



# A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination With Carboplatin and Paclitaxel for the Treatment of Subjects With Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)

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## Main Information

**Primary registry identifying number**

LBCTR2018120171

**Protocol number**

MB02-C-02-17

**MOH registration number**

2018/2/9597

**Study registered at the country of origin**

Yes

**Study registered at the country of origin: Specify**

**Type of registration**

Retrospective

**Type of registration: Justify**

LBCTR was not available

**Date of registration in national regulatory agency**

05/03/2018

**Primary sponsor**

mAbxience Research S.L.

**Primary sponsor: Country of origin**

Spain

**Date of registration in primary registry**

21/12/2018

**Date of registration in national regulatory agency**

05/03/2018

**Public title**

A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination With Carboplatin and Paclitaxel for the Treatment of Subjects With Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)

**Acronym**

STELLA

**Scientific title**

A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination With Carboplatin and Paclitaxel for the Treatment of Subjects With Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)

**Acronym**

STELLA

**Brief summary of the study: English**





This is a multicenter, multinational, double-blind, 1:1 randomized, parallel-group, equivalence Phase 3 study to compare the efficacy and safety of MB02 versus Avastin® in subjects with Stage IIIB/IV non-squamous NSCLC in combination with Carboplatin and Paclitaxel.

MB02/Avastin® plus chemotherapy will be repeated every 21 days for 6 cycles. After 6 cycles, subjects can continue to receive MB02/Avastin® monotherapy treatment every 3 weeks. Patients will stay on treatment until evidence of disease progression, intolerance or until unacceptable toxic effects develop. The study ends at Week 52; no further study assessments will be made after this time.

#### Brief summary of the study: Arabic

١:١ هذه الدراسة هي دراسة تكافؤ في المرحلة الثالثة وهي متعددة المراكز، متعددة الجنسيات، مزدوجة التعمية، بتوزيع عشوائي بنسبة بمجموعتين متوازيتين، والغرض منها مقارنة فعالية وسلامة العقار

MB02

بالمقارنة مع العقار أفاستين® لدى المشاركين المُصابين بسرطان الرئة ذي الخلايا غير الصغيرة وغير الحرفشية (NSCLC)

في المرحلة

IIIB/IV

مع العقارين كاربوبلاتين و باكليتاكسيل

سيتم تكرار العلاج بواسطة

@أفاستين/MB02

دورات، بإمكان المشاركين الاستمرار بتلقي العلاج الأحادي ٦ دورات. بعد ٦ يوم ولـ ٢١ بالإضافة إلى العلاج الكيميائي كل

@أفاستين/MB02 -

أسابيع. وسيستمر المرضى على هذا العلاج إلى حين ظهور دليل على تطور المرض أو على عدم تحمل العلاج أو إلى حين تطور آثار ٣ كل ؛ ولن يتم بعد ذلك الوقت إجراء أي تقييمات خاصة بالدراسة ٥٢ سمية غير مقبولة. وتنتهي الدراسة في الأسبوع رقم

#### Health conditions/problem studied: Specify

Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer

#### Interventions: Specify

Cycle 1 through Cycle 6 (Monoclonal Immunoglobulin therapy in combination with chemotherapy administered on Day 1 of every 3 week treatment cycle)

- Arm 1:

MB02 (bevacizumab biosimilar) IV at an intended dose of 15 mg/ kg

Paclitaxel IV at an intended dose of 200 mg/ m2

Carboplatin IV to achieve and AUC 6

- Arm 2:

Avastin (bevacizumab) IV at an intended dose of 15 mg/ kg

Paclitaxel IV at an intended dose of 200 mg/ m2

Carboplatin IV to achieve and AUC 6

From Cycle 7 onwards (Monoclonal Immunoglobulin monotherapy):

Arm 1: MB02 (bevacizumab biosimilar) IV at an intended dose of 15 mg/ kg

- Arm 2: Avastin (bevacizumab) IV at an intended dose of 15 mg/ kg

#### Key inclusion and exclusion criteria: Inclusion criteria

##### Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Males and female subjects aged  $\geq 18$  years to  $\leq 80$  years.
2. Signed informed consent must be obtained before initiation of any study-specific procedures or treatment as confirmation of the subject's awareness and willingness to comply with the study requirements.
3. Subjects should have newly diagnosed or recurrent Stage IIIB/IV (defined by seventh edition of the TNM classification for Lung Cancer, 2010) non-squamous NSCLC not amenable to curative intent surgery, and not have received any systemic therapy for advanced disease (exclusion criteria 3 and 4). For subjects with recurrent disease, at least 6 months must have elapsed before randomization from previous adjuvant treatment.
4. Previous radiation therapy if completed  $>4$  weeks before randomization. Palliative radiotherapy to bone lesions is allowed if completed  $>2$  weeks of randomization.
5. Subjects must have at least 1 unidimensional measurable lesion per RECIST version 1.1 (assessed locally).
6. Subjects must have an ECOG performance status  $\leq 1$  at Screening.
7. Subjects must have adequate hepatic, renal and hematologic function defined as:
  - Hepatic function: bilirubin level  $<1.5$  ULN, ALT and AST levels  $<2.5 \times$  ULN.
  - Renal function: serum creatinine level  $<1.5 \times$  ULN, calculated creatinine clearance (CrCl)  $>30$  mL/min (Cockcroft-Gault formula), urine protein to creatinine ratio  $<1$ . Subjects with urine protein-to-creatinine ratio  $>1$  may be enrolled if they have  $<1$  g of protein in 24-hour urine collection.
  - Hematological function: Absolute neutrophil count  $>1.5 \times 10^9$  /L; platelets  $>100 \times 10^9$  /L, hemoglobin (Hb)  $>9$  g/dL.
  - Adequate coagulation parameters such as: INR  $\leq 2.0$  and aPTT  $\leq 1.5 \times$  ULN within 7 days prior to randomization for patients not receiving anticoagulation therapy.
8. Eligible subjects must have a systolic blood pressure of  $\leq 140$  mm Hg and a diastolic blood pressure of  $< 100$  mm Hg at screening.



9. Women of childbearing potential, and their partners, must agree to adhere to pregnancy prevention methods throughout the duration of the study (including the Follow-up visits, where applicable). Women of childbearing potential are defined as those who are not surgically sterile (did not undergo bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) and not postmenopausal. Subjects and their partners must agree to use a highly effective method of contraception, to avoid women becoming pregnant throughout the course of the study. Medically acceptable forms of birth control can include the following, with approval of the treating physician:

-Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, sexual abstinence.

10. Non fertile women can be included, that is, those who are physiologically incapable of becoming pregnant, because of:

- Hysterectomy.
- Bilateral oophorectomy (ovariectomy).
- Bilateral tubal ligation or,
- Postmenopausal women defined as:

Subjects not using HRT and have experienced total cessation of menses for 1 year and be greater than 45 years of age, OR, in questionable cases, have a follicle stimulating hormone >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L).

Subjects must discontinue HRT before study enrolment because of the potential for inhibition of cytochrome enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of HRT and determination of menopausal status; the length of this interval depends on the type and dosage of HRT.

If a female subject is determined not to be postmenopausal, that subject must use adequate contraception, as defined immediately above (inclusion 8).

**Key inclusion and exclusion criteria: Gender**

Both

**Key inclusion and exclusion criteria: Specify gender**

**Key inclusion and exclusion criteria: Age minimum**

18

**Key inclusion and exclusion criteria: Age maximum**

80

**Key inclusion and exclusion criteria: Exclusion criteria**

Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Inability to comply with protocol procedures.
2. Participation in another clinical trial or treatment with another investigational agent within 4 weeks or 5 half-lives of investigational agent before randomization, whichever is longer.
3. Subjects previously treated with monoclonal antibodies or small molecule inhibitors against VEGF or VEGF receptors, including Avastin®.
4. Subjects who have received previous chemotherapy, immunotherapy, targeted therapy, or biological therapy for their lung cancer. Note: Adjuvant and neoadjuvant therapy are permitted (see: inclusion criterion 3).
5. Subjects who have known central nervous system disease, with the exception of subjects with treated brain metastases who have completed treatment (radiation, surgery or stereotactic surgery) and have not received steroids for at least 4 weeks before randomization. Subjects with central nervous system metastases treated by neurosurgical resection or brain biopsy performed within 8 weeks before randomization will be excluded. Subjects with known or history of brain metastases must undergo brain imaging during screening.
6. Current or recent (within 10 days of the first dose of study treatment) use of aspirin (at least 325 mg/day) or other nonsteroidal anti-inflammatory drugs with antiplatelet activity or treatment with dipyridamole (Persantine®), ticlopidine (Ticlid®), clopidogrel (Plavix®), or cilostazol (Pletal®).
7. Current or recent (within 5 days) use of therapeutic anticoagulation or use of thrombolytic agent. Prophylactic use of low molecular weight heparin is allowed.
8. Subjects with an INR >2, unless receiving active anticoagulation treatment, will be excluded.
9. Subjects who have a diagnosis of small cell carcinoma of the lung or squamous cell carcinoma of the lung. Mixed tumors should be categorized according to the predominant histology. If small cell elements are present, the subject will be excluded.
10. Subjects with known tumors that harbor activating epidermal growth factor receptor and anaplastic lymphoma receptor tyrosine kinase (assessed locally).
11. Subjects who have a history of hypersensitivity to the active substance (bevacizumab, carboplatin, and/or paclitaxel) or any of the excipients (such as trehalose dehydrate, sodium phosphate, or polysorbate 20).
12. Subjects with known active viral infection: hepatitis B, hepatitis C, or HIV.
13. Subjects who are pregnant or breastfeeding. Women of child-bearing potential must have a negative pregnancy test at Screening.
14. Subjects with previous major surgery, open biopsy, open pleurodesis, or significant traumatic injury within 4 weeks before randomization or those anticipated to require major surgery during the study.
15. Subjects who have had a core biopsy taken or have had another minor surgical procedure, excluding placement of vascular access device, closed pleurodesis, thoracentesis, and mediastinoscopy, within 1 week of randomization.
16. Subjects with a history of abdominal fistula, GI perforation, intra-abdominal abscess within 6 months of randomization.
17. Subjects with a nonhealing wound, active ulcer, or untreated bone fracture.
18. Subjects with previous history of hypertensive crisis or hypertensive encephalopathy.
19. Subjects with New York Heart Association Grade II or greater congestive heart failure, or angina, myocardial infarction within 6 months before randomization; symptomatic arrhythmia or serious cardiac arrhythmia requiring medication; abnormal left ventricular ejection fraction < 50% assessed by ultrasound or multigated acquisition scan.
20. Subjects with a previous malignancy within 3 years of randomization (other than superficial basal cell and superficial squamous (skin) cell carcinoma, or carcinoma in situ of the uterine cervix, bladder, or prostate).
21. Subjects with history of a significant vascular event within 6 months before randomization (including, but not limited to myocardial infarction and stroke or transient ischemic attack).



22. Subjects with known bleeding diathesis or significant coagulopathy within 3 months before randomization.  
23. Subjects with history of grade  $\geq 2$  hemoptysis within 6 months before randomization ( $\geq 0.5$  teaspoons of bright red blood per event).  
24. Subjects with a tumor(s) invading or compressing major blood vessels.

**Type of study**

Interventional

**Type of intervention**

Pharmaceutical

**Type of intervention: Specify type**

N/A

**Trial scope**

Therapy

**Trial scope: Specify scope**

N/A

**Study design: Allocation**

Randomized controlled trial

**Study design: Masking**

Blinded (masking used)

**Study design: Control**

Active

**Study phase**

3

**Study design: Purpose**

Treatment

**Study design: Specify purpose**

N/A

**Study design: Assignment**

Parallel

**Study design: Specify assignment**

N/A

**IMP has market authorization**

No

**IMP has market authorization: Specify****Name of IMP**

MB02

**Year of authorization****Month of authorization****Type of IMP**

Others

**Pharmaceutical class**

Monoclonal immunoglobulin G1 antibody

**Therapeutic indication**

Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer

**Therapeutic benefit**

The study population will comprise subjects with Stage IIIB/IV non-squamous NSCLC not amenable to curative intent surgery and, who have not received any systemic therapy for advanced disease.

**Study model**

N/A

**Study model: Explain model**

N/A

**Study model: Specify model**

N/A

**Time perspective**

N/A

**Time perspective: Explain time perspective****Time perspective: Specify perspective**

N/A



N/A

**Target follow-up duration**

**Target follow-up duration: Unit**

**Number of groups/cohorts**

**Biospecimen retention**

None retained

**Biospecimen description**

Hematology, clinical chemistry, coagulation and urine laboratory analyses will be performed at a central laboratory. Blood samples will be taken to determine serum biomarkers (antidrug antibodies) through 52 weeks after first study drug administration. Analysis of immunogenicity endpoints will be conducted by an external provider.

**Target sample size**

576

**Actual enrollment target size**

576

**Date of first enrollment: Type**

Actual

**Date of first enrollment: Date**

06/02/2018

**Date of study closure: Type**

Actual

**Date of study closure: Date**

28/02/2019

**Recruitment status**

Recruiting

**Recruitment status: Specify**

**Date of completion**

**IPD sharing statement plan**

No

**IPD sharing statement description**

Not Applicable

**Additional data URL**

<https://clinicaltrials.gov/ct2/show/NCT03296163>

**Admin comments**

**Trial status**

Approved



## Secondary Identifying Numbers

No Numbers

## Sources of Monetary or Material Support

Name

mAbxience

## Secondary Sponsors

No Sponsors

## Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Pavel Tyan	Germany	Germany	+49 8999 3913302	pavel.tyan2@syneoshealth.com@syneoshealth.com	INC Research
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Scientific	Jawad Makarem	Ain Wazein, El Chouf, Lebanon	Lebanon	00961 3 484 288	jawad.makarem@awmedicalvillage.org	Ain Wazein Medical Village
Scientific	Paul Khoueiry	Jbeil, Lebanon	Lebanon	00961 3 887 995	drpaulkhoeiry@yahoo.com	Centre Hospitalier Universitaire Notre Dame de Secours



## Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Hammoud Hospital University Medical Center	Dr. Fadi Farhat	Oncologist	Approved
Lebanese American University- University Medical Center Rizk Hospital	Dr. Hady Ghanem	Oncologist	Approved
Ain w Zein Medical Village	Dr. Jawad Makarem	Oncologist	Approved
Notre Dame des Secours Centre Hospitalier Universitaire	Dr. Paul Khoueiry	Oncologist	Approved

## Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Hammoud Hospital University Medical Center	25/09/2017	Ghada Aoun	medical@hammoudhospital.org	009613408 947
Lebanese American University- University Medical Center Rizk Hospital	09/01/2018	Christine Chalhoub	christine.chalhoub@lau.edu.lb	009613212 327
Ain w Zein Medical Village	23/12/2017	Hayat Kamaledine	cru@awzmedicalvillage.org	009613853 017
Notre Dame des Secours Centre Hospitalier Universitaire	19/02/2018	Sally Nassour	dm@chu-nds.org	009619940 413



## Countries of Recruitment

Name
Ukraine
Thailand
Republic of Serbia
Russian Federation
Philippines
Mexico
Malaysia
Lebanon
India
Hungary
Greece
Georgia
Chile
Bulgaria
Brazil
Peru
South Africa
Spain
Turkey

## Health Conditions or Problems Studied

Condition	Code	Keyword
Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer	Malignant neoplasm of bronchus and lung (C34)	Lung Cancer





## Interventions

Intervention	Description	Keyword
Arm 1	MB02 + Paclitaxel + Carboplatin	MB02
Arm 2	Avastin + Paclitaxel + Carboplatin	Avastin

## Primary Outcomes

Name	Time Points	Measure
Objective Response Rate	Week 18 after initiation of treatment	Recist 1.1 tumor assessment

## Key Secondary Outcomes

Name	Time Points	Measure
Safety profile of MB02 compared with Avastin®	During study	NCI-CTCAE; v4.03
Potential immunogenicity of MB02 compared with that of Avastin®	During study	Antidrug antibodies
Progression-free survival and Overall survival	Week 18 and Week 52	Recist 1.1 tumor assessment



## Trial Results

**Summary results**

**Study results globally**

**Date of posting of results summaries**

**Date of first journal publication of results**

**Results URL link**

**Baseline characteristics**

**Participant flow**

**Adverse events**

**Outcome measures**

**URL to protocol files**