly diagnosed poor-risk AML, 9/18 patients in first remission, and 5/27 patients with primary refractory disease. 7 patients achieved PR, for an overall response rate of 48% following one cycle of treatment. VEGF receptor FLT-1 on bone marrow cells was greater than in normal bone marrow in 12/13 patients examined. On day 8, blasts continued to express FLT-1 in 8/10 patients. Serum free-VEGF was detectable in 14/21 patients prior to treatment (median concentration 12 pg/mL). Day 8 concentrations were higher than on day 0 in 11 patients including 4 patients in whom VEGF had been undetectable, while VEGF concentration had decreased in 6.

Among 15 patients in whom serum was sampled two hours following bevacizumab infusion, 10 had complete suppression of detectable VEGF, while 4 patients had VEGF concentrations ranging from 24 – 82% of the pre-bevacizumab baseline. Sequential examination of bone marrow microvessel density revealed significant decreases in 8/11 patients.

This study confirmed the widespread expression of VEGF in patients with relapsed and refractory AML, and suggested that effective VEGF inhibition could substitute for a toxic second administration of chemotherapy drugs in a timed sequential chemotherapy model, leading to a very promising response rate. This combination was not further developed due to lack of priority from the manufacturer of bevacizumab, despite great interest from the Johns Hopkins group and the Cancer Therapy Evaluation Program. (Personal communication).

1.2.3 Nintedanib, an oral VEGF inhibitor

Nintedanib[33,34] is an orally bioavailable VEGFR inhibitor with an IC50 ranging from 100 – 300 nM. Nintedanib also inhibits the different isoforms of FGF and PDGFR. In a trial in lung cancer in combination with paclitaxel and carboplatin in non-small cell lung cancer[35], mean Cmax was 63 ng/mL, similar to that in monotherapy trials[36-39] and in combination with docetaxel in prostate cancer patients. Nintedanib administration was associated with decrements in plasma soluble VEGFR2.

Nintedanib is being investigated in several cancer indications[40]. Two completed phase III NSCLC[35,41] studies and one phase III in ovarian cancer is still ongoing; the development for colorectal cancer, renal cell carcinoma, and hepatocellular carcinoma is in phase II. Additionally, nintedanib is also registered for the non-cancer indication idiopathic pulmonary fibrosis (IPF) [42,43] (150mg bid). As of 15 Apr 2014, a total of 3470 cancer patients, 143 healthy volunteers and 1529 patients with IPF have been treated with nintedanib. Among the cancer patients, 672 were treated with monotherapy, 1255 with combination of nintedanib and various backbone therapies, 162 with the combination of afatinib[44], an EGFR/HER2 inhibitor, approved in the treatment of patients with NSCLC carrying EGFR mutation and 30 patients with the combination of volasertib, a PLK1 inhibitor. 1351patients were treated with either nintedanib or nintedanib-matching placebo in ongoing blinded studies.

Based on the phase I dose escalation trials[36-39], the MTD (maximum tolerated dose) was determined to be 250 mg bid for twice daily dosing in Caucasians and 200 mg bid in Japanese patients[45] with a

manageable safety profile in advanced cancer patients. The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate severity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, □-GT) which increased dose-dependently. Most cases occurring at doses of 250 mg and above, and a very low incidence at doses below 200 mg and were reversible after discontinuation of nintedanib treatment. All adverse events observed after single administration of single doses of nintedanib to healthy volunteers were only of CTCAE grade 1 severity and fully reversible.

1.2.4 Combination of chemotherapy and Nintedanib in relapsed/refractory AML

The availability of an orally bioavailable VEGF inhibitor with tolerable toxicity profile provides an opportunity to follow the signal from the bevacizumab study in the development of VEGF inhibition in reinduction therapy. The tolerability of the combination will be confirmed in a short phase Ib followed by a randomized phase II study evaluating the potential benefit of such a combination as compared to convention care. An adaptive design will be used for the randomized part. This will allow to quickly conclude on the potential lack of efficacy of any of the arm of the study as compared to historical controls.

1.3 Objectives

1.3.1 Primary objective

Phase I: To determine the safety and tolerability of Nintedanib in combination with intensive AML chemotherapy; Idarubicin and cytarabine after 1 cycle of treatment

Randomized Phase II: To determine the complete remission rate (CR+ CRp) of chemotherapy ; Idarubicin and cytarabine + nintedanib compared to chemotherapy Idarubicin and cytarabine +placebo after 1 cycle of treatment

1.3.2 Secondary Objectives

To determine overall response rate of nintedanib+ chemotherapy as compared to placebo + chemotherapy

To determine the overall survival and leukemia free survival of patients treated with nintedanib+chemotherapy as compared to placebo+chemotherapy.

To determine the percentage of patients bridging to allogeneic transplantation as well as time to transplantation after nintedanib+chemotherapy as compared to placebo+chemotherapy

To determine hematological response rate of the nintedanib+ chemotherapy as compared to placebo + chemotherapy

Phase II: To determine the safety and tolerability of nintedanib+chemotherapy as compared to placebo+chemotherapy

1.3.3 Exploratory objectives

To determine the role and correlate biomarkers of nintedanib activity in relapse/refractory AML (see below)

1.4 Endpoints

1.4.1 Primary endpoint

Phase I: Safety evaluated according to NCI CTCAE V4.03 criteria

Phase II: Complete remission rate (including CR and CRp) evaluated according to IWG AML 2003 criteria after 1 cycle of treatment

1.4.2 Secondary endpoints

Overall response rate will be defined according to IWG 2003 criteria[46] and includes: CR, CRp, CRi, PR, and marrow leukemia free state (MLFS). Rates of hematological improvements (as defined by IWG 2006 Myelodysplastic syndromes criteria[47]) will also be recorded.

Overall Survival will be defined from time of treatment initiation to the time of last follow-up or death. Survival with censoring patients at the time of transplantation will also be evaluated.

Leukemia free survival will be defined from time of documentation of complete remission (CR+CRp+CRi) to the time of last follow-up, relapse, or death of any cause. Survival with censoring patients at the time of transplantation will also be evaluated.

1.5 Treatment Plan

1.5.1 Global treatment strategy

Phase I: This is an initial exploratory phase to confirm the safety and tolerability of the combination of Nintedanib+chemotherapy The AML chemotherapy induction and consolidation regimen occur at an inpatient hospital stay typically averaging 5 weeks and is Standard of Care (SOC) per local hospital policy. The induction and consolidation regimen combines Idarubicin 12mg/m2/d IV push over 10-15 minutes days 1 to 3 and Cytarabine 0.667g/m2/d (24 hr. IV infusion) day 1 to 3. During Phase I, all patients will receive the combination chemotherapy in addition to Nintedanib 200mg bid starting at Day 8 through day 28 (end of cycle). If a significant incidence of dose limiting toxicities is demonstrated, Nintedanib will be given at a lower dose level (150mg bid). Patients may be discharged based on local site SOC and re-admitted prior to the start of the next cycle however, some patients will stay in the hospital continuously (especially between the first two induction cycles). Induction cycle 2 can begin as early as study day 29 regardless of count recovery status if the investigator believes it would be clinically beneficial. Patients can be given a "break" between cycles of induction based on investigator's clinical judgement and clinical response. Count recovery is necessary before a consolidation cycle can begin. If count recovery is not achieved 60 days after Cycle 1 Day 1, the patient is removed from the study.

Phase II: Based on the phase I dose, in the randomized phase II, the combination of chemotherapy + Nintedanib will be compared with chemotherapy+placebo. The AML chemotherapy induction and consolidation regimen occur at an inpatient hospital stay typically averaging 5 weeks and is Standard of Care (SOC) per local hospital policy. The induction and consolidation chemotherapy regimen for Phase II are identical to that in Phase I and combines Idarubicin 12mg/m2/d IV push over 10-15 minutes days 1 to 3 and Cytarabine 0.667g/m2/d (24 hr. IV infusion) day 1 to 3. In Phase II, patients will be randomized to receive the combination chemotherapy in addition to Nintedanib (dose determined in Phase I) at Day 8 through day 28 (end of cycle) or placebo at Day 8 until day 28 (end of cycle). . Patients may be discharged based on local SOC and re-admitted prior to the start of the next cycle however, some patients will stay in the hospital continuously (especially between the first two induction cycles). Induction cycle 2 can begin as early as study day 29 regardless of count recovery status if the investigator believes it would be clinically beneficial. Patients can be given a "break" between cycles of induction based on investigator's clinical judgement and clinical response. Count recovery is necessary before a consolidation cycle can begin. If count recovery is not achieved 60 days after Cycle 1 Day 1, the patient is removed from the study. **Figure 2.** describes the overall

strategy of the Phase II portion of the study. All patients will be evaluated for response based upon count recovery or following day 45, whichever comes first. Patients without count recovery and without signs of bone marrow leukemia at day 45 will be followed up to day 60. If no recovery is observed at day 60, patients will be removed from protocol and considered a failure.

In phase I, patients who fail to achieve CR or CRp based on IWG 2003 AML response criteria (pg. 77) after first cycle of treatment may receive a second cycle of treatment using Nintedanib+ chemotherapy. Patients who achieve CR or CRp after one or two induction cycles may receive up to 2 cycles of consolidation using the same regimen.

In phase II, patients failing to achieve response based on IWG 2003 AML response criteria after cycle 1 will be unblinded, and all those who had been receiving placebo will be offered a cycle of Nintedanib+ chemotherapy (cross over). Patients in the Nintedanib arm may receive a second induction cycle of Nintedanib. Based on clinical judgement, patients can receive up to 2 cycles of consolidation after induction cycle (s) are complete.

Patients are eligible for allogeneic transplantation as soon as remission is achieved and a donor is identified. All transplant procedures occur off study. For responding patients not eligible for transplantation, maintenance therapy with Nintedanib/Placebo will be provided until documented progression.

Patients should NOT start Cycle 1 day 1 on a Thursday or Friday in order to facilitate sample collection, processing and shipment to Sponsor to avoid weekend deliveries.

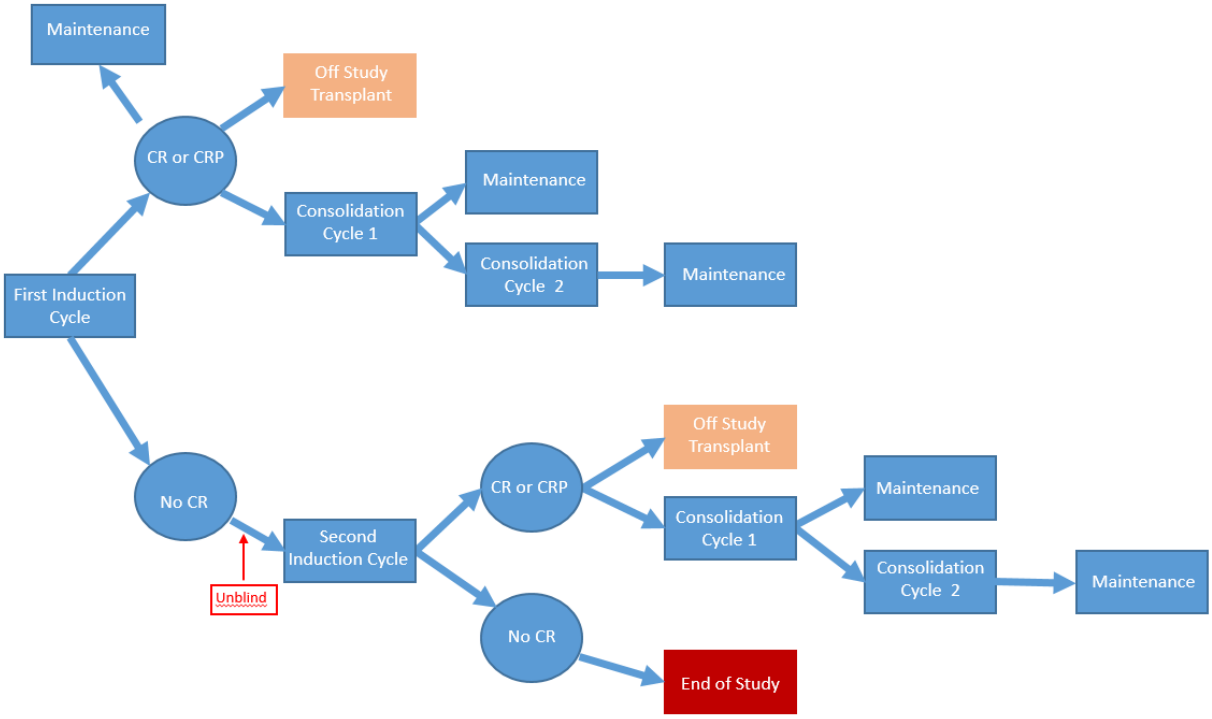

Figure 2. Global treatment strategy of the Phase II portion of the study

NIN/PLA: Nintedanib/ Placebo, CR: complete response, CRp: CR with incomplete counts recovery. Patients can receive up to 2 induction and 2 consolidation cycles.

1.5.2 Drug Dose adjustments

1.5.2.1 Criteria for interruption of treatment with nintedanib/placebo

Treatment with nintedanib must be interrupted if any of the criteria listed in Table1 is fulfilled and in the absence of alternative probable cause.

Table 1: Criteria when to interrupt treatment with nintedanib /placebo due to an adverse event

If one criterion is met, nintedanib/placebo must be interrupted
□ nausea of CTCAE grade ≥ 3 despite supportive care
□ vomiting of CTCAE grade ≥ 2 despite supportive care
□ diarrhea of CTCAE grade ≥ 2 for more than 3 consecutive days despite supportive care
□ AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN persisting after repeat testing over a 24-hour period. AST and/or ALT elevations of > 5x ULN
□ other non-hematological adverse event of CTCAE grade ≥ 3 considered drug-related

1.5.2.2 Criteria to restart nintedanib/placebo treatment

A patient is eligible to restart nintedanib (BIBF1120)/placebo if all criteria listed in table 2 are met. If a patient has to interrupt intake of nintedanib/placebo due to an adverse event for more than *7* days, the decision to restart treatment with nintedanib (BIBF1120) needs to be discussed and agreed upon between the investigator and the sponsor.

Table 2: Criteria to assess eligibility to restart/continue nintedanib (BIBF1120)/placebo treatment

All criteria must be met in order to restart nintedanib/placebo, meaning AEs have to return to Grade 1 or baseline, with the exceptions of the specific managements of the AE listed below
□ nausea CTCAE grade ≤ 2
□ vomiting CTCAE grade ≤ 1
□ diarrhea CTCAE grade < 2
□ AST and ALT < 2.5 x ULN; bilirubin < 1.5 x ULN
□ no other non-hematological adverse event grade CTCAE ≥ 3 which is considered drug-related

1.5.2.3 Dose adjustments during treatment

After cycle 1, if the lifetime cumulative dose of anthracycline reaches 500mg/m2, idarubicin will be switched to etoposide 100mg/m2/d day 1 to 3.

In case of severe hematologic or non-hematologic adverse events, dose of nintedanib/idarubicin/cytarabine could be adjusted **for the subsequent cycles of treatment (IDA/CYTA) or when NINTEDANIB is restarted.** Dose adjustment should be systematically discussed with coordinating investigator and may qualify for the definition of SAE and its related procedure. Given the toxicity profile of the different drugs it is likely that hematological toxicities will be related to idarubicin and/or cytarabine and dose adjustment will be done accordingly. Drugs are dose reduced independently and after discussion with the Protocol PI. Specific procedure should be applied in case of potential drug induced liver toxicity (**see Appendices section**).

Table 3

Drug	Dose level 1	Dose level -1	Dose level -2
Idarubicin (IV Push over 10-15 minutes Days 1-3	12mg/m2/d	8mg/m2/d	Stop drug
Cytarabine Daily (24 hr.) IV infusion Days 1-3	0.667 g/m2/d	0.300 g/m2/d	150mg/m2
Nintedanib PO Days 8-28	200mg bid	150 mg bid	100 mg bid

For patients with a prior dose reduction, it could be discussed with the sponsor to re increase the dose of medication if the adverse event has fully resolved and if it was the first episode of this specific drug related AE.

Recommended dose adjustments for Nintedanib (BIBF1120)

As an initial measure for the management of side effects treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 4 shown below. In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with nintedanib should be discontinued.

Phase II dose reduction will be dependent on the MTD determined in Phase I. Dose reductions during phase II will be managed in 50mg increments to a minimum dose of 100mg. Patients who cannot tolerate the 100mg dose will be taken off treatment.

Table 4:

CTCAE* Adverse reaction	Dose adjustment
Diarrhea > grade 2 for more than 7 consecutive days despite anti-diarrheal treatment OR diarrhea > grade 3 despite anti-diarrheal treatment	1st episode Reduce dose from 200 mg twice daily to 150 mg twice daily 2nd episode Reduce dose from 150 mg twice daily to 100 mg twice daily 3rd episode Stop treatment
Vomiting ** > grade 2 AND/OR Nausea > grade 3 despite anti-emetic treatment	
AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN persisting after repeat testing over a 24-hour period. OR AST and/or ALT elevations of > 5x ULN Dose adjustment/reduction will occur per dosing table 3 if Nintedanib is re-started after being held	
Other non-hematological adverse reaction of > grade 3	
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP < 2 x ULN	Unless there is an alternative cause established, Nintedanib should be permanently discontinued

*CTCAE: Common Terminology Criteria for Adverse Events

Patients should PERMANENTLY discontinue treatment with nintedanib (BIBF1120) in the event of:

- Intolerable Adverse Events (CTCAE grade 3 or 4) that cannot be managed by dose reduction.
- Withdrawal of informed consent.

1.6 Definition of dose limiting toxicities (DLT) during phase I

In order to determine safety of the combination, all adverse events will be recorded on the case report forms and graded using the NCI CTC criteria (version 4.03). Toxicities not listed on the CTC will be graded as mild, moderate, or severe. The local Investigator, in consultation with the clinical staff caring for the patient, and the Protocol PI will determine the relationship to study drugs (unrelated, unlikely, possibly related, probably related, related). Dose limiting toxicity (DLT) will be either as specified below; for organ systems not included, DLT will also include any Grade III or IV non-hematologic toxicity thought possibly or probably related to study drug administration.

Specifically defined DLTs: Drug-related vomiting and nausea CTCAE grade >/= 2 for 5 or more consecutive days despite optimal supportive care. Drug-related diarrhea CTCAE grade >/= 2 persisting for 8 or more consecutive days despite optimal supportive care. Drug-related hypertension CTCAE grade >/= 3 despite optimal supportive care or intervention.

Drug-related transaminase elevation (ALT and/or AST) CTCAE grade >/= 3 or transaminase elevation CTCAE grade >/= 2 (ALT and/or AST) in conjunction with bilirubin CTCAE grade >1. All other drug-related non-hematological toxicities of CTCAE grade >/= 3, except for isolated GGT increases. All other drug-related non-hematological toxicities of CTCAE grade 2 leading to an interruption of the BIBF 1120 treatment for >/=14 consecutive days

Because all patients will be receiving cytarabine and idarubicin in conjunction with nintedanib, patients will not be evaluable for nintedanib- associated hematological toxicity.

Patients will have bone marrow assessed at physician's discretion by day 35 of treatment. If blood counts have not recovered, but marrow is free of morphologic evidence of leukemia, patients may be followed clinically until day 45. If counts have not recovered by day 60 and there is no morphologic evidence of leukemia, this will be considered a nintedanib- associated hematologic DLT.

If <2/6 patients experience Nintedanib attributable dose limiting toxicity, we will proceed to the randomized Phase II trial. If >/= 2 patients experience attributable DLT, six additional patients will be treated with dose level - 1 of nintedanib (150 mg BID). Assuming that <2/6 patients experience Nintedanib attributable dose limiting toxicity at the reduced dose, we will proceed to the randomized Phase II trial -1 dose level of nintedanib.

1.7 Statistical plan

The feasibility phase is structured similar to a classic 3 + 3 Phase I study. The first six patients will be treated at the targeted dose. Like most Phase I studies, this dose will be considered feasible if <2/6 patients experience attributable DLT. If at least two patients experience attributable DLT, six additional patients will be treated at dose level -1. If fewer than 2 patients experience attributable DLT, that dose will be used in the Randomized Phase II portion of the trial.

The primary endpoint of the Randomized Phase II portion is the complete remission rate. The randomized phase II portion of the study utilizes a group sequential design to test the hypothesis that arm A (nintedanib+chemotherapy) will have a complete response rate of 40% after one cycle of treatment compared to 15% in arm B (Placebo+chemotherapy). Estey, Thall, and David reviewed the outcomes of salvage therapy for AML[48]. They stratified patients based on length of first remission (S1: if greater than 2 years) and whether the therapy was first or subsequent salvage (S2: first remission 1 – 2 years, S3: First remission 0- 1 year, first salvage: S4: First remission 0 – 1 year, receiving > first salvage). CR rates for S2, 3, and 4 were 47%, 14%, and 0. We will not be treating S1 in this protocol. Thus, a 40% response rate appears to be very robust for a mix of S2 to S4 patients. While it is highly unlikely that the control (placebo) arm will have a comparable CR rate, without the control arm the success of the addition of nintedanib will not be clear. Using the group sequential design we will minimize the number of patients receiving placebo. For example, if 0/8 patients in the placebo arm achieve remission, the arm will be stopped for futility. In contrast, if 5/11 patients in the nintedanib arm achieve CR, the study can be declared a success.

For Phase II, OnCore will be used to randomize the patients by assigning a sequence number that will correspond to the treatment assignment. The list that includes the sequence number with the corresponding treatment assignment will be generated by the study statistician and released only to the research pharmacist at the site. The group sequential design allows termination of either arm at early time points due to either futility or efficacy. In a randomized Phase II trial, each arm is compared to a historic control. The studies are not powered to officially compare the arms. Rather, they serve as “pick the winner” strategies. The null hypothesis is that each arm achieves a 15% response rate. The trial is powered to select an arm (presumably the experimental arm) which achieves a 40% response rate. At the point at which either arm can no longer demonstrate a 40% response rate, the arm is terminated for futility. Each arm is monitored following each accrual beginning with patient 8. The design assumes overall Type I error of 10% (1-sided) and 80% power.

The following table demonstrates the number of responses at each accrual which would stop the trial for either futility (third column) or efficacy (fourth column):

Analysis	Number of included patients	Number of responses to stop for futility	Number of responses to stop for efficacy
1	8	0	4
2	9	1	4
3	10	1	5
4	11	1	5
5	12	2	5
6	13	2	5
7	14	2	6
8	15	2	6
9	16	3	6
10	17	3	7
11	18	3	7
12	19	3	7
13	20	4	7
14	21	4	8
15	22	4	8
16	23	4	8
17	24	5	8

While this is a randomized Phase II study and each arm is ultimately statistically compared to the historical control, the response rates will be qualitatively compared between the two arms in order to get a sense whether the positive signal in the nintedanib arm is strong enough to warrant further development in larger trials.

1.8 Patient selection

1.8.1 Inclusion criteria

Patient must meet all of the following criteria to be eligible for the study

1/ Patient aged 18y or older

2/ Diagnosis of AML according to WHO 2008 criteria[49]. Therapy related AML may be included if in complete response and off treatment for their prior malignancy for more than 2 years. AML arising after documented MPD are excluded.

3/ Patient must meet one of the following criteria: a/ patient refractory to one or two standard induction regimen b/ patients with a first untreated relapse within 2 years of documentation of clinical remission. Patients relapsing after allogeneic stem cell transplantation are eligible if more than 6 months after transplantation and without sign of active GVHD.

4/ Patient may have been pretreated with intermediate to high dose cytarabine (more than 1000mg/m2/d over 5d) if the day of the last infusion was at least 90 days before inclusion in the study.

5/ ECOG performance status of 2 or less

6/ Patient is willing to participate to the study, has the ability to adhere to the study visit schedule and other protocol procedures, and has the ability to understand and signs an informed consent form.

7/ Women of childbearing potential must agree to use effective contraception without interruption throughout the study and for a further 3 months after the end of treatment;

8/ Men must agree to not conceive during the treatment and to use effective contraception during the treatment period (including periods of dose reduction or temporary suspension) and for a further 3 months after the end of treatment if their partner is of childbearing potential.

1.8.2 Exclusion criteria

Any of the following criteria excludes the patient from participating to the study.

1/ Patient with documented acute promyelocytic leukemia and/or PML-RAR transcript.

2/ Patient relapsing more than 2 years after initial remission.

3/ Use of any active treatment for relapse/refractory AML including but not restricted to chemotherapy, targeted agents, hypomethylating agents or investigational drugs. Use of hydroxyurea up to 6g per day for cytoreduction is allowed for a maximum of 30 days prior treatment.

4/ Patients with clinical evidences of active CNS disease at inclusion

5/ LVEF below 45% or lifetime exposure to anthracyclines over 350mg/m2 of daunorubicin equivalent

6/ Liver function tests: AST ALT above 2.5 ULN, total bilirubin above 2.5 ULN in the absence of Hemolysis or diagnosis of Gilbert's syndrome

7/ Serum creatinine above 2.0mg/dl

8/ Any sign of active uncontrolled disease including but not restricted to cardiac disease, infections, hepatitis. Any severe chronic disease potentially interfering with the protocol including HIV infection, active hepatitis B or C. It includes major injuries and/or surgery within the past 4 weeks prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period.

9/ Documented platelet refractoriness.

10/ Patient has a history of GI surgical procedures, non-surgical procedures or conditions that might interfere with the absorption or swallowing of the study drugs.

11/ Women who are pregnant, or who are currently breastfeeding

12/ Prior treatment with nintedanib or any other VEGFR inhibitor, With the exception of treatment of prior malignancies with a VEGFR inhibitor.

13/ Known hypersensitivity to nintedanib, any other trial drug, or their excipients

14/ Persistence of any clinically relevant (CTCAE grade 2 or above) non-haematological toxicities from previous AML therapy
15/ Active alcohol or drug abuse

16/ Any other condition that, according to the investigator, may forbid the administration of the idarubicin+cytarabine regimen

17/ Therapeutic anticoagulation with INR modifying drug of or use of antiplatelet therapy (with the exception of low dose aspirin<325mg/d)

18/ Any malignancies requiring active treatment within the past year other than basal cell skin cancer or carcinoma in situ of the cervix. Patients actively treated with hormonotherapy for prostate cancer or breast cancer are eligible.

1.9 Enrollment Procedure

Prior to obtaining signed consent from a patient, the site principal investigator or coordinator must email the project manager to inquire about study space availability. If a slot is available, the potential study participant will complete the consent process. The informed consent process must be completed before any study screening procedures may begin. Following consent patients will have all required screening procedures outlined in Section 10. The site principal investigator or other approved investigator must document that the patient has met all inclusion criteria and has none of the exclusion criteria. Following completion of eligibility testing, eligibility documents will be sent to the YCCI project manager. Examples of required documents are listed in the manual of operations.

Upon review and approval by the Project Manager, the PM will send back the patients' study ID # and dose assignment (for Phase II) to the study team via email. The study team will register the patient into the Clinical Trials Management System, OnCore. During the Phase II portion of the study, the study sites will use OnCore to randomize the patient and receive a sequence # that corresponds to the study arm.

1.10 Assessments

Written informed consent will be obtained from the patient before any study specific procedure is undertaken and documented in the patients' medical record.

Patients will be informed about the study, both verbally and by reviewing the consent form with the study investigator. The patient must be given the opportunity to ask questions and given time to consider his or her participation. The investigator and the patient will both sign and personally date the consent form as confirmation of consent. A copy of the consent form will be given to the patient.

The screening assessments and study procedures apply to both Phase I and Phase II.

1.10.1 Screening period

The screening period is the time preceding registration and includes the 14-day period for performing screening assessments.

The following assessments will be completed within 2 weeks prior to the first dose of study drug:

- Informed Consent
- Medical history,
- Complete physical examination,
- Body weight, height and vital signs,
- ECOG performance status,
- EKG,
- Chest X-ray,
- assess left ventricular ejection fraction (LVEF); using 3D Echocardiogram or the biplane Simpson method.
- Concomitant medication,
- Hematology: Complete Blood Cell Count (CBC) with differential (differential done as per hospital standard of care) entire panel is required at screening
- Serum chemistry: AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate, total protein, albumin, uric acid, LDH, and Beta HCG (women of childbearing potential only)

- Hepatitis B and C, HIV1 and 2 serologies
- Coagulation profile: prothrombin time, activated partial-thromboplastin time, fibrinogen,
- Additional examination when clinically indicated (lumbar puncture, CT-scan, PET CT scan).
- Bone marrow evaluation including a new cytogenetic and molecular characterization at the time of relapse,
- Pharmacodynamic assessment: collection of blood (5 x 4mL) and bone marrow samples (8mL).

The following assessments will be performed just prior to treatment from day – 1 to 1: If these tests are performed within 24 hours of the Cycle 1 Day 1 visit, prior to administration of study drug, they do not need to be repeated on Cycle 1 Day 1, unless otherwise determined by the Principal Investigator.

- Physical examination,
- Body weight,
- ECOG performance status,
- Hematology = CBC with differential (differential done per hospital standard of care)
- Serum chemistry. It includes AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate, total protein, albumin and LDH.
- Coagulation profile: prothrombin time, activated partial-thromboplastin time, fibrinogen,
- Bacterial, fungal and viral cultures of throat, stool and urine, if clinically indicated,
- Pregnancy test (women of childbearing potential only)

1.10.2 Evaluation during treatment period

The treatment period begins Cycle 1 Day 1 and can continues until up to 30 days after the last dose of Nintedanib. The treatment period can include a maximum of 2 (28 day) induction and 2 (28 day) consolidation cycles. If Maintenance therapy is indicated, patients will be followed monthly for the first 12 months and then every three months for the following year (a maximum of 24 months). Number and type of cycle will vary by patient and according to local SOC procedures.

Labs between day 8 and counts recovery can be done +/-2day

The following assessments need to be completed:

- Physical examination daily from day 1 to day 6 and then twice weekly during the induction cycle(s) 1 and 2 (if receiving a second cycle). During consolidation cycle(s) 1 and 2 at day 1, then weekly, and at the end of each cycle.
- ECOG performance status weekly during the first induction cycle and at the end of each cycle thereafter,
- Any adverse event,
- Concomitant medication,
- CBC with differential daily from day 1 to day 5 and then every other day for the first cycle and three times weekly of each cycle thereafter, (differential done as per hospital standard of care) entire panel required at response evaluation
- Serum chemistry daily from day 1-5. Then at a minimum of twice weekly,3-4 days apart (+/- 2 days) during the first cycle and every other week each cycle thereafter. It includes AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, chloride, bicarbonate, total protein, albumin, LDH and magnesium
- Pregnancy test prior the beginning of each new treatment cycle (women of childbearing potential only)
- Coagulation profile daily from Day 1-5 of cycle 1 and then weekly during the first two cycles: prothrombin time, activated partial-thromboplastin time, fibrinogen,
- Bone marrow evaluation will be performed in patients with complete clearance of blasts in the blood on Day 14 (+/- 1 day) and at the end of cycle 1 Day 28 (+/- 7 days) and decided by local investigator based on count recovery. Threshold: ANC at 1 and PLT at 50,
- Assess LVEF before cycle 2; this can be done any time after Cycle 1 day 14 up to the start of cycle 2, ideally closer to cycle 2 Day 1 using 3D Echocardiogram or the biplane Simpson method.

- Pharmacodynamic assessment: collection of blood (5 x 4mL) and bone marrow samples (5-6mL if a bone marrow aspirate is performed) at day 8, 14 (+/-1d) and at the end of the cycle (in patients with complete clearance of blasts in the blood). Day 8 bone marrow aspirate is optional and will be performed in patients who specifically consented. If patient consents to D8 optional BMBX, start Nintedanib/placebo on afternoon dose after BMBX and continue until D29 morning dose.

1.10.3 Maintenance

If maintenance therapy is indicated, patients will continue to be followed monthly (+/-3d) for the first 12 months and every 3 months for the following year (+/-7d), (a maximum follow-up of 24 months). Follow-up will include

- Physical examination,
- ECOG performance status
- Adverse events,
- Concomitant medication,
- CBC with differential; monthly for the first 12 months than every other month for an additional 6 months (differential done as per hospital standard of care)
- Serum chemistry monthly for 6 months then every other month. It includes AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, chloride, bicarbonate, total protein and albumin.
- Pregnancy test prior to the beginning of each new treatment cycle (women of childbearing potential only)
- Coagulation profile every other month for 6 months: It includes prothrombin time, activated partial-thromboplastin time, fibrinogen

1.10.4 End of study treatment evaluation

A clinical work-up is to be performed at the end of treatment with Nintedanib within 30 days after the last administration of Nintedanib:

- Complete physical examination,
- Weight,
- ECOG performance status,
- Vital signs,
- Any adverse event,
- EKG,
- Assess LVEF, using 3D Echocardiogram or the biplane Simpson method, after Cycle 1 EOT visit ONLY
- Concomitant medication,
- Hematology: CBC with differential and hemoglobin,

- Serum chemistry including AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate, total protein, albumin, and LDH
- Bone marrow evaluation will be performed in patients with complete clearance of blasts in the blood,
- Pregnancy test up to 3 months after last dose of Nintedanib (women of childbearing potential only)
- Pharmacodynamic assessment: collection of blood (5 x 4mL) and bone marrow samples (5-6 mL if a bone marrow aspirate is performed).

1.11 Concomitant treatments

Patients may not receive chemotherapy, radiation therapy, or any investigational antineoplastic agent. Immunosuppressive agents are prohibited during the course of trial participation. Systemic and chronic inhaled steroids may not be used during participation, with the exception of intermittent use of corticoids for the treatment of nausea and vomiting, or as part of an anti-emetic regime or as treatment of immunoallergic reactions during platelets or blood transfusions.

During the induction cycles, G- and GM-CSF may be used only in case of prolonged neutropenia or neutropenic sepsis if non-blastic aplasia is obtained; there will be no such constraints in subsequent cycles. Use of growth factors during consolidation and maintenance is allowed.

Antibiotics and antifungals can be given according to institutional rules. Antifungal ***prophylaxis*** with systemic azoles (fluconazole, voriconazole) should be avoided due to the risk of liver toxicity. For other drugs, See drug interaction paragraph below for details.

Patients should receive all necessary supportive care, including blood product transfusions, erythropoietin, and pain medications. The related information will be reported in the CRF. Given the risk of bleeding shown with Nintedanib in previous studies, it is recommended to maintain platelet levels above 10^9/L. in the absence of platelet refractoriness. Moreover, the use of anticoagulation during treatment should be limited if possible and if therapeutic anticoagulation is mandatory, discontinuation of Nintedanib need to be discussed with principal investigator.

All treatments given in addition to the study treatment(s) on entry to the study or at any time during the study are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

1.12 Drug interactions

Nintedanib is a substrate of P-gp. Co administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61 fold based on AUC and 1.83 fold based on Cmax in a dedicated drug-drug interaction study. In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3 % based on AUC and to 60.3 % based on Cmax upon co-administration with rifampicin compared to administration of nintedanib alone. If co-administered with nintedanib, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Co administration with nintedanib should be carefully considered.

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Co administration with nintedanib should be carefully considered.

Cytochrome (CYP) enzymes: Only a minor extent of the biotransformation of nintedanib depends on CYP pathways. Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies. The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

1.13 Correlative studies

Sampling flow chart

Peripheral Blood (PB)=20 ml EDTA, bone Marrow Aspirate (BMA)= 8 ml baseline, 5-6 ml follow-up, Bone marrow biopsy (BMB), * potential significant hypoplasia

- Baseline (day -14 to – 5): PB, BMA, BMB
- Day 8 (day 5 post chemo, day 0 of Nintedanib) = PB*
- Day 8 OPTIONAL CONSENT (day 5 post chemo, day 0 of Nintedanib) = BMA
- Day 14 (day 11 post chemo, day 6 of Nintedanib) = PB*, BMA*, BMB*
- Day 28 (day 25 post chemo, day 20 of Nintedanib) = PB, BMA, BMB
- End of Treatment= PB, BMA, BMB

Correlative studies

1/ Genomic profiling (baseline)

There is a significant diversity in molecular profiling of relapse/refractory AML and specific aberrations may be associated with differential response to chemo/nintedanib. Moreover, it is anticipated that several of the pathways that will be evaluated by CyToF may already been triggered by activating mutations at baseline (e.g. FLT3 ITD and STAT).

Objective: Determine the mutational landscape of the population. Correlate with response and pathway activation

Methods: Whole exome sequencing/ Ion Torrent 490 gene panel / RNA sequencing

2/ Bone Marrow microvessel density (Baseline, day 14, day 28)

Microvessel density is a classical pharmacodynamic read out of VEGF inhibition. It can be evaluated on BM biospies routinely

Objective: determine the density of microvessel on bone marrow biopsies and correlate it with Nintedanib exposure and response

Methods: Immunostaining on BM trephine biopsy sample (VWF, CD31, CD34 staining)

Optional= Stem cell niche evaluation

3/ VEGF expression levels (Baseline, day 8, 14, and 28)

VEGF can be secreted by bone marrow stroma and has been also described as potentially secreted by some AML blasts. Bone Marrow stress induced by chemotherapy can also trigger a VEGF response that may subsequently affect survival of AML blast and normal cells recovery pattern. VEGF inhibition by bevacizumab has been described as associated with an increase in VEGF levels.

Objective: Determine patterns of VEGF expression before and during treatment. Evaluate the effect of Nintedanib on these patterns. Correlate it with Response

Methods: Quantitative assessment by ELISA (Quantikine R&D).

Optional: Aliquoted frozen serum will be stored and can be used to evaluate other cytokines related to Nintedanib (FGF, PDGF).

4/ Nintedanib target receptors and downstream pathways analysis (Baseline, day 8, 14, and 28)

Nintedanib is inhibiting the 3 isoforms of VEGFR, (1 to 3) the 3 isoforms of FGF (1 to 3), and the 2 isoforms of PDGFR (A and B). With the exception of FGFR2, all of these receptors have been described in subsets of AML. Downstream pathways are converging to PI3K/AKT, MEK/ERK, and STAT signaling. As previously mentioned some of these pathways may be constitutively active or triggered by other AML related pathways.

Objective: Determine the expression pattern for the receptors and pathways (pAKT, pERK, pSTAT3, and pSTAT5 will be evaluated) before and during treatment . Correlate it with baseline molecular profile, Nintedanib exposure, and clinical response.

Methods: CyToF (Viability, Gating, Pathways, apoptosis)

Backup plan/ validation= IHC on BM trephine biospies (Flash frozen sample vs FFPE?)

5/ Evaluation of Nintedanib impact in specific cell subsets (Baseline, day 8, 14, and 28)

The effect of Nintedanib may be different according to the cell types and it may consequently influence response, toxicity, and risk of relapse. It seems interesting to evaluate Leukemic Stem Cells subpopulation (CD45+, CD34+, CD38-, CD123+, CD90-) marrow stromal cells (CD45-, CD31-, CD34-, CD73+, CD90+, CD105+) , peripheral blood/ marrow endothelial cells (CD45-, CD31+, CD34+, CD105+/-) lymphocytes (CD45+, CD3+ or CD19+), and potentially residual normal hematopoietic stem cells (CD45+, CD34+, CD38-, CD123+, CD90+)

Objective: Evaluate the differences of impact of Nintedanib in AML cells vs the above mentioned subtypes (LSC, MSC, CEC, Lymphocytes)

Methods: Cytof (Viability, Gating, pathways, apoptosis)

Optional: Cell culture assays. When adequate cells are present, bone marrow mononuclear cells will be plated in methylcellulose for determination of CFU-L, a surrogate for leukemic stem cells. By comparing day 14 marrow CFU-L growth in patients on the two treatment arms, we can gain insight into whether nintedanib inhibits the proliferation and survival of leukemic stem cells (ie patients in chemo arm should grow more CFU-L on day 14 than patients in arm nintedanib+chemo).

1.14 Study treatments

1.14.1 Nintedanib

Nintedanib (BIBF 1120) is a potent small molecule triple receptor tyrosine kinase inhibitor (PDGFR [platelet derived growth factor receptor], FGFR 1-3 [fibroblast growth factor receptor], VEGFR 1-3 [vascular endothelial growth factor receptor]). VEGFR- 2 is considered to be the crucial receptor involved in initiation of the formation as well as the maintenance of tumour vasculature. On the molecular level, nintedanib is thought to inhibit the signaling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain, thus interfering with cross-activation via autophosphorylation of the receptor homodimers. Besides inhibition of neo-angiogenesis, tumour regression may also be achieved by inducing apoptosis of tumour blood vessel endothelial cells. Inhibition of receptor kinases may also interfere with autocrine and paracrine stimulation of tumour angiogenesis via activation loops involving VEGF, PDGF, and bFGF utilized by perivascular cells such as pericytes and vascular smooth muscle cells. In vitro, the target receptors are all inhibited by nintedanib in low nanomolar concentrations. In in vivo nude mouse models, nintedanib showed good anti-tumour efficacy at doses of 50 – 100 mg/kg, leading to a substantial delay of tumour growth or even complete tumour stasis in xenografts of a broad range of differing human tumour types. Histological examination of treated tumours showed a marked reduction of tumour vessel density by approximately 80%.

In animals, nintedanib showed moderate to low bioavailability. In the repeated dose toxicity studies, the no adverse effect level (NOAEL) was 3 mg/kg in the 13 week study in Cynomolgus monkeys, 5 mg/kg in the 26 week study in rats, and 10 mg/kg in the 52 week study in Rhesus monkeys. Toxicities at the next higher dose levels were mild (incisor dentopathy in rats, gastrointestinal symptoms in monkeys). Relevant histopathological findings above NOAEL were observed in the gastrointestinal tract, kidneys, liver, extrahepatic bile duct, lymphatic tissues, bone marrow, exocrine glands, skin and corpora lutea. Thickening of epiphyseal growth plate in growing animals was interpreted as a typical mechanism-related toxicity associated with a VEGFR-2 inhibitor and was seen across species. Mild changes of haematological and clinical chemistry parameters (increases of aldolase, □-GT, ALT, AST, LAP, GLDH) were seen in rats. Minimal to slight changes in immunotoxicological parameters and lymphoid tissues may be the correlate to the additional inhibition of src family non-receptor tyrosine kinases such as lymphocyte specific protein kinase (lck) and lyn. Overall, the histopathological findings and changes of laboratory parameters were mild to moderate and generally were confined to the high-dose groups.

Nintedanib is non-mutagenic, even at high doses. As expected, based on the mechanism of action, two exploratory reproductive toxicity studies in rats revealed a teratogenic effect of nintedanib with a steep dose / effect relationship and an early onset of embryofetal deaths at low dosages.

A soft gelatin capsule formulation of nintedanib is used in man. After oral administration, nintedanib is absorbed quickly. Maximum plasma concentrations (C_{max}) generally occur 2 to 4 hours after administration. So far, no evidence for a deviation from dose proportionality of the PK of nintedanib has been observed. Steady state is reached latest after one week of dosing. The absolute bioavailability of nintedanib was slightly below 5% after administration as soft gelatine capsule to healthy volunteers. After food intake, a trend towards an increased systemic exposure (around 20%) and a delayed absorption was observed compared to administration of nintedanib under fasted conditions. Nintedanib displayed a high volume of distribution during the terminal phase (Vz) and a high total plasma clearance; the terminal half-life of nintedanib is in the range of 7 to 19 h. Nintedanib is mainly eliminated via faeces. Only 0.7% of total [14C] radioactivity was eliminated via the urine. The major metabolites are BIBF 1202 and its glucuronide, which is formed by UGT1A1 (liver and intestine) as well as UGT1A7, UGT1A8 and UGT1A10 (intestine) enzymes. Nintedanib is a substrate and a weak inhibitor of P-gp. Co-administration with the potent P-gp inhibitor ketoconazole in a dedicated drug-drug interaction study increased exposure to nintedanib by about 60 – 70% for AUC and by about 80% for Cmax compared to administration without ketoconazole. Co-administration with the P-gp inducer, rifampicin, decreased exposure to nintedanib to approximately 50% based on AUC and to approximately 60% based on Cmax of the estimate after administration without rifampicin. PopPK analyses revealed relevant influences of age, weight, race, and smoking habits on the PK of nintedanib; effect sizes were moderate. There was no relevant drug-drug interaction between nintedanib and paclitaxel, docetaxel, carboplatin, pemetrexed, or mFOLFOX6 (5-FU/LV & Oxaliplatin) at clinically used doses.

Based on the phase I dose escalation trials, the MTD (maximum tolerated dose) was determined to be 250 mg bid for twice daily dosing in Caucasians and 200 mg bid in Japanese patients with a manageable safety profile in advanced cancer patients. The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate severity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, □-GT) which increased dose-dependently. Most cases occurring at doses of 250 mg and above, and a very low incidence at doses below 200 mg and were reversible after discontinuation of nintedanib treatment. All adverse events observed after single administration of single doses of nintedanib to

healthy volunteers were only of CTCAE grade 1 severity and fully reversible.

Regarding the phase I trials combining nintedanib with pemetrexed, docetaxel, paclitaxel/ carboplatin, mFOLFOX or gemcitabine/cisplatin, the recommended dose of nintedanib is 200 mg bid. The pattern of the adverse events was comparable to the adverse event profile of the phase I monotherapy trials except for the chemotherapy related toxicities. There was no clinically relevant change in the pharmacokinetic parameters of nintedanib or in that of the cytotoxic compounds in the combined treatment. Dose limiting toxicity consisted mostly of liver transaminase elevations as in the monotherapy phase I trials with the exception of the combination of nintedanib with pemetrexed, where fatigue was the most relevant DLT. As in phase I monotherapy studies, CTCAE grade 3 transaminase elevations occurred more frequently at doses of 250 mg bid than at doses of 200 mg bid or below. In these studies, encouraging signs of efficacy were observed including some complete and partial responses with single agent treatment.

With respect to the phase II trials which have been concluded thus far and which all employed nintedanib as monotherapy, the pattern of the adverse events in patients with advanced solid tumours was similar to that observed in phase I monotherapy trials with gastrointestinal adverse events as the most frequent events. The majority of CTCAE grade 3 liver enzyme increases was reported in the higher dose group of 250 mg bid in phase II trials. They were reversible and occurred early after start of treatment. Overall in the phase I and II studies ALT increases were generally more frequent than AST increases. In patients with advanced NSCLC, nintedanib showed comparable signs of efficacy in Eastern Cooperative Oncology Group (ECOG) 0-1 patients compared to historical data of other VEGFR inhibitors in a similar patient population. Data from the randomised phase II trial 1199.9 suggest signs of efficacy of nintedanib for ovarian cancer patients as well as in Asian patients with advanced hepatocellular carcinoma (1199.39), advanced colorectal cancer based on the data from phase II combination trial 1199.51with mFOLFOX6 and in Renal Cell Carcinoma (1199.26).

Based on the overall safety profile, 200 mg bid of nintedanib is the recommended phase III dose for combination treatments with pemetrexed, docetaxel and paclitaxel/carboplatin. Available pharmacokinetic data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg qd nintedanib.

With respect to the phase III trials, nintedanib in combination with docetaxel (1199.13) and in combination with pemetrexed (1199.14) in patients with advanced non-small-cell-lung- cancer (NSCLC), the safety of nintedanib in combination with either docetaxel or pemetrexed was in line

with the known profile of nintedanib, with gastrointestinal AEs and liver enzyme elevations as the most frequent adverse events. Overall, adverse events were manageable in the majority of patients with symptomatic therapy and dose reductions. Nintedanib in combination with docetaxel significantly prolonged PFS in patients with stage IIIB/IV or recurrent NSCLC after failure of first-line chemotherapy. In the adenocarcinoma population, nintedanib plus docetaxel significantly prolonged centrally assessed PFS and OS. In the combination with pemetrexed, the addition of nintedanib to pemetrexed showed a relevant prolongation of PFS by central independent review, compared with placebo plus pemetrexed, although the trial was stopped prematurely.

Additional precautions for nintedanib (BIBF1120)

- *Diarrhea*
  Diarrhea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel in the clinical trial LUME-Lung 1. The majority of patients had mild to moderate diarrhea. 6.3 % of the patients had diarrhea of grade ≥3 in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhea should be treated at first signs with adequate hydration and anti-diarrheal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with nintedanib.

- *Nausea and vomiting*
  Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events in the clinical trial LUME-Lung 1. Interruption, dose reduction or discontinuation of therapy with nintedanib (BIBF1120) may be required despite appropriate supportive care. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration. In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

Pharmaceutical/Drug Distribution

Study drug will be supplied to each study site by Almac Clinical Services. Participating sites are responsible to ensure processes, procedures, and documentation are in place for storage, distribution, inventory control, and disposition.

Accountability

The study drug provided for this study is for use only as directed in the study protocol. It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

1. Deliveries of such products from Almac are correctly received by a responsible person

2. Such deliveries are recorded

3. Study treatments are handled and stored safely and properly as stated on the label

4. Study treatments are only dispensed to study patients in accordance with the protocol

The study personnel will account for all study medications dispensed and returned. Certificates of delivery and return should be signed. At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the investigator. This record is in addition to any drug accountability information recorded on the CRF. Any discrepancies must be accounted for Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

1.14.2 Idarubicin

Idarubicin hydrochloride is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II. The absence of a methoxy group at position 4 of the anthracycline structure gives the compound a high lipophilicity which results in an increased rate of cellular uptake compared with other anthracyclines. Its principal indication is the treatment of acute myeloid leukemia (frontline and relapse) in combination with other chemotherapeutic drugs, cytarabine in particular.

General Pharmacokinetics: Pharmacokinetic studies have been performed in adult leukemia patients with normal renal and hepatic function following intravenous administration of 10 to 12 mg/m2 of Idarubicin daily for 3 to 4 days as a single agent or combined with cytarabine. The plasma concentrations of Idarubicin are best described by a two or three compartment open model. The elimination rate of Idarubicin from plasma is slow with an estimated mean terminal half-life of 22 hours (range, 4 to 48 hours) when used as a single agent and 20 hours (range, 7 to 38 hours) when used in combination with cytarabine. The elimination of the primary active metabolite, Idarubicinol, is considerably slower than that of the parent drug with an estimated mean terminal half-life that exceeds 45 hours; hence, its plasma levels are sustained for a period greater than 8 days. Distribution: The disposition profile shows a rapid distributive phase with a very high volume of distribution presumably reflecting extensive tissue binding. Studies of cellular (nucleated blood and bone marrow cells) drug concentrations in leukemia patients have shown that peak cellular Idarubicin concentrations are reached a few minutes after injection. Concentrations of Idarubicin and Idarubicinol in nucleated blood and bone marrow cells are more than a hundred times the plasma concentrations. Idarubicin disappearance rates in plasma and cells were comparable with a terminal

half-life of about 15 hours. The terminal half-life of Idarubicinol in cells was about 72 hours. The extent of drug and metabolite accumulation predicted in leukemia patients for Days 2 and 3 of dosing, based on the mean plasma levels and half-life obtained after the first dose, is 1.7- and 2.3-fold, respectively, and suggests no change in kinetics following a daily x 3 regimen. The percentages of Idarubicin and Idarubicinol bound to human plasma proteins averaged 97% and 94%, respectively, at concentrations similar to maximum plasma levels obtained in the pharmacokinetic studies. The binding is concentration independent. The plasma clearance is twice the expected hepatic plasma flow indicating extensive extrahepatic metabolism.
Metabolism: The primary active metabolite formed is Idarubicinol. As Idarubicinol has cytotoxic activity, it presumably contributes to the effects of Idarubicin.
Elimination: The drug is eliminated predominately by biliary and to a lesser extent by renal excretion, mostly in the form of Idarubicinol.

Hepatic and Renal Impairment: The pharmacokinetics of Idarubicin have not been evaluated in leukemia patients with hepatic impairment. It is expected that in patients with moderate or severe hepatic dysfunction, the metabolism of Idarubicin may be impaired and lead to higher systemic drug levels. The disposition of Idarubicin may be also affected by renal impairment. Therefore, a dose reduction should be considered in patients with hepatic and/or renal impairment

Severe myelosuppression will occur in all patients given a therapeutic dose of this agent for induction, consolidation or maintenance. Careful hematologic monitoring is required. Deaths due to infection and/or bleeding have been reported during the period of severe myelosuppression. Pre-existing heart disease and previous therapy with anthracyclines at high cumulative doses or other potentially cardiotoxic agents are co-factors for increased risk of Idarubicin-induced cardiac toxicity and the benefit to risk ratio of Idarubicin therapy in such patients should be weighed before starting treatment with Idarubicin. Myocardial toxicity as manifested by potentially fatal congestive heart failure, acute life-threatening arrhythmias or other cardiomyopathies may occur following therapy with Idarubicin. So cardiac function should be carefully monitored during treatment in order to minimize the risk of cardiac toxicity of the type described for other anthracycline compounds. The risk of such myocardial toxicity may be higher following concomitant or previous radiation to the mediastinal-pericardial area or in patients with anemia, bone marrow depression, infections, leukemic pericarditis and/or myocarditis. Idarubicin was embryotoxic and teratogenic in the rat at a dose of 1.2 mg/m2/day or one tenth the human dose, which was nontoxic to dams. Idarubicin was embryotoxic but not teratogenic in the rabbit even at a dose of 2.4 mg/m2/day or two tenths the human dose, which was toxic to dams. There is no conclusive information about Idarubicin adversely

affecting human fertility or causing teratogenesis.

Drug interactions seems limited.

1.14.3 Cytarabine

Cytarabine is considered to be the most effective drug in the treatment of AML (Döhner M., 2010). It is a cell-cycle specific anti-metabolite that is phosphorylated intracellularly and incorporated into DNA, resulting in the inhibition of DNA polymerases and DNA synthesis. For initial treatment of AML, cytarabine is typically administered by intravenous continuous infusion for 5-7 days at doses of 100-200 mg/m2/day, usually in combination with an anthracycline. In the relapsed setting, cytarabine remains an option for treatment but is generally administered at higher doses either alone or in combination with other agents, and in a variety of schedules. Cytarabine is a well-known myelotoxic drug. High dose cytarabine (2 to 3 g/m2/day) regimens may cause severe non-hematologic adverse events, including the following: mucositis, diarrhea, ileus, abdominal pain, conjunctivitis, skin rash, anaphylaxis, non-cardiogenic pulmonary edema, cholestatic jaundice, elevations of transaminases and alkaline phosphatase, and cerebral and cerebrellar dysfunction. Because of those toxicities, intermediate-dose cytarabine (500 mg to 1 g/m2/day) regimens are generally used in patients 60 years old or older [Milano G., 2002].

Elimination of cytarabine is rapid with biphasic kinetics characterized by initial and terminal half- life of 15 minutes and from 1 to 3h respectively. It is a prodrug that must be converted in the cells into the 5'triphosphate ara-CTP to be active. In plasma, cytarabine is rapidly transformed by deamination through the cytidine deaminase in a inactive metabolite: Uracil arabinoside (Ara-U). Ara-U is the major metabolite and the only one detectable in plasma. This deamination mechanism is not saturated even at high dose (up to 3 g/m2/day) [Liliemark JO, 1985]. Given that cytarabine is activated intracellularly, no relationship is evidenced between cytarabine plasma concentrations and cytotoxic effects. In addition, there is no correlation between cytarabine plasma concentrations and Ara-CTP intracellular concentrations [Milano G., 2002]. Indeed, the accumulation of Ara-CTP into cells appears to be saturated at plasma concentrations above a rate of administration of 250mg/m2/h [Milano G., 2002]. [Plunkett W., 1992].

Given the unique metabolism pathway of cytarabine involving specific enzyme (cytidine deaminase) and the rate limited accumulation of intracellular Ara-CTP, any clinically relevant interaction of Nintedanib on the PK of cytarabine is unlikely. To date no publication has documented such an interaction effect when cytarabine is combined with other cytotoxics.

1.15 Premature discontinuation of treatment

The treatment may be discontinued prematurely for the following reasons:

- toxicity,
- disease progression,
- refusal to continue the trial,
- withdrawal of consent,
- patient lost to follow up,
- major protocol violation.

Where possible, patients who have discontinued their treatment prematurely will receive the same follow-up as other patients.

1.16 Unblinding procedure

Unblinding will be considered for a specific patient

1/ if he/she is not achieving response after first cycle of treatment (crossover) or

2/ in case of unexpected serious adverse event potentially related to the study drug. In case of an unexpected serious adverse event potentially related to the study drug, the investigator will request the sponsor to unblind the study. In all cases and until the procedure of unblinding has been fully discussed and completed, the drug/placebo should be suspended. If the unblinding is done, the patient will continue to be followed according to the protocol recommendations, including a potential premature discontinuation of treatment if appropriate.

1.17 Criteria for terminating the study

The trial can be suspended or terminated by the sponsor after consultation with the review Board (IRB), or other regulatory body for the following reasons:

- an unexpectedly high frequency and/or severity of toxicity,

- insufficient patient recruitment,

- insufficient quality of data collection.

1.18 Follow-up

1.18.1 Phase I:

Phase I patients will be followed up to 60 days after the last study drug administration in order to determine if any DLTs are attributable to Nintedanib. When counts have not recovered by day 60 and there is no morphological evidence of leukemia it is considered a Nintedanib associated hematologic DLT Sixty days is the maximum length of time to wait for someone to recover before they are removed from the study.

Patients will then be followed every 3 months +/- 7 days for 24 months or until the patient begins receiving subsequent anti-cancer therapy or death, whichever comes first. The following information will be collected; first subsequent anti-cancer therapy (if applicable), documentation of last disease progression/relapse, and date of death. Patients or their caregivers will be contacted by phone.

1.18.2 Phase II:

Phase II patients will be followed every 3 months +/- 7 days for 24 months or until the patient begins receiving subsequent anti-cancer therapy or death, whichever comes first. The following information will be collected; Information regarding the first subsequent anti-cancer therapy (if applicable), documentation/date of last disease progression/relapse, and date of death. Patients or their caregivers will be contacted by phone.

1.19 Serious Adverse events

1.19.1 General definition

An adverse event (AE) is any expected or unexpected harmful and unintended occurrence or exacerbation in a clinical trial subject, whether or not related to the trial or the investigational product. It can be a new intercurrent disease, exacerbation of a concomitant disease, an accident, or any other deterioration in the patient's health, including abnormal laboratory findings. All AEs will be reported from the time that consent is obtained.

Any medical condition that existed before the start of the study treatment and that remains unchanged or improves must not be recorded as an AE. If a medical condition worsens, it must be recorded as an AE. The diagnosis or syndrome rather than the individual signs or symptoms must be recorded on the AE pages of the case report form.

An event is considered a serious adverse event (SAE) if it:

- Results in death; Death due to disease progression is excluded
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Cause any persistent or significant disability/ incapacity,
- Causes a congenital anomaly, birth defect or abortion,
- Is a new cancer (that is not the condition of the study)
- Is associated with an overdose
- Is another medically significant event

The terms *disability* and *incapacity* refer to any clinically significant physical or mental handicap, whether temporary or permanent, that affects the patient's physical activity and/or quality of life.

A *medically significant* event is any clinical event or laboratory finding considered by the investigator to be serious that does not meet the seriousness criteria defined above. It may pose a risk to the patient and require medical intervention to prevent one of the serious outcomes mentioned previously (*e.g. an overdose, second cancer, pregnancy, and new information can be considered medically significant).*

The following are not considered as serious adverse events:

- Death due to disease progression
- Hospitalization for < 24 hours
- Hospitalization scheduled before the start of the trial and/or stipulated in the protocol (e.g. for biopsy or chemotherapy)

The AE pages of the case report form and an SAE form should be completed for each AE considered serious.

For each AE, the investigator shall provide information about the intensity, start and end dates, causality, the action taken, and the outcome

1.19.2 Definition of an expected serious adverse event (SAE-E)

An expected SAE is an event already mentioned in the most recent version of the Investigator Brochure, or in the Summary of Product Characteristics (SmPC) for medicinal products that have already been granted marketing authorization (MA). This definition also applies to the trial drug when it is administered for the same population but for an unlicensed indication.

1.19.3 Definition of an unexpected serious adverse event (SAE-U)

Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product. [21CFR312.32(a)]

1.19.4 Intensity

The term *intensity* (severity) should not be confused with the term *seriousness* that serves as a guide for defining reporting obligations.

The intensity of events shall be evaluated according to the excerpt from the CTC-AE classification, version 4.0 (Appendix 7). The intensity of adverse events not listed in this classification will be rated using the following terms:

Mild (grade 1): does not affect the patient's usual daily activities

Moderate (grade 2): interferes with the patient's usual daily activities

Severe (grade 3): prevents the patient's usual daily activities

Very severe (grade 4): requires intensive care / is life-threatening

Death (grade 5)

1.19.5 Causal relationship between an adverse event (SAE/AE) and the study treatment

Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after occurrence of the event, including diagnostic tests to assess the cause of the event. Clinically relevant data include, but are not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered.

An adverse event is *associated with the use of the drug* when there is a reasonable possibility that the experience may have been caused by the drug. [21CFR312.32(a)]

Attribution Standards per NCI – CTEP:

Unrelated	The Adverse Event is **clearly not** related to the investigational agent (s)
Unlikely	The Adverse Event is **doubtfully** related to the investigational agent(s)
Possible	The Adverse Event **may be** related to the investigational agent(s)
Probable	The Adverse Event **is likely** related to the investigational agent(s)
Definite	The Adverse Event **is clearly** related to the investigational agent(s)

1.19.6 What to do in the event of a serious adverse event

The investigator must report any Expected Serious Adverse Event (SAE-E) or Unexpected Serious Adverse Event (SAE-U) and adverse events of special interest (AESI) (see section 19.7) that occurs during the treatment period starting at the time consent is signed, or within 30 days after the last administration of the study drug, regardless of whether it is attributable to the study. The event must be reported within 24 hours of learning of the event to the Yale Project Manager and Sponsor PI who will report to Boehringer Ingelheim. Sites are responsible for reporting to their IRB per local policy. All events will be forwarded by the PM to Boehringer Ingelheim as required.

All SAEs should be entered into OnCore within 24 hours of the site becoming aware of the event.

The Yale Project Manager shall provide SAEs and AESI to BI as per the method and timeline specified in section 1:19.9

Any delayed serious adverse event (occurring after the 30-day period) that may reasonably be considered related to the treatment(s) described in the protocol or to the study must be reported, and no time limit applies to such adverse events.

For each event, the investigator shall complete the SAE reporting form provided at start-up.

Additional information may be requested by the monitor (by fax, post, telephone, or during a visit).

Nevertheless, any event that qualifies as expected but differs in its intensity, clinical course, or frequency will be considered as an unexpected event by the pharmacovigilance unit at Boehringer Ingelheim.

1.19.7 Adverse events and laboratory values of special interest

The following events are considered as Protocol-specified events of special interests:

Any gastrointestinal- and non-gastrointestinal perforation, leakage, fistula formation, abscess

- In such cases the following additional information needs to be collected, documented in the respective comment field of the CRF page and the respective narratives of the SAE form and emailed or faxed to the Yale Project Manager and Sponsor PI.
- Location of perforation, leakage, fistula, abscess
- Location/extent of abdominal tumor manifestations,
- Imaging & reports (CT, ultrasound, endoscopy, pathology, etc.)
- Prior surgery (location, wound healing complications)
- Concomitant diseases with GI involvement (e.g., M Crohn, vasculitis, tuberculosis, diverticulitis)
- Thromboembolic events (or predisposition)

Drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified adverse event of special interest (AESI). Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the investigational drug from other causes are important for patient safety and for the medical and scientific interpretation of the finding.

The following are considered as protocol-specified AESI:

- An elevation of ALT and / or AST > 5x ULN without bilirubin elevation measured in the same blood draw sample
- An elevation of AST and/or ALT >2.5 fold ULN combined with an elevation of bilirubin to >1.5 fold ULN measured in the same blood draw sample

Patients showing above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met.

Protocol-specified AESI are to be reported in an expedited manner to by the PM to BI, similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

1.19.8 Reporting to the IRB

Sites are responsible for reporting to their IRB per local policy.

The PM will report to the Yale IRB all SAEs meeting the criteria for expedited reporting using HIC Form 710 FR 4: Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOs), including Adverse Events (AEs) Reporting Form as per Yale IRB Policy 710.

1.19.9 Reporting to Boehringer Ingelheim

Upon inclusion into a trial, the patient's condition is assessed (e.g. documentation of history / concomitant diagnoses and diseases), and relevant changes from baseline are noted subsequently.

All adverse events, serious and non-serious, that occur from the time of signing the informed consent through 30 days following cessation of Nintedanib will be collected and documented by the investigator.

The Yale Project Manager shall report all SAEs and non-serious AEs which are relevant to a reported SAE by fax using BIs SAE form to BI Unique Entry Point as detailed below in accordance with the following timelines:

• within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;

• within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Road

Ridgefield, CT 06877

Fax: 1-203-837-4329

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, causal relationship and action taken with the investigational drug. The investigator will also determine the expectedness of each AE based on the listed adverse event section of Boehringer Ingelheim's (BI's) Investigator Brochure for the Product.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period/Residual effect period), it should be reported to the PM if investigator considers it as relevant to the study drug. The PM will report to BI as required.

1.19.10 Follow-up of SAEs

The investigator is responsible for providing appropriate medical follow-up for patients until the event has resolved or stabilized or until the patient's death. Sometimes this may mean that follow-up will extend beyond the patient's withdrawal from the trial.

The investigator shall send additional information to the Project Manager and Sponsor PI using the SAE report form provided at start-up specifying that this is a follow-up report and not an initial report) within 48 hours of receiving the information. The investigator must also send the final follow-up once the SAE has resolved or stabilized.

The investigator shall keep the documents about the presumed adverse effect, in case anything needs to be added to the information previously sent.

The investigator shall respond to requests for additional information in order to document the initial report.

If an SAE is suspected of having been caused by Nintedanib, the Project Manager shall send the report to BI.

1.20 Multicenter management and coordination

1.20.1 Data Management

1.20.1.1 Data Submission

Data will be collected and managed in Yale's web-based clinical trial management system, OnCore. The schedule for completion and submission of the electronic case report forms will be indicated within OnCore. The investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data that are derived from source documents and reported on the eCRF must be consistent with the source documents or the discrepancies must be explained.

1.20.1.2 Monitoring

The study principal investigator and YCCI are responsible for monitoring the performance of all of the participating sites. This will be performed by conducting a study site initiation visit, as well as regularly scheduled monitoring visits and/or remote monitoring throughout the life of the protocol. At the end of the trial, the monitor will then perform a study site close-out visit at all participating sites.

YCCI will utilize their institution's initiation, monitoring and close-out visit reports. Following each site visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be sent to each investigative site.

During these monitoring visits, some of the items that will be reviewed are the following:

- Training of the sites
- Site personnel qualifications to participate in the trial
- Confirmation that study related documents are current
- Regulatory documents and compliance
- Completion of informed consent by each subject
- Compliance with the protocol
- Confirm all SAEs and AEs have been reported to the local regulatory and Ethics/IRB Committees, BI and YCCI, as appropriate
- Verify source documentation for completed CRFs
- YCCI will document the required study monitoring activities in a Monitoring Plan.

1.20.2 Safety Evaluations

Safety analysis will be conducted on all participants who have received at least one dose of therapy, and will include the frequency of all AEs and laboratory abnormalities as well as frequency of dose interruptions, dose reductions, and treatment discontinuation. Participants who receive one total cycle of treatment will be considered as having completed the evaluation for safety. Additional treatment cycles may be delivered if there are no safety concerns, there is no disease progression, and/or there is an indication of clinical benefit. Maintenance monitoring will occur on day 1 of every additional treatment cycle, unless indicated.

Any safety concern or new information that might affect either the safety or the ethical conduct of this trial will be immediately forwarded to the principal investigator in written form. The principal investigator will be responsible for informing the IRB and Data and Safety Monitoring Committee (DSMC). If trends in toxicities are noted or stopping rules are met, the principal investigator will temporarily suspend enrollment while reviewing the episodes with the IRB and DSMC. Toxicity data must be submitted via OnCore at the end of each cycle of therapy.

1.20.3 Safety Monitoring

1.20.3.1 Data and Safety Monitoring Committee

The Yale Cancer Center Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, Adverse Events, Deviations and survival); audit results, and monitoring reports as applicable. Other information (e.g. scans, laboratory values) will be provided upon request.

1.20.3.2 Independent safety review committee (SRC)

An independent safety review committee (SRC) assembled by the PI and comprised of one Investigator from both Yale, and Vanderbilt, two external AML experts and a statistician will meet, when required by the sponsor of the trial, and at least once after the inclusion of the first 6 patients, to analyze tolerance and adverse events and decide on any action to be taken.

1.20.4 Audit Plan

The YCCI Office of Quality Assurance and Training will audit the trial at least annually or as determined by the DSMC. The overall principal investigator, project manager and/or monitor may request access to all source documents and other study documentation for on-site or remote monitoring, audit or inspection.

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or Yale. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

1.20.5 Protocol Research Team Meetings

Scheduled meetings will be held via teleconference monthly, or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and research staff involved with the conduct of the protocol.

During these meetings the investigators will discuss:

- Safety of protocol participants (adverse events and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrolment rate relative to expectation of target accrual, (eligible and ineligible participants)
- Retention of participants, adherence to the protocol and protocol violations
- Protocol amendments

1.21 Ownership of data and confidentiality

The investigator undertakes that he/she and anyone who monitors the conduct of the trial will ensure the confidentiality of all of the information until the trial results are published. This confidentiality requirement shall not apply to information that the investigator gives to patients in connection with their participation in the trial or to previously published information.

The investigator undertakes not to publish, disclose, or use any trial-related scientific or technical information, in any way, either directly or indirectly.

No written or verbal comments can be made about the trial without the sponsor's consent, since all of the information provided or obtained while the trial is being conducted legally belongs to the sponsor, which can use the information at its own discretion.

1.22 Publication

All of the information arising from this trial shall be considered confidential, at least until completion of the appropriate analysis and subsequent checks by the trial sponsor, coordinating investigator, and statistician.

Any publications, abstracts or presentations that include results from the trial must be submitted to the sponsor for approval.

Any communications, articles, or presentations must also include a section mentioning the Yale University and the organizations that supported the research financially.

The trial's coordinating investigator will be the main (first or last) author.

The first or last author (depending on the position given to the coordinating investigator) will be jointly selected by the sponsor and the CI.

The investigators will be cited in order of the number of patients recruited for multicenter trials or based on their involvement in the protocol and/or the disease. The trial statistician will also be cited.

Similarly, publications of ancillary results (biological studies) shall include the name of the person who carried out the ancillary study, as well as the names of anyone else involved in the ancillary study.

1.23 Ethical and regulatory aspects

The clinical trial must be conducted in accordance with:

- the ethical principles of the current version of the Declaration of Helsinki,

- the guideline for Good Clinical Practice of the International Conference on Harmonization (ICH–E6, 07/17/96),

1.23.1 Institutional Review Board (IRB)

Before conducting biomedical research on human subjects, sites are responsible for submission to their IRB per local policy, including amendments and renewals.

1.23.2 Competent Authority

Before conducting a clinical trial or having one conducted, the sponsor of the trial shall apply to the FDA for authorization.

1.23.3 Subject information and consent

Before biomedical research is conducted on a person, their voluntary, written, informed consent must be obtained, after they have been fully informed by the investigator during a consultation and given enough time to consider their decision.

The consent form must be signed and dated personally by the trial subject and the investigator (the original copy shall be archived by the investigator, and one copy will be given to the trial subject).

1.23.4 Responsibilities of the sponsor

The sponsor of the clinical trial is the individual or legal entity that takes the initiative for the biomedical research on human subjects, manages the trial, and ensures that provision has been made for its funding.

The sponsor's main responsibilities are to:

- request the opinion of the IRB on the initial project and substantial amendments,

- request authorization for the initial project and substantial amendments from the IRB and regulatory authority,

- provide information about the trial to the site directors, investigators, and pharmacists,

- report any suspected unexpected serious adverse events related to any of the trial treatments to the regulatory authority, BI, and the trial investigators,

- submit the annual safety report to the regulatory authority,

- notify the regulatory authority of the start and end of the trial,

- write the final clinical study report,

- send the trial results to the regulatory authority and trial subjects,

- archive essential trial documents in the sponsor's Trial Master File (TMF) folder for a minimum of 15 years after the trial has ended.

1.23.5 Responsibilities of investigators

The principal investigator of each site undertakes to conduct the clinical trial in accordance with the protocol approved by the IRB

The investigator must not make any changes to the protocol without the written authorization of the sponsor and unless the IRB has approved the proposed changes.

It is the responsibility of the principal investigator at each site to:

- provide the sponsor with his/her curriculum vitae as well as those of his/her co-investigators,

- identify the members of his/her team who are participating in the trial and define their responsibilities,

- recruit patients once authorized to do so by the sponsor.

It is the responsibility of each investigator to:

- obtain informed consent, personally signed and dated by the subject, before carrying out any trial-specific screening procedures,

- regularly complete the case report form (CRF) of each patient enrolled in the trial and allow the clinical research assistant (CRA) to have direct access to source documents, so that the latter can validate the data on the CRF,

- date, correct, and sign corrections on the CRF of each patient enrolled in the trial,

- accept regular visits by the monitor, and any auditors appointed by the sponsor or inspectors from the regulatory authorities.

All of the trial-related documentation (the protocol, consent forms, case report forms, investigator brochure, etc.) and source documents (laboratory results, X-rays, consultation reports, physical exam reports, etc.) are considered confidential and must be kept in a safe place. The principal investigator must store the data and a patient identification list for a minimum of 15 years after the end of the study.

1.24 References

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1.25 Appendices

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1.25.1 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added) 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) 59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

- The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

- Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

- It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

- The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

- Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

- In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

- In medical practice and in medical research, most interventions involve risks and burdens.

- Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

- Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

- It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

- Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

- The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

- The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

- Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health

care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

- Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

- Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

- Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

- Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

- Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

- Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
- In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
- For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

- When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship

- For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

- Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

- The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: · The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

- At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

- The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

- In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

1.25.2 WHO PS

KARNOFSKY (%)		WHO PS	
100 90	Normal, no complaints, no evidence of disease Able to carry on normal activity, minor signs or symptoms of disease	0	Able to carry out all normal activity without restriction
80 70	Normal activity with effort, some signs or symptoms of disease Cares for self, unable to carry on normal activity or to do active works.	1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
60 50	Requires occasional assistance but is able to care for most needs. Requires considerable assistance and frequent medical care.	2	Ambulatory and capable of all self-care but unable to carry out any work ; up about more than 50% of waking hours.
40 30	Disabled, requires special care and assistance Severely disabled, hospitalisation is indicated although death not imminent	3	Capable of only limited self-care ; confined to bed or chair more than 50 % of waking hours.
20 10	Very sick, hospitalisation necessary, active supportive treatment necessary Moribund, fatal processes progressing rapidly	4	Completely disabled ; cannot carry out any self-care ; totally confined to bed or chair.
0	Dead	5	Dead

1.25.3 IWG response criteria

Primary endpoint will be based on IWG 2003 AML response criteria[46]

- **Morphologic complete remission (CR):** ANC ≥ 1,000/mcl, platelet count ≥ 100,000/mcl, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).

- **Morphologic complete remission with incomplete blood count recovery (CRi):** Same as CR but ANC may be < 1,000/mcl but >500 mcl and/or platelet count < 100,000/mcl but >20,000/mcl

- **Partial remission (PR):** ANC ≥ 1,000/mcl, platelet count > 100,000/mcl, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods.

- **Marrow Leukemia Free State:** < 5% bone marrow blasts, no Auer rods, no extra medullary disease. No requirement on cytopenias

Secondary Endpoint will also include evaluation of hematological improvement based on IWG MDS 2006 criteria[47]

- **Erythroid response (pretreatment <11 g/dL):** Hgb increase at least by 1.5 g/dL. Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of below or equal to 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation

- **Platelet response (pretreatment 100x10^9/L):** Absolute increase of at least 30x109/L for patients starting with more than 20x109/L platelets. Increase from less than 20x109/L to more than 20x109/L and by at least 100%

- **Neutrophil response (pretreatment, <1.0x10^9/L)** At least 100% increase and an absolute increase of at least 0.5x109/L

1.25.4 Common toxicity criteria for adverse events (CTCAE)

Please refer to CTCAE v4.03, a new version of the CTEP, NCI CTC v4.0, includes Adverse Events applicable to all oncology clinical trials regardless of chronicity or modality:

1.25.5 Procedures for the follow-up of a potential DILI case in IIS with nintedanib

Introduction

Drug-induced liver injury

Drug-induced liver injury (DILI) has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Accordingly, detection of drug-induced liver injury of an investigational compound has become an important aspect of patient´s safety guarding in drug development.

The US-FDA has published a Guidance for Industry entitled, “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” which outlines the detection, evaluation, follow-up and reporting of drug-induced liver injury in clinical trials. Drugs that have the potential for inducing severe liver injury may be identified by marked peak aminotransferase elevations (10x-, 15xULN), or the combination of hepatocellular injury (aminotransferase elevation ≥3xULN) and altered liver function (hyperbilirubinemia ≥2xULN) which is defined as potential “Hy´s law case” if not explained by other causes including evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase, ALP, >2X ULN) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis, concomitant use of other known hepatotoxic drugs). This constellation predicts a poor outcome and although very rare, these potential cases have to be well characterized as soon as being identified as other confounding conditions may be the cause.

In further consideration of this FDA Guidance, any potential “Hy’s Law case” has to be reported in an expedited manner to the FDA (i.e., even before all other possible causes of liver injury have been excluded) and be followed-up appropriately. The follow-up includes a detailed clinical evaluation and identification of possible alternative etiologies for the “Hy´s Law case” constellation such as concomitant diseases (e.g. Hepatitis B) and/or other concomitant therapies that might potentially be hepatotoxic.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

The concept below has been worked out by Boehringer Ingelheim (BI) in order to guard patient´s safety and to respond to regulatory requirements. It is the basis for all clinical studies and should be applied as appropriate.

Definition

The following changes in the laboratory values are considered to be a protocol-specific significant adverse event for all patients with normal values for ALT/AST at baseline:

- an elevation of ALT and / or AST > 5x ULN without bilirubin elevation measured in the same blood draw sample
- an elevation of AST and/or ALT >2.5 fold ULN combined with an elevation of bilirubin to >1.5 fold ULN measured in the same blood draw sample.

These definitions are in line with the current dose reduction recommendations as outlined in all study protocols for BIBF 1120.

Patients showing these laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met

For patients with elevated ALT/AST values at baseline special considerations apply, if they are eligible for inclusion into the trial, e.g. if liver metastasis are present and do not qualify as exclusion criterion. For those special cases the BI contact person should be involved.

Procedures

1. Protocol-specified significant events are to be reported in an expedited manner similar as Serious Adverse Events, even if they do not meet any of the seriousness criteria and documented in the eCRF

2. Replication of the following laboratory tests for confirmation within 48 hours:

    - AST, ALT,
    - bilirubin measurement (total and direct bilirubin)
    - Alkaline Phosphatase
    - Haptoglobin
    - Complete blood count and cell morphology
    - Reticulocyte count
    - CK
    - LDH

    The results of these repeated laboratory tests must be documented on the eCRF /CRF forms and reported immediately via the SAE form to the Project Manager who will report it to BI.

3. An evaluation of the patient within 48 hours with respect to but not limited to:

    - Abdominal ultrasound or clinically appropriate other imaging and investigations adequate to rule out biliary tract, pancreatic, intra- or extrahepatic pathology, e.g. bile duct stones, neoplasm, hepatic tumour involvement, biliary tract, pancreatic or intrahepatic pathology, vascular hepatic conditions such as portal vein thrombosis or right heart failure. These data need to be collected, documented in the respective field of the eCRF / CRF / additional documentation form, and the respective SAE form has to be updated and forwarded to BI

    - detailed history of current symptoms and concurrent diagnoses and medical history

    - detailed history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations and eg steroids as concomittant suppportive treatment), alcohol use, recreational drug use, and special diets detailed history of exposure to environmental chemical agents

4. In case that both imaging and laboratory value did not unequivocally confirm cholestasis as the reason of ALT / AST increase, in particular if AP < 2x ULN, then please complete the following laboratory tests:

    - <u>Clinical chemistry</u>
      alkaline phosphatase, cholinesterase (either plasma or red blood cell), albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*,

transferrin, ferritin, amylase*, lipase*, fasting glucose*, cholesterol, triglycerides

- Serology
  Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG)*, Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive)*, Anti-Smooth Muscle antibody (titer)*, Anti-nuclear antibody (titer)*, Anti-LKM (liver-kidney microsomes) antibody*, Anti-mitochondrial antibody*, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM)
- Hormones,
  TSH*
- Hematology
  Thrombocytes*, eosinophils*

  *If clinically indicated and in case that additional investigations are needed (e.g immunocompromised patients.)

5. Initiate close observation of all patients with elevated liver enzyme and bilirubin elevations by repeat testing of ALT, AST,bilirubin (with fractionation into total and direct) and AP at least weekly until the laboratory values return to normal or to the values as defined in the protocol.

6. In case that transaminases and/or bilirubin increase despite cessation of the experimental therapy, more frequent intervals will be warranted.
   Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices

1.25.6 Protocol Signature Page

Acknowledgment of the Investigators

PROTOCOL TITLE: A phase I-II randomized trial of a combination of Nintedanib/placebo in combination with induction chemotherapy for patients with refractory or first relapse acute myeloid leukemia

Version 7; May 21, 2019

1.) I have read this protocol and agree that the study is ethical

2.) I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines

3.) I agree to maintain the confidentiality of all information received or developed in connection with this protocol

_____ _____

Signature of Investigator: Date:

_____

Name of Investigator (Printed or Typed

1.25.7 Study Calendar

Screening and Cycle 1 (Induction Therapy)

	Screening		Day																											
	-14 to -5	-1	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	END Of Treatment
Informed Consent	x																														
Medical History	x																														
Additional exams (Lumbar puncture, CT, Pet-CT)[b]	x																														
EKG, Cardiac Echo, and CXR[m]	x																														x
Hepatitis B, C, HIV1 & HIV2 serologies	x																														
Bacterial, fungal & viral cultures throat, stool & urine [b]		x																													
Bone Marrow Evaluation & Cytogenetics	x																														
Correlative Studies (Blood)	x									x[l]						x[l]														x	x
Correlative Studies (Bone Marrow)	x									x[gl]						x[l]														x	x
Concomitant Medications[q]	x	Ongoing basis																													
Bone Marrow Biopsy[k]																x[l]														x[p]	x
Physical Exam [c, o]	x	x	x[a]	x	x	x	x	x			x[h]		x[h]				x[h]				x[h]			x[h]			x[h]			x	x
ECOG PS	x	x				x[i]							x[i]						x[i]					x[i]							x
CBC with differential[n]	x	x	x[a]	x	x	x	x		x[j]		x[j]		x[j]		x[j]		x[j]		x[j]		x[j]		x[j]		x[j]		x[j]		x[j]		x
Serum chemistry [d]	x	x	x[a]	x	x	x	x				x[h]		x[h]				x[h]				x[h]			x[h]			x[h]				x
Pregnancy testing	x	x	x[a]																												
Coagulation Profile [e]	x	x	x[a]	x	x	x	x				x[i]						x[i]							x[i]							
Idarubicin [f]			x	x	x																										
Cytarabine			x	x	x																										
Study Drug (nintedanib/placebo)										X[g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
AEs [q]			Ongoing basis																												

a: If these tests are performed within 24 hours of the Cycle 1 Day 1 visit, prior to administration of study drug, they do not need to be repeated on C1 D1, unless otherwise determined by the Principal Investigator.

b: If clinically indicated

c: Complete physical exam and vitals including, weight, blood pressure, pulse, temperature, respiratory frequency, height required at screening only

d: Serum chemistry: AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate, total protein, albumin, LDH, **and uric acid at screening only**

e: Coagulation profile: prothrombin time, activated partial-thromboplastin time, and fibrinogen,

f: Idarubicin may be dose reduced, replace, or omitted according to total dose of anthracycline received by the patient

g: Day 8 Bone Marrow aspirate is optional. If patient consents to D8 optional BMBX, start Nintedanib/placebo on afternoon dose after BMBX and continue until D29 morning dose.

h: Twice weekly

i: Weekly

j: Every other day

k: Performed in patients with complete clearance of blasts in the blood

l: (+/- 1 day)

m: All three tests are required at screening, CXR not required at End of Treatment evaluation; 3d Echocardiogram or biplane Simpson method are acceptable methods for obtaining LVEF

n: differential for CBC done as per hospital standard of care (Required at screening, response evaluation and end of treatment visit)

p: (+/- 7 Days) and decided based on count recovery: Threshold: ANC at 1 and PLT at 50

q: AEs and Concomitant Medications will be assessed on an ongoing basis. AE assessment should begin following C1D1 treatment,

Cycles 2, 3 and 4 (Induction or Consolidation) * To be followed if Cycles, 2, 3 and 4 are Induction and/or consolidation cycles, if patient goes to Maintenance refer to Maintenance Calendar

	Day																												
	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 END	END Of Treatment
Bidimensional Echography [j]	x																												
Con Meds [o]	Ongoing basis																												
Physical Exam [c]	x	x[a]	x[a]	x[a]	x[a]	x[a]			x[g]		x[g,b]				x[g]				x[g,b]			x[g,b]			x[g,]			x	x
ECOG PS																												x	x
CBC with differential [m]		x[i]		x[i]		x[i]			x[i]		x[i]		x[i]			x[i]		x[i]		x[i]			x[i]		x[i]		x[i]		x
Serum chemistry [d]											x[l]													x[l]				x	x
Pregnancy testing [p]	x																												
Coagulation Profile [e]				x[h]							x[h]						x[h]							x[h]					
Idarubicin [f]	x	x	x																										
Cytarabine	x	x	x																										
Study Drug (nintedanib/placebo)								x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
AEs [o]	Ongoing basis																												x
Correlative Studies (Blood& Bone Marrow)																													x
Bone Marrow Evaluation																													x[k]

a: Induction cycle ONLY
b: Weekly for a Consolidation cycle
c: Complete physical exam and vitals including weight, blood pressure, pulse, temperature, respiratory frequency
d: Serum chemistry: AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate, total protein, albumin, LDH,
e: Coagulation profile: prothrombin time, activated partial-thromboplastin time, and fibrinogen
f: Idarubicin may be dose reduced, replace, or omitted according to total dose of anthracycline received by the patient
g: Twice weekly for an Induction Cycle
h: Weekly; Cycle 2 ONLY
i: Three times weekly
j: Prior to Cycle 2: Any time after Cycle 1 day 14 up to the start of cycle 2; 3d Echocardiogram or biplane Simpson method are acceptable methods for obtaining LVEF
k: Performed in patients with complete clearance of blasts in the blood
l: Every other week
m: differential for CBC will only be done as per hospital standard of care (Required at screening, response evaluation and end of treatment visit)
o: AEs and Concomitant Medications will be assessed on an ongoing basis
p: prior to the start if each new treatment cycle

Maintenance Cycle, End of Treatment & Follow Up

	Maintenance Therapy Monthly (+/- 3 days) for the first 12 months then every 3 months (+/-7 Days) until disease progression or up to 2 years																				**End of Treatment**	Every 3 months (+/-7 Days) up to 2 years **Follow-Up**
Month	1	2	3	4	5	6	7	8	9	10	11	12	14	15	16	18	20	21	22	24		
Nintedanib [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	X		
Concomitant Medications [i]	Ongoing basis																					
Physical Exam [b]	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	x	
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X	x	
AEs [i]	Ongoing basis																					
CBC with differential [f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X						
Serum chemistry [c]	X	X	X	X	X	X		X		X		X	X		X	X	X		X	x	x	
Pregnancy Testing [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x[j]	x[j]
Coagulation Profile [d]	X		X		X																	
EKG, Cardiac Echo [g]																					x	
Bone Marrow Evaluation [e]																					x	
Correlative Studies (Blood & Bone Marrow)																					x	
Hematology, CBC & hemoglobin																					x	
Subsequent anti-cancer therapy, documentation/date of last disease progression/relapse, date of death																						x

a: Continuous/daily

b: Complete physical exam and vitals including weight, blood pressure, pulse, temperature, respiratory frequency

c: Serum chemistry: AST, ALT, alkaline phosphatase, total bilirubin, BUN, serum creatinine, glucose, calcium, sodium, potassium, chloride, bicarbonate, total protein, albumin,

d: Coagulation profile: prothrombin time, activated partial-thromboplastin time, fibrinogen,

e: Performed in patients with complete clearance of blasts in the blood (+/- 7 Days)

f: differential for CBC will only be done as per hospital standard of care (Required at screening, response evaluation and end of treatment visit)

g: 3d Echocardiogram or biplane Simpson method are acceptable methods for obtaining LVEF

i: AEs and Concomitant Medications will be assessed on an ongoing basis

j: Monthly at the beginning of each Maintenance cycle up until 3 months after last dose of Nintedanib