C-22

Phase 2 Trial of Lu-177-DOTATATE in Metastatic or Inoperable Pheochromocytoma/Paraganglioma: Interim Analysis Results

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BACKGROUND

Pheochromocytoma/Paraganglioma (PPGL) are rare neuroendocrine tumors that expresses somatostatin receptors (SSTR) and can be treated with radiolabeled somatostatin analogues such as Lu-177-DOTATATE. This study is the first prospective study to examine the safety and efficacy of Lu-177-DOTATATE in the treatment of metastatic or inoperable PPGL in a phase 2 clinical trial setting, and results from a planned interim analysis are presented.

METHODS

This is an open-label, single-arm phase 2 study being conducted at the National Institutes of Health to evaluate the efficacy and safety of Lu-177-DOTATATE in patients with PPGL (NCT03206060). Patients are divided into 2 cohorts (SDHx or apparent sporadic). The primary endpoint is Progression Free Surival (PFS) rate at 6 months after starting treatment. Eligibility includes having SSTR+ tumor, histologically-confirmed diagnosis, and evidence of progression by RECIST 1.1 within 12 months of study enrollment. Anatomic scans as well as both F-18-FDG and Ga-68-DOTATATE PET scans are acquired at baseline, 4 weeks after the second cycle of Lu-177-DOTATATE, 8 weeks after the fourth cycle, and then every 3 months (anatomic scans) to 6 months (PET scans). The study opened for enrollment in August 2017 and is conducted using a Simon two-stage optimal design. An interim analysis is built-in when each of the cohort reaches 18 participants, and the study will continue onto the second stage if 11 or more out of 18 patients meet the primary endpoint. Full accrual for the study will be 90 patients, 45 per cohort.

RESULTS

36 patients (18 per cohort) were evaluated for safety and efficacy. For the sporadic cohort, 16 patients achieved stable disease (SD) while 2 had partial response (PR) by RECIST 1.1 at 6 months. In the SDHx cohort, 10 patients had SD, 3 patients had PR, and 5 patients had progression at 6 months. In conglomerate 31/36 (86%) met the primary study end point, and the median PFS is 21.0 months. Rates of adverse and serious adverse events (SAE) attributable to Lu-177-DOTATATE were similar to those previously reported in other studies such as NETTER-1, with hematologic SAEs being the most common.

Catecholamine release syndrome (flushing, hypertension, tachycardia, constipation) is observable starting as early as during Lu-177-DOTATATE infusion and persisting for days to weeks after treatment, with 10% incidence of grade 3+ events. Peak risk appears to be within 24-48 hours of infusion and is likely related to significant surge in serum catecholamine levels (median increase = 60%, max increase 10x baseline) in this time frame. In select high risk patients, elective ICU intervention is advisable. Despite the acute increases and associated symptoms, however, catecholamine levels in most patients return to baseline by Day 28.

CONCLUSIONS

Interim analysis results demonstrate that Lu-177-DOTATATE has high efficacy and good safety profile when used to treat metastatic PPGL, especially in patients with no associated genetic mutations. While catecholamine crisis related to surging serum catecholamine levels can be observed, levels usually return to near baseline and patients can be safety treated.

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