Pierre Fabre and its partner Array BioPharma announce 15.3 months median overall survival observed from the Phase 3 BEACON colorectal cancer safety lead-in of the combination of BRAFTOVI®, MEKTOVI® and ERBITUX® in BRAF-mutant metastatic CRC

– Data will be presented at ASCO 2019 Gastrointestinal Cancers Symposium –
– Updated confirmed ORR remains 48% and updated median PFS remains 8.0 months –

Castres, France (15 January 2019) – Pierre Fabre today announced updated safety and efficacy results, including mature overall survival (OS), from the safety lead-in of the Phase 3 BEACON CRC trial evaluating the triplet combination of BRAFTOVI® (encorafenib), a BRAF inhibitor, MEKTOVI® (binimetinib), a MEK inhibitor and ERBITUX® (cetuximab), an anti-EGFR antibody, in patients with BRAFV600E-mutant metastatic colorectal cancer (mCRC). The results showed that mature median OS was 15.3 months (95% CI, 9.6–not reached) for patients treated with the triplet combination therapy. These data will be presented on Saturday 19 January at the ASCO 2019 Gastrointestinal Cancers Symposium in San Francisco, California.

Updated median progression-free survival (mPFS) and updated confirmed overall response rate (ORR) results for patients treated with the triplet in the safety lead-in remain the same, as previously reported, with 8 months mPFS (95% CI, 5.6–9.3) and a 48% ORR (95% CI, 29.4–67.5). Among the 17 patients who received only one prior line of therapy, the ORR was 62%.

“We are delighted to see such encouraging data from the BEACON CRC trial, where the mature median overall survival of 15.3 months represents a marked improvement in comparison with the current standards of care for patients with BRAF-mutant mCRC,” said Josep Tabernero, MD, PhD, BEACON CRC trial lead investigator and director of the Vall d’Hebron Institute of Oncology in Barcelona, Spain. “These latest data bring us one step closer to understanding the full potential of this triplet therapy, as a possible new treatment option for these patients.”

A BRAF mutation is present in up to 15% of all patients with mCRC, and V600E is the most common BRAF mutation.1–5 BRAFV600E-mutant mCRC patients have a mortality risk more than double that of mCRC patients without the mutation, and currently there are no European Commission (EC)-approved therapies specifically indicated for this high unmet need population.3–10

The most common grade 3 or 4 adverse events seen in at least 10% of patients were fatigue (13%), anaemia (10%), increased creatine phosphokinase (10%), increased aspartate aminotransferase (10%) and urinary tract infections (10%). The rate of grade 3 or 4 skin toxicities continued to be lower than generally observed with ERBITUX in mCRC.

“The encouraging OS data from the updated BEACON CRC safety lead-in trial clearly demonstrate the therapeutic potential of the triplet combination of BRAFTOVI, MEKTOVI and ERBITUX for the treatment patients with BRAFV600E-mutant mCRC, a notoriously difficult-to-treat cancer,” said Frédéric Duchesne, President & CEO of the Pierre Fabre Pharmaceuticals Division. “We are extremely delighted with these recent results, which are in line with our R&D strategy to target those cancers where the greatest patient need exists through an emphasis on biomarker-driven treatments.”

On 20 September 2018, the EC granted marketing authorisation for the combination of BRAFTOVI and MEKTOVI for the treatment of adult patients with unresectable or metastatic melanoma with a BRAFV600E mutation.
mutation, as detected by a validated test. The EC decision is applicable to all 28 European Union member states plus Liechtenstein, Iceland and Norway.

On 7 August 2018, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to BRAFTOVI, in combination with MEKTOVI and ERBITUX, for the treatment of patients with BRAFV600E-mutant mCRC as detected by an FDA-approved test, after failure of one to two prior lines of therapy for metastatic disease.

The triplet combination of BRAFTOVI, MEKTOVI and ERBITUX for the treatment of patients with BRAFV600E-mutant mCRC is investigational and not approved by the EC.

About Colorectal Cancer

Worldwide, colorectal cancer is the third most common type of cancer in men and the second most common in women, with approximately 1.4 million new diagnoses in 2012. Globally in 2012, approximately 694,000 deaths were attributed to colorectal cancer. In the US alone, an estimated 140,250 patients will be diagnosed with cancer of the colon or rectum in 2018, and approximately 50,000 are estimated to die of their disease. BRAF mutations are estimated to occur in 10% to 15% of patients with mCRC and represent a poor prognosis for these patients. The V600 mutation is the most common BRAF mutation and the risk of mortality in CRC patients with the BRAFV600E mutation is more than two times higher than for those with wild-type BRAF. Several irinotecan and cetuximab-containing regimens, similar to the BEACON CRC control arm, have established historical published benchmarks in BRAFV600E-mutant mCRC patients, whose disease has progressed after one or two prior lines of therapy. These benchmarks include ORR of 4% to 8%, mPFS of 2 to 3 months and median OS of 4 to 6 months.

About BEACON CRC

BEACON CRC is a randomised, open-label, global trial evaluating the efficacy and safety of BRAFTOVI, MEKTOVI and ERBITUX in patients with BRAFV600E-mutant mCRC whose disease has progressed after one or two prior regimens. BEACON CRC is the first and only Phase 3 trial designed to test a BRAF/MEK combination targeted therapy in BRAFV600E-mutant mCRC. Thirty patients were treated in the safety lead-in and received the triplet combination (BRAFTOVI 300 mg daily, MEKTOVI 45 mg twice daily and ERBITUX per label). Of the 30 patients, 29 had a BRAFV600 mutation. MSI-H, resulting from defective DNA mismatch repair, was detected in only 1 patient. As previously announced, the triplet combination demonstrated good tolerability, supporting initiation of the randomised portion of the trial. The randomised portion of the BEACON CRC trial is designed to assess the efficacy of BRAFTOVI in combination with ERBITUX with or without MEKTOVI compared with ERBITUX and irinotecan-based therapy. Approximately 615 patients are expected to be randomised 1:1:1 to receive triplet combination, doublet combination (BRAFTOVI and ERBITUX) or the control arm (irinotecan-based therapy and ERBITUX). The study has been amended to include an interim analysis of endpoints including ORR. The primary overall survival endpoint is a comparison of the triplet combination to the control arm. Secondary endpoints address efficacy of the doublet combination compared with the control arm, and the triplet combination compared with the doublet therapy. Other secondary endpoints include PFS, duration of response, safety and tolerability. Health-related quality of life data will also be assessed. The trial is being conducted at over 200 investigational sites in North America, South America, Europe and the Asia-Pacific region. Trial recruitment was completed in 2018. The BEACON CRC trial is being conducted with support from Ono Pharmaceutical Co., Pierre Fabre and Merck KGaA, Darmstadt, Germany (support is for sites outside of North America).

About BRAFTOVI (encorafenib) and MEKTOVI (binimetinib)

BRAFTOVI (encorafenib) is an oral small-molecule BRAF kinase inhibitor and MEKTOVI (binimetinib) is an oral small-molecule MEK inhibitor that targets key enzymes in the MAPK signalling pathway (RAS-RAF-MEK-ERK). Inappropriate activation of proteins in this pathway has been shown to occur in many cancers, including melanoma, colorectal cancer, non-small-cell lung cancer and others.

In Europe, the combination is approved for adult patients with unresectable or metastatic melanoma with a BRAFV600 mutation, as detected by a validated test. On 27 June 2018, Pierre Fabre’s partner Array BioPharma, which has exclusive rights for these medicines in the United States (US), announced that the combination of BRAFTOVI and MEKTOVI was approved by the US Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma with a BRAFV600E or
**BRAF**V600K mutation, as detected by an FDA-approved test.\(^{18,19}\) BRAFTOVI is not indicated for treatment of patients with wild-type **BRAF** melanoma. BRAFTOVI and MEKTOVI have also received regulatory approval in Japan. The Swiss Medicines Agency (Swissmedic) is currently reviewing the Marketing Authorization Applications for BRAFTOVI and MEKTOVI submitted by Pierre Fabre.

**About Pierre Fabre**

With a portfolio representing a continuum of activities spanning from prescription drugs and consumer healthcare products to dermo-cosmetics, Pierre Fabre is the 2nd largest dermo-cosmetics laboratory in the world, the 2nd largest private French pharmaceutical group and the market leader in France for products sold over the counter in pharmacies. Its portfolio includes several global brands and franchises, which include Eau Thermale Avène, Klorane, Ducray, René Furterer, A-Derma, Galénic, Elancyl, Naturactive, Pierre Fabre Health Care, Pierre Fabre Oral Care, Pierre Fabre Dermatologie and Pierre Fabre Oncologie.

In 2017, Pierre Fabre generated 2,318 million euros in revenues, of which 62% came from its international business and 61% from its dermo-cosmetics division. Pierre Fabre, which has always been headquartered in the South-West of France, counts about 13,500 employees worldwide, owns subsidiaries and offices in 47 countries and enjoys distribution agreements in over 130 countries. In 2017, Pierre Fabre dedicated ca. 175 million euros to R&D efforts, split between oncology, central nervous system, consumer healthcare, dermatology and dermo-cosmetics.

Pierre Fabre is 86%-owned by the Pierre Fabre Foundation, a government-recognised public-interest foundation, and secondarily by its own employees through an international employee stock ownership plan.

The independent French certification group AFNOR audited in 2015 Pierre Fabre for its corporate social responsibility policy at the "exemplary" level, according to the ISO 26000 standard for CSR.

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**References**

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