FONDAZIONE Buzzi Unicem ONLUS

MESOTELIOMA PLEURICO

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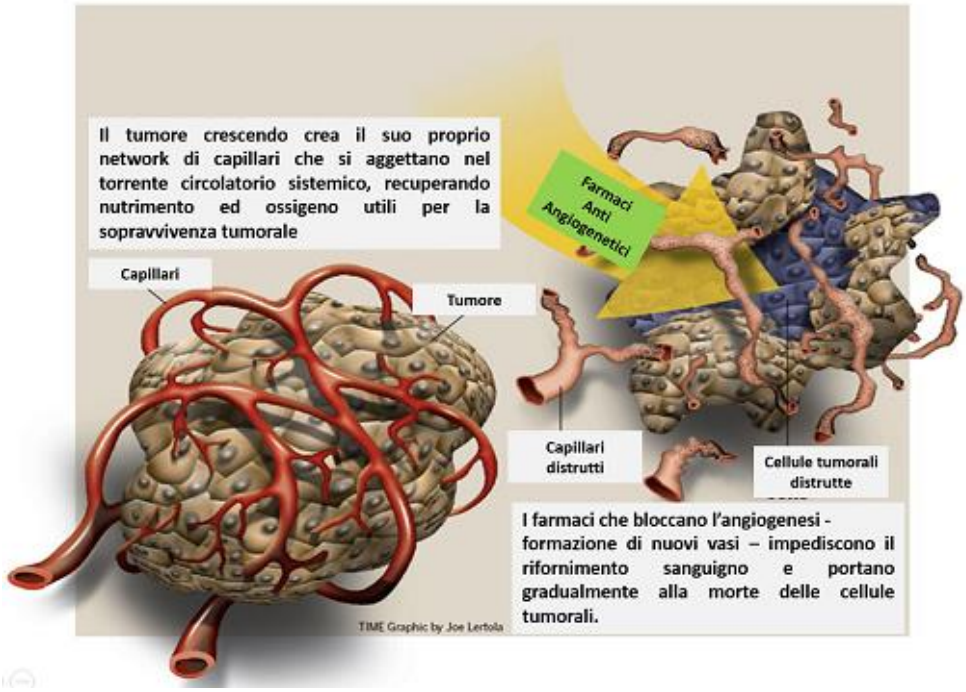
Elisa Roca (elisaroca@gmail.com)

Nintedanib:
New treatment for Malignant Pleural Mesothelioma

Introduction

A major change has been brought to thoracic oncology by the advent of biological therapies, and by "targeted" treatments in particular. These new approaches have changed the natural course of disease in patients with lung cancer, particularly those whose lung cancer is characterized by specific genetic mutations and rearrangements who may benefit from therapies that target these biomolecular alterations.
Among these drugs, molecules acting against multiple molecular targets have also been investigated, particularly Vargatef, which is a mult-target TKI that inhibits the VEGFR, FGFR and PDGFR receptors. It is currently approved in combination with docetaxel for advanced/metastatic lung adenocarcinoma after front-line chemotherapy. The scientific data for this treatment in lung cancer has shown benefit compared to standard chemotherapy alone in terms of progression-free survival (PFS) (4,0 vs 2,8) and overall survival (OS) (12,6 vs 10,3), with a reduction of 17% in the risk of death and a disease control rate of 60,2% (vs 44,0%). An analysis of the European population of the Lume-Lung 1 study showed a further increase in survival (13,4 vs 8,7).
This treatment was therefore considered as potentially useful also for MPM, an aggressive disease with a poor prognosis.
The purpose of this bibliographic review is to provide preliminary data on the use of nintedanib in mesothelioma.

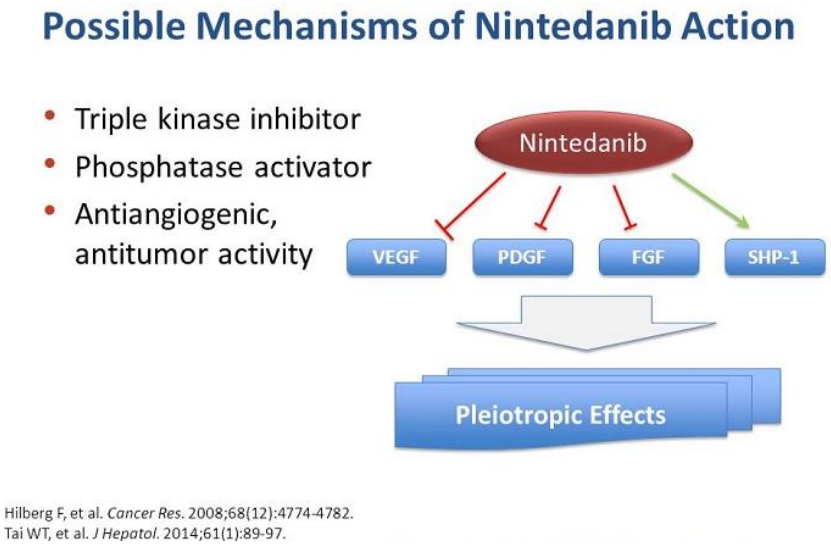
Malignant pleural mesothelioma (MPM) is a cancerous disease that is no longer rare and unfortunately is very aggressive: if it is not treated, the average survival is 6-9 months (1-4).
The standard first-line treatment for unresectable MPM is cisplatin and pemetrexed chemotherapy (5-9). Although this therapy helps increase median survival, it is still only reaches approximately one year so it is essential that new first-line treatments are developed (10-13).
One approach to fulfil this goal is the investigation of antiangiogenics (14-22).



Specifically, the effectiveness of bevacizumab in combination with standard treatment as demonstrated in the MAPS study (Mesothelioma Avastin Cisplatin Pemetrexed Study), has led to renewed interest in inhibiting VEGF (vascular endothelial growth factor) as a therapeutic approach. In fact, many signaling molecules, which are involved in the angiogenesis regulation processes, are involved in both the pathogenesis and the prognosis of MPM (23,24). The VEGF pathway therefore plays a key role in regulating angiogenesis and consequently tumor growth, and is an important factor that can induce the proliferation of MPM cells (25). MPM patients also have high blood levels of VEGF, which is considered a negative prognostic factor (25).
In the MAPS study, survival was shown to be significantly greater in MPM patients treated with cisplatin and pemetrexed plus bevacizumab, compared to those who received chemotherapy alone (18.8 months [confidence interval 95% (CI), 15.9-22.6] vs 16.1 months [95% CI 14.0-17.9]; hazard ratio [HR], 0.77 [95% CI 0.62-0.95]; P =.0167) (26). Up until then, no therapy had ever been shown to increase survival in MPM since the approval of pemetrexed by the US Food and Drug Administration in 2004. These results show that VEGF could be an effective approach as a therapeutic target.
One such drug is **nintedanib**, which acts on different signal transduction pathways that are involved in the pathogenesis of MPM. Specifically, the VEGF receptor is one of the targets of nintedanib and so this molecule is also considered an angiogenesis inhibitor.
The Phase III portion of the global Phase II/III **LUME-Meso** is evaluating the safety and efficacy of nintedanib in combination with pemetrexed and cisplatin in patients with unresectable epithelioid MPM.
Initially, this was a randomized, double-blind exploratory Phase II study, which was amended to include a confirmatory Phase III study, following an evaluation by an Internal Data Monitoring Committee after they had reviewed the Phase II results.
The Phase III study will enroll 450 patients not previously treated with chemotherapy, who will be randomized to receive pemetrexed/cisplatin on Day 1 and nintedanib or placebo from Day 2 to 21 for up to 6 cycles. Patients without progressive disease who are eligible to continue treatment in the study may receive maintenance treatment with nintedanib or placebo until disease progression or excessive toxicity. The primary endpoint of the study is progression-free survival (PFS); the key secondary endpoint is overall survival (OS). The study will also include interim analyses to ensure it is adequately powered for the statistical survival analyses. The study is currently enrolling patients.

The drug

Nintedanib is a tyrosine kinase inhibitor (TKI) that targets three growth factor receptors: the vascular endothelial growth factor receptor (VEGFR), the fibroblast growth factor receptor (FGFR), and the platelet-derived growth factor receptor (PDGFR), as well as other targets such as FLT3, RET, Abl and Src tyrosine-protein kinase signaling (27,28).



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This drug is also indicated for idiopathic pulmonary fibrosis (IPF), which is a non-cancerous disease characterized by slow progression and fatal (29-31).
It is associated with dyspnea, cough and reduced quality of life. Currently, the objectives of patient care include improving outcomes, obtained by slowing disease progression, increasing life expectancy and improving the quality of life (32-34). Timely and accurate diagnosis is important so that patients can be treated in the early stages of the disease and also so they can be considered for a lung transplant (35).
The conditional recommendation of nintedanib for IPF is based on the results of the TOMORROW and INPULSIS studies, which showed that nintedanib 150 mg administered twice daily lowered the annual rate of change in FVC compared to patients who received placebo (36-41). The INPULSIS study results showed that nintedanib was consistently effective across the various subgroups defined by different characteristics such as age (<65 vs ≥65 years), race (Caucasian vs Asian), predicted FVC % (≤70% vs >70%; ≤80% vs >80%, <90% vs >90%), predicted DLCO % (>40% vs ≤40%), and several other diagnostic criteria (such as the presence of honeycombing on high-resolution CT and or confirmation of the presence of UIP by biopsy vs the potential presence of UIP with traction bronchiectasis detected by high-resolution CT, without biopsy evaluation) (42-46).
The TOMORROW and INPULSIS studies also showed that nintedanib reduced exacerbations and mortality due to IPF vs. placebo (47).
Regarding the tolerability profile, adverse events occurred in more than 10% of patients treated with nintedanib. These adverse events included diarrhea, nausea, abdominal pain, vomiting, and raised liver enzymes, which occurred more frequently in patients receiving nintedanib than placebo (48,49). For the most part, the adverse events were managed by reducing the dose of the drug or discontinuing treatment (50).
Results from INPULSIS_ON, the ongoing extension of the INPULSIS study, confirm the good tolerability profile of nintedanib and its effectiveness in lowering FVC for over three years (51).
In oncology, nintedanib (BIBF 1120) in combination with docetaxel was approved by the European Medicines Agency (EMA) for use in the European Union and several other countries for the treatment of locally advanced, metastatic or locally recurrent NSCLC after first-line chemotherapy (52).
It can also be given in combination with various anti-neoplastic treatments due to the efficacy and good safety profile it has shown when used for the treatment of different types of tumors (27).
The ability of nintedanib to act on the three major pro-antiangiogenic signaling pathways (VEGF, PDGF and FGF) may offer greater clinical benefit to patients with unresectable MPM than that obtained with agents that target other known anti-angiogenic targets. Nintedanib also inhibits Src, (27) a molecule that plays an

important role in several neoplastic pathways and is involved in the pathogenesis of mesothelioma. Inhibition of Src has also been proposed as a therapeutic target for MPM (53). In preclinical studies, nintedanib reduced the growth and ability of MPM cell lines to metastasize and increased survival in an orthotopic xenograft model of MPM. It is therefore considered a valid candidate for the treatment of unresectable MPM (54).

The study

LUME-Meso is a randomized, double-blind, placebo-controlled Phase II/III study.
The study compares the efficacy of nintedanib in combination with backbone pemetrexed+cisplatin chemotherapy followed by maintenance treatment with nintedanib, vs. placebo in combination with pemetrexed+cisplatin followed by placebo monotherapy in patients with unresectable MPM.
The study was initially an exploratory randomized, double-blind Phase II study only, but it was enlarged to include a confirmatory Phase III following the recommendation of an Internal Data Monitoring Committee after a review of the Phase II results.
After completing enrollment in the Phase II study, the results for the primary endpoint of PFS were presented.(55) This led to nintedanib being granted Orphan Drug Designation by the US FDA on 12 December 2016. The Phase III study is currently enrolling and the data will be reviewed by an independent committee.

Study Purpose and Design and Treatment Regimen

The purpose of the study is to evaluate the tolerability and efficacy of backbone chemotherapy in combination with nintedanib followed by maintenance therapy with nintedanib, vs. backbone chemotherapy of cisplatin+pemetrexed in combination with placebo, followed by placebo monotherapy, as first-line treatment of unresectable MPM.
Patients are randomized 1:1 to receive pemetrexed (500 mg/m2)/cisplatin (75 mg/m2) on Day 1 for up to 6 cycles, in combination with nintedanib (200 mg twice per day) or placebo (twice per day) from Day 2 to Day 21. Patients will subsequently receive maintenance therapy with nintedanib or placebo until evidence of progressive disease (PD), the development of severe toxicity, withdrawal of consent or death. Patients who, in the opinion of the investigator, may derive a clinical benefit from continuing treatment after disease progression may continue treatment with nintedanib/placebo.
Based on the results of the Phase II study, which included patients with epithelioid and biphasic MPM histologies, the Phase III will enroll 450 patients with epithelioid MPM only.

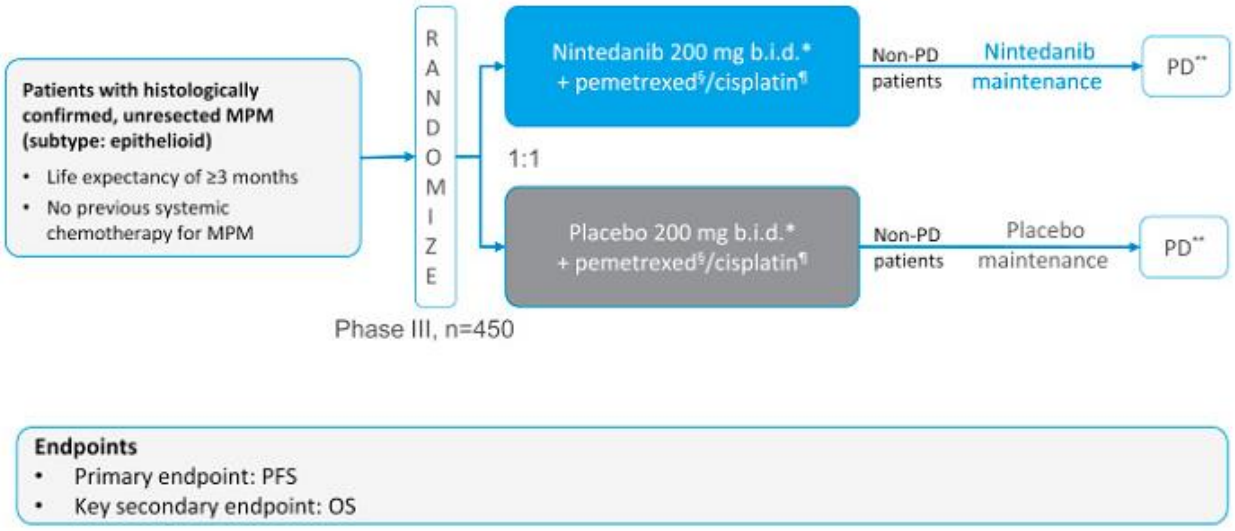

Figure 1. Design of the Phase III LUME-Meso trial

*Nintedanib is administered from Day 2 to 21;
¶Cisplatin 75 mg/m2 intravenously for 2 hours on Day 1 of each cycle, for a duration of 21 days, for up to 6 cycles; §Pemetrexed 500 mg/m2 intravenously for 10 minutes on Day 1 of each cycle, for a duration of 21 days, for up to 6 cycles; &lowest;
**Treatment after progression is permitted if clinical benefit is anticipated.
Abbreviations: b.i.d. = twice daily; I.V. = intravenous; MPM = malignant pleural mesothelioma; OS = overall survival; PD = Progressive disease; PFS = progression-free survival.

Inclusion criteria

The study is conducted in accordance with the Helsinki Declaration and following approval by the Ethics Committee.
All patients must provide their informed consent in writing. The Phase III study is currently enrolling patients with histologically confirmed unresectable epithelioid MPM. Although patients eligible for radical resection or elective surgery (e.g., pleurectomy) are not eligible for enrollment, prior surgery, if performed at least 4 weeks before randomization, is permitted if the patient is fully healed and still has measurable disease.

Study Endpoint

The primary endpoint is PFS, while OS is the main secondary endpoint. Other secondary endpoints include overall response rate (ORR) and the percentage of patients with a complete or partial response, or stable disease control rate (DCR), as measured by modified RECIST Criteria (56). Another objective of the Phase III study includes evaluating the quality of life associated with health status as measured by the EuroQoL-5 self-evaluation questionnaire and the Lung Cancer Symptom Scale (LCSS-Meso) for mesothelioma (57,58).
Biological samples will be tested by immunohistochemical or molecular genetic analysis to determine the value of markers such as mesothelin, merlin protein (produced by the NF2 gene) and protein 1 associated with BRCA1, as predictive or prognostic factors.
During the study, tolerability of the treatment will be monitored by evaluating variations in the laboratory parameters and the frequency and severity of adverse events in accordance with the CTCAE criteria (Common Terminology Criteria for Adverse Events version 4.03), established by National Cancer Institute (NCI) (59).

Conclusion

As always, the main objective of the study is to increase survival and improve the quality of life.
The study of the new therapy aims to achieve these objectives, although the research requires time in order to validate the data before the results can be applied in clinical practice.
The Phase II/III LUME-Meso study will determine whether nintedanib in combination with the backbone of cisplatin+pemetrexed can provide clinical benefit to patients.
The Phase III study is currently underway, and eligible patients with unresectable MPM are being enrolled at sites in North and South America, Europe, Africa, Australia and Asia.

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