1333TiP CAPTEM or FOLFIRI as second-line therapy in neuroendocrine carcinomas and exploratory analysis of predictive role of PET imaging and biological markers (SENECA study)

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Background: Patients with metastatic or locally advanced, non-resectable, grade 3 neuroendocrine carcinoma (NEC) of the lung or gastroenteropancreatic system (GEP NEC) are usually treated with first-line platinum-based chemotherapy. There is no standard second-line treatment when progression occurs. Different second-line chemotherapy combinations have been evaluated retrospectively, but with poor results. FOLFIRI was evaluated in a retrospective monocentric study, showing a disease control rate (DCR) of 62%. In another retrospective study, temozolomide-based chemotherapy obtained a DCR of 71%. There is growing evidence that the current grading system for NECs has a number of inconsistencies, highlighting the need for more accurate biomarkers to better understand the natural history of this very aggressive disease.

Trial design: SENECA study is a randomized, non-comparative, multicenter phase II trial designed to evaluate the efficacy and safety of FOLFIRI or capecitabine plus temozolomide (CAPTEM) after failure of first-line treatment in lung and GEP NECs. Primary aim is to assess DCR of the regimens, with safety as a co-primary. Secondary aims are the evaluation of overall survival (OS), progression-free survival (PFS) and quality of life. It is also planned to assess Gallium-PET/CT and tissue and circulating biomarkers as prognostic and predictive factors. Eligibility criteria are age $\geq$18 years, metastatic or locally advanced, non-resectable, lung or GEP NEC, and documented evidence of progressive disease during or after first-line platinum-based chemotherapy (cisplatin/carboplatin and etoposide; FOLFOX4 or CAPOX). Each patient is randomized to receive FOLFIRI or CAPTEM, considering Ki-67 (21-55 % vs $>$ 55%) and primary tumor site (lung vs. GEP) as stratification factors. The randomized study design allows for two active treatments to be evaluated in a comparable patient population. Analysis will be performed for each regimen separately. 56 patients will be enrolled in each arm of the study (total of 112 patients). Sixteen centers are taking part in the study and recruitment is ongoing. The first patient was randomized on March 6, 2017.

Clinical trial identification: IRST100.22

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