Nintedanib (BIBF 1120) plus pemetrexed/cisplatin followed by maintenance nintedanib for unresectable malignant pleural mesothelioma—an international, multicenter, randomized, double-blind, placebo-controlled phase II study

#218A

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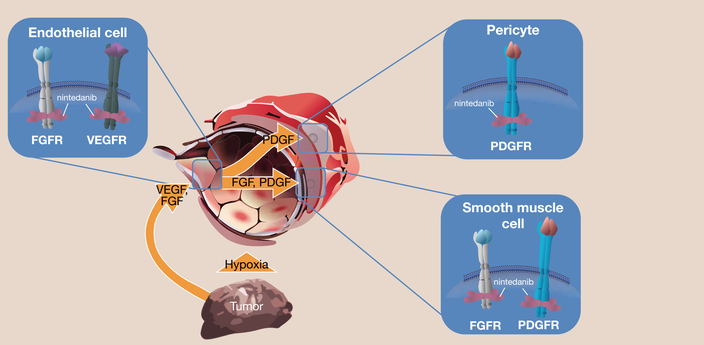
BACKGROUND

- Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer originating from the mesothelial cells lining the pleura[1]
  - of the three histological subtypes (sarcomatoid, epithelioid, and biphasic), epithelioid cell type is the most prevalent, accounting for up to 50% of MPM tumors[1]
- The development of MPM is primarily associated with exposure to asbestos[1]
  - radiation, exposure to other mineral fibers (erionite), Simian Virus 40, and genetic predisposition have also been highlighted as causative factors for MPM[1]
- In occupationally exposed populations, the incidence of MPM is reported to reach up to 100 cases per million per year compared with fewer cases in the general population (1 case per million per year)[1,2]
  - the incidence of MPM is expected to rise later this decade, 20 to 40 years after the peak of asbestos use[3]
  - MPM is 5-fold more common in men than in women[1]
- Typically, symptoms of MPM are uncommon early in the disease and diagnosis often occurs at an advanced stage[1]
- Owing in part to late-stage diagnoses, rapid disease progression, and lack of effective treatments, prognosis for patients with MPM is poor[1]

STUDY RATIONALE

- Pemetrexed/cisplatin (Pem/Cis) is the gold standard for 1st-line combination treatment for MPM
- With median survival of approximately one year in patients with MPM, Pem/Cis combination chemotherapy does not offer improvements beyond the majority of single-modality therapies[1,4]
- Proteins involved in regulating angiogenesis, including vascular endothelial growth factor receptors (VEGF/VEGFR) and platelet-derived growth factor receptors (PDGF/PDGFR), have been implicated in the prognosis of MPM
  - VEGFR is a receptor tyrosine kinase that is overexpressed in various malignancies and has been shown to be co-expressed with VEGF in MPM[5,6]
  - an inverse relationship has been found between VEGF expression and overall survival (OS) of MPM patients[6]
  - VEGF and VEGF-C have been reported to be overexpressed in MPM tissue samples[7]
    - VEGF-C stimulates lymphatic vascular growth
    - a strong correlation has been reported between the expression of VEGF-C, its receptor VEGFR-3 (Flt-4), and microlymphatic vessel density in tissue samples from MPM patients[8]
- Several small molecule inhibitors of the VEGFR tyrosine kinase (eg, sorafenib, sunitinib, cediranib, pazopanib) have been evaluated in Phase II studies in 1st- and 2nd-line settings as monotherapy[8-11]
- Bevacizumab, a monoclonal anti-VEGF-A antibody that does not neutralize other members of the VEGF family, is being evaluated in combination with standard chemotherapy in MPM[12]
- Nintedanib (also known as BIBF 1120) is an oral, twice-daily, triple angiokinase inhibitor of VEGFR-1–3, PDGFR-α/β, and fibroblast growth factor receptors (FGFR)-1–3, as well as RET, Src, and Abl kinases (Figure 1)[13,14]
  - the signaling pathways targeted by nintedanib are involved in regulating tumor angiogenesis, growth, and metastasis of MPM and are also implicated in its pathogenesis and maintenance[15,16]
- Nintedanib has demonstrated clinical activity in various solid tumors within a comprehensive clinical trial program that includes, most recently, Phase III studies in non-small cell lung cancer (NSCLC) and ovarian cancer[14,17]
  - nintedanib is a strong candidate for evaluation in MPM
  - nintedanib also shows in-vitro inhibitory activity against Src and Abl signaling proteins, which may contribute to its effect in MPM
  - nintedanib is currently undergoing Phase III clinical evaluation for the treatment of idiopathic pulmonary fibrosis (NCT01979952; 1199.187)
- Earlier clinical studies showed that nintedanib can be co-administered with various anti-cancer drugs, including pemetrexed[14,18-20]
  - LUME-Lung 1 (NCT00805194; 1199.13) was a randomized, placebo-controlled Phase III trial investigating nintedanib + docetaxel in advanced NSCLC after failure of 1st-line chemotherapy. The study demonstrated that treatment with nintedanib + docetaxel significantly increased centrally reviewed progression-free survival (PFS) regardless of histology and OS for patients with adenocarcinoma histology[14]
  - LUME-Lung 2 (NCT00806819; 1199.14) was a randomized, placebo-controlled Phase III trial investigating nintedanib + pemetrexed in advanced NSCLC after failure of 1st-line chemotherapy. Although prematurely halted, the study demonstrated that treatment with nintedanib + pemetrexed significantly improved centrally reviewed PFS in patients with advanced NSCLC previously treated with chemotherapy[20]
- This Phase II study (NCT01907100; 1199.93) aims to investigate the efficacy and safety of nintedanib when administered with the 1st-line combination Pem/Cis for the treatment of unresectable MPM

Figure 1. Nintedanib mechanism of action



FGF, fibroblast growth factor; FGFR, FGF receptor; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

METHODS

Study objectives

Primary endpoint

- PFS defined as the time from randomization to disease progression according to modified response evaluation criteria in solid tumors (RECIST) or death due to any cause, whichever occurs earlier[21]

Secondary endpoint

- OS defined as the time from randomization to death due to any cause
- Change from baseline in forced vital capacity (FVC) as a measure of pulmonary function

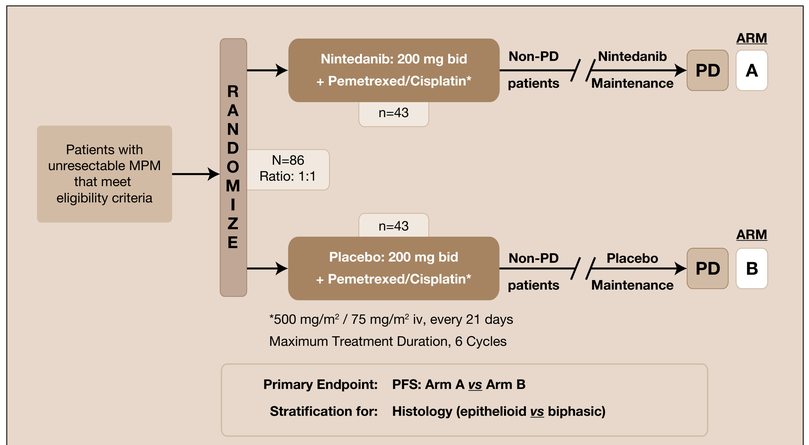
Study assessments

- Safety of nintedanib will be assessed as documented by the frequency and severity of adverse events graded according to the common terminology criteria for adverse events (CTCAE v3.0)
- Tumor imaging by computed tomography (CT) will be performed at baseline and every 6 weeks thereafter until progressive disease (PD) or study discontinuation
- FVC, the volume of air that can be forcibly blown out after full inspiration, will be measured using a spirometer at baseline, at the beginning of every cycle (before treatment), and at the end of treatment (EoT)

Study design

- The trial is designed as a multicenter, randomized, double-blind, placebo-controlled, two-arm study to evaluate the efficacy and safety of nintedanib + Pem/Cis followed by nintedanib monotherapy (Arm A), compared with a matching placebo + Pem/Cis followed by placebo monotherapy (Arm B), until disease progression in patients with histologically confirmed, unresectable MPM (Figure 2)
- A total of 86 patients will be randomized 1:1 into either Arm A or Arm B treatment
  - randomization will be stratified for epithelioid versus biphasic histology
  - as of 14 April 2014, 40 enrolled patients had undergone a 2-week screening period
  - since October 2013, 33 patients have been randomized to treatment
- Patients will attend an end-of-trial visit after permanent discontinuation of study treatment, and return for the first follow-up after 28 (± 2) days and subsequent follow-up visits at 6- to 12-week intervals until trial end, death, or loss to follow-up, whichever occurs first

Figure 2. Study design



bid, twice daily; MPM, malignant pleural mesothelioma; PFS, progression-free survival; PD, progressive disease.

Key eligibility criteria

- Adult patients with histologically confirmed unresectable MPM and an ECOG score of 0 or 1
- The major inclusion and exclusion criteria are summarized in the Table

Table. Eligibility criteria

Inclusion criteria
Age ≥18 years
Histologically confirmed MPM (subtype: epithelioid or biphasic)
Life expectancy of ≥3 months in the opinion of the investigator
ECOG score of 0 or 1
Measurable disease according to modified RECIST criteria
Exclusion criteria
Previous systemic chemotherapy for MPM
Prior treatment with nintedanib or any other VEGFR inhibitor
Sarcomatoid subtype MPM
Symptomatic neuropathy
Radiotherapy (except extremities) within 3 months prior to baseline imaging
Active brain metastases
Radiographic evidence of cavitary or necrotic tumors or local invasion of major blood vessels by MPM
Significant cardiovascular diseases
Inadequate hematologic, renal, or hepatic function

ECOG, Eastern Cooperative Oncology Group; MPM, malignant pleural mesothelioma; RECIST, response evaluation criteria in solid tumors; VEGFR, vascular endothelial growth factor receptor.

Study treatment

- Pem and Cis will be administered intravenously at standard doses of 500 mg/m² and 75 mg/m², respectively, on day 1 of a 21-day cycle followed by oral nintedanib 200 mg bid or placebo on day 2 of the same 21-day cycle. Safety will be monitored on a continuous basis throughout the study. Dose delays or dose reductions may occur in the case of treatment-limiting adverse events. Patients will be evaluated for eligibility to receive study drug before initiation of each treatment cycle
- The trial will comprise four periods
  - screening (up to 2 weeks): during this period, the investigators will screen the patient's eligibility
  - combination chemotherapy (maximum of 6 cycles): 86 patients will be randomized to receive treatment with either nintedanib + Pem/Cis (Arm A) or placebo + Pem/Cis (Arm B)
  - monotherapy: once the treatment of Pem/Cis is discontinued at the end of cycle 6 or earlier if necessary, patients who have not experienced disease progression will continue to receive nintedanib monotherapy (Arm A) or placebo monotherapy (Arm B) until PD
  - EoT and follow-up period: All patients will attend an EoT visit when they discontinue study treatment permanently. All patients will then return for the first follow-up visit 28 (±2 days) after EoT. Thereafter, patients will continue to be followed at 6-12 week intervals until the end of the trial, death, or lost to follow-up, whichever occurs first

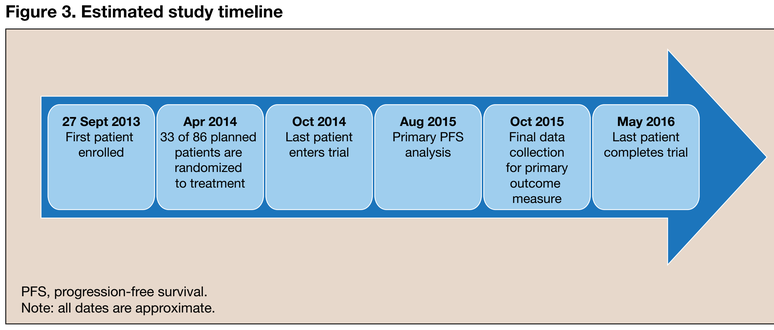
Statistical methods

- All randomized patients, regardless of whether they received study treatment, will comprise the intent-to-treat population for efficacy analyses
- The safety analyses will be conducted in all treated patients who received any dose of the study medication
- Time to event endpoints of PFS and OS will be analyzed by Kaplan-Meier estimation, stratified (epithelioid vs biphasic) log-rank test, and Cox Proportional Hazard modeling
- Analysis of variance, stratified for MPM subtype, will be employed to evaluate change from baseline in FVC
- Safety data will be presented and summarized descriptively
- Descriptive statistics will be used to describe changes in laboratory values over time between the two treatment groups

Patient enrollment

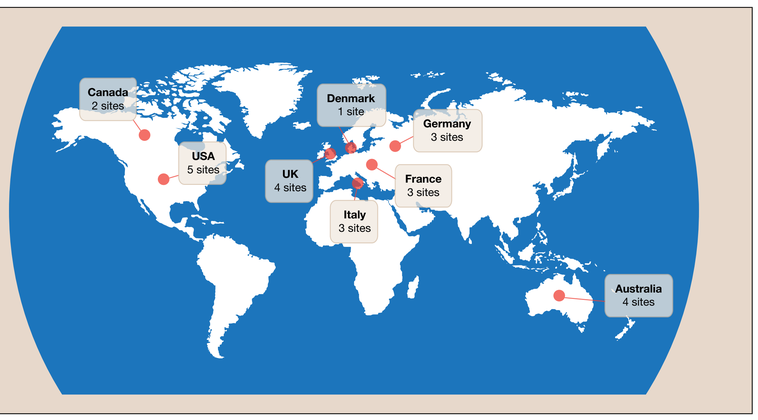
- An estimated study timeline is shown in Figure 3
- As of 14 April 2014, 40 patients have been enrolled across various sites (26 planned) in Europe, North America, and Australia (Figure 4)
- This international study is partly recruited, with 33 of the total planned 86 patients randomized to treatment

Figure 3. Estimated study timeline



PFS, progression-free survival.
Note: all dates are approximate.

Figure 4. Locations of participating study sites



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