SYNOPSIS

Name of Sponsor/Company: Grupo Español Multidisciplinar de Melanoma (GEM) Name of Finished Product: Cobimetinib and vemurafenib Name of Active Ingredient: Cobimetinib and vemurafenib	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)
Title of Study: A Randomized Phase II Study of Vemurafenib Plus Cobimetinib Continuous Versus Intermittent, in Previously Untreated BRAFV600- Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma.		
Investigators: Principal Investigators: Alfonso Berrocal, MD, PhD* José Antonio López-Martín, MD, PhD** Maria Martinez Gonzalez Cao, MD, PhD***		
Study centre(s): Hospital Universitario Donostia - San Sebastián, Guipuzcoa, Spain Hospital General Universitario Santa Lucía - Cartagena, Murcia, Spain Hospital Clínic - Barcelona, Spain Hospital del Mar - Barcelona, Spain Hospital Universitario Vall d'Hebron - Barcelona, Spain Hospital Insular Materno-Infantil de Gran Canaria - Las Palmas de Gran Canaria, Spain Hospital Universitario Lucus Augusti - Lugo, Spain **Hospital Universitario 12 de Octubre - Madrid, Spain Hospital Universitario La Paz - Madrid, Spain Hospital Regional Universitario de Málaga - Málaga, Spain Hospital Clínico Universitario de Salamanca - Salamanca, Spain Hospital Universitario Virgen Macarena - Sevilla, Spain Hospital Universitario de Canarias - Tenerife, Spain *Hospital General Universitario de Valencia - Valencia, Spain Hospital Universitario Doctor Peset - Valencia, Spain Hospital Universitario y Politécnico La Fe - Valencia, Spain Hospital Álvaro Cunqueiro (Complejo Hospitalario Universitario de Vigo) - Vigo, Spain Hospital Universitario Miguel Servet - Zaragoza, Spain Hospital Clínico San Carlos – Madrid, Spain		
Central Lab. Translational Sub-Study ***Instituto Oncológico Dr. Rosell – Hospital Universitari Dexeus - Barcelona, Spain		
Publication (reference) A randomized phase II study of vemurafenib plus cobimetinib continuous versus intermittent in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma. Jose A. Lopez-Martin, Alfonso Berrocal, and María González-Cao. Journal of Clinical Oncology 2017 35:15_suppl, TPS9599-TPS9599		
Studied period (years): Recruitment Status: Completed. date of the first enrolment: June 30th, 2015 (FPI) date of last completed: September 30th, 2019 (LPO)		
Phase of development: Phase II		

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Objectives:
To evaluate the efficacy in terms of Progression-Free Survival (PFS) and safety of two different schedules of administration of vemurafenib in combination with cobimetinib (continuous and intermittent) in previously untreated BRAFV600- mutation-positive patients with unresectable locally advanced or metastatic melanoma

Methodology: Allocation: Randomized - Intervention Model: Parallel Assignment - Masking: None (Open Label)
Primary Purpose: Treatment, Multicenter.

Number of patients (planned and analyzed): It will be necessary to include 34 patients per treatment group (at least 61 events are required). Considering 10% of losses to follow-up, it will be necessary to recruit around 38 patients per group (76 in total). As of September 2017, a total of 70 patients were included, all of them analyzed in the ITT population.

Diagnosis and main criteria for inclusion:
Patients with histologically confirmed melanoma, either unresectable stage IIIc or stage IV metastatic melanoma.
Patients must be naïve to treatment for locally advanced unresectable or metastatic disease.
Documentation of BRAFV600 mutation-positive status in melanoma tumor tissue, Measurable disease per RECIST v1.1, ECOG performance status of 0 or 1.
Additionally, patients to be included in the biomarker substudy should meet the following criteria: Consent to provide archival tissue for biomarker analyses, Consent to undergo tumor biopsies

Test product, dose and mode of administration, batch number:
Experimental: A - Continuous Administration: 960 mg of vemurafenib po, bid, days 1 to 28 and 60 mg of cobimetinib po, od, days 1 to 21, for each 28-days' cycle.
Experimental: B - Intermittent Administration: 960 mg of vemurafenib po, bid, days 1 to 28 and 60 mg of cobimetinib po, od, days 1 to 21, for each 28-days' cycle, for 12 weeks.
After that period, patients were treated with both drugs at the same doses indicated previously, but with an intermittent pattern: vemurafenib days 1 to 28 followed by 14 days off (4 weeks on and 2 weeks off) and cobimetinib days 1 to 21 followed by 21 days off (3 weeks on and 3 weeks off)
Intervention: Drug: vemurafenib and cobimetinib, comparison between different treatment regimens.
Cobimetinib batch numbers: 1149149, 1151236, 1152227, 1154632, 1156357, 1157633 and 1159023.
Vemurafenib batch numbers: not applicable. Commercial medication.

Duration of treatment: Recruitment period: 27 months: June 2015 (date of inclusion of the 1st patient) - September 2017 (date of inclusion of the last patient). Follow-up period: 24 months from the inclusion of the last patient. Date of completion of the study: September 2019.

Criteria for evaluation:

- **Efficacy:** Progression-free survival (PFS): time elapsed between randomization and the first occurrence of disease progression, as determined by the investigator using the RECIST criteria, V1.1 (Appendix 1), or death from any cause, whatever happens first. Overall Survival Time (OS): elapsed between randomization and death from any cause. Objective response (ORR): The proportion of objective responses (ORR) is defined as the percentage of patients who reach a complete (CR) or partial (RP) response: the response was evaluated following the RECIST V1.1 criteria (Appendix 1). PFS at 1-2 years Estimated percentage of patients who remain free from progression at 1 or 2 years. OS at 1-2 years Estimated percentage of patients who are still alive at 1 or 2 years.
- **Safety:** Toxicity were evaluated according to the criteria of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. (http://evs.nci.nih.gov/ftp1/CTCAE/About.html), and It were coded by the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical methods:
For an error $\alpha = 0.1$ and an error $\beta = 0.20$, 34 evaluable patients were recruited per treatment group, using a Log-rank method (Tablecloth). Cox two-tailed (Brookmeyer R. et al (32). With this sample size, a power of 80% was obtained to detect a difference of 23% in the percentage of patients free of progression at 1 year (with an error $\alpha = 0.1$) in the Kaplan-Meier curves, assuming 27 months of

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recruitment, 24 months of follow-up, a Hazard ratio (HR) of 0.53 and a total of 61 events. A maximum loss of 10% of patients was estimated at follow-up and before progression, 38 patients per group, which gives an estimated total of 76 patients. From previous studies, it is estimated that 50% of patients with unresectable or metastatic melanoma present the BRAF V600 mutation, therefore, considering the possible losses due to errors in screening and other reasons, they should undergo screening tests. about 175 patients.
Summary – Conclusions
Efficacy Results: The Primary efficacy Variables analyzed showed significant statistical differences in median PFS and PFS at 1 and 2 years (p=0,07), although the OS and OS at 1 and 2 year were not statistically significant between the treatments Groups A-Continuous vs B-Intermittent.
Safety Results: the safety profile observed with continuous administration (Group A) and intermittent administration (Group B) with the combination of vemurafenib and cobimetinib is comparable, although there is a trend towards greater toxicity in the Group A (continuous regimen), possibly explained by the higher intensity of the dose received.
Conclusion: In patients with positive BRAF V600 mutations without previous treatment, with locally advanced or unresectable metastatic melanoma, the combination of vemurafenib and cobimetinib given in two different administration schedules (continuous or intermittent) showed significant statistical differences in median PFS (and PFS at 1 and 2 years), in favor the continuous regimen, no differences in Overall Survival, were observed between the 2 Experimental treatments schedules, Groups A and B.
Date of report: February 10th, 2021

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