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First International Randomized Study in Malignant Progressive Pheochromocytoma and Paragangliomas (FIRSTMAPPP): An academic double-blind trial investigating sunitinib

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Background

Malignant pheochromocytoma and paraganglioma (MPP) is a very rare cancer (annual incidence < 1 per million). Here, we report the first academic randomized double-blind phase II study results assessing Sunitinib efficacy compared to placebo.

Methods

Patients with progressive MPP with 1.5year according to (RECIST) were randomized 1/1 for Sunitinib therapy 37.5 mg/d or Placebo and stratified for SDHB status and line of treatment. Primary endpoint: progression-free survival (PFS) at 12 months according to real-time central review (RECIST 1.1), analyzed every 3 months (ITT). Key secondary endpoints: ORR, response (delay, duration), overall PFS, overall survival, safety (NCI CTCAE v.4). On the basis of a two-step Simon model (alpha 10%, power 90%), we aimed for 74 patients, assuming a PFS improvement at 12 months from 20 to 40%. 11 or more patients out of 37 with no progression at 12 months were expected to conclude that Sunitinib is effective. The placebo group served as an internal control to validate the hypothesis of the Simon design with a 12-m PFS equal to 20%. An IDMC was set up to review the accrual, toxicity, and interim analysis.

Results

78 patients were enrolled (median age, 53 yrs; 59% men). Main characteristics: adrenal/PGL primaries, each 50%; 32% SDHx inherited, 71% secreting, distant lymph node/bone/lung/liver mets, 73%/65%/51%/49%; 60% prior therapy. 39 patients were randomized in each arm. The primary endpoint was met: PFS at 12 months was 35.9% (Sunitinib) vs. 18.9% (Placebo; within the 90%CI confirming the Simon design conclusion). Median PFS was 8.9 (95CI: 5.5-12.7) vs. 3.6 months (3.1-6.1). Reasons for drug discontinuation were AE/tumor progression in 14%/64% (Sunitinib) and 0%/86% (Placebo). 54% patients with Sunitinib vs. 49% with Placebo experienced SAE; most frequent grade 3-4 were asthenia/fatigue (18% vs. 3%) and hypertension (10% vs. 6%).One death occurred in each arm.

Conclusions

After 8 years of enrolment, this first randomized study in the field of MPP provides the highest level of evidence ever reached in this very rare cancer. Sunitinib becomes the first-line option in patients with progressive MPP.

Clinical trial identification

NCT01371201.

Legal entity responsible for the study

Gustave Roussy.

Funding

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Disclosure

E. Baudin: Financial Interests, Personal and Institutional, Advisory Board, research grant and principal investigator: Novartis; Financial Interests, Personal and Institutional, Advisory Board, and research grant: HRA; Financial Interests, Personal and Institutional, Project Lead, Principal investigation: Ipsen; Financial Interests, Personal and Institutional, Advisory Board, research grant (drug supply for trial): AAA; Financial Interests, Personal and Institutional, Research Grant, drug supply for trial: Pfizer; Financial Interests, Personal and Institutional, Advisory Board: Hutchinson Pharma. All other authors have declared no conflicts of interest.