INTRODUCTION

Review question / Objective: The aim of this systematic review is to identify and summarize the use of [177Lu]Lu-DOTA-TATE as a treatment for neuroendocrine tumors (NETs) of non-gastroenteropancreatic (GEP) origin to understand evolving clinical practice.

Rationale: There is currently a high unmet medical need for bronchial NETs, thymic NETs, NETs of unknown origin, and pheochromocytoma/paraganglioma.

Protocol for a systematic literature review of efficacy and safety of [177Lu]Lu-DOTA-TATE in adults with inoperable or metastatic somatostatin receptor-positive pheochromocytomas/paragangliomas, bronchial and unknown origin neuroendocrine tumors, and medullary thyroid carcinoma

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(PPGL), with limited approved therapeutic treatment options. [177Lu]Lu-DOTA-TATE is the first radiolabeled somatostatin analog approved for the treatment of somatostatin-receptor (SSTR)-positive GEP-NETs in adults. There are reports in the literature of [177Lu]Lu-DOTA-TATE being used to treat NETs of non-GEP origin. To further understand this evolving clinical practice and describe the use of [177Lu]Lu-DOTA-TATE as a treatment for NETs of non-GEP origin, we performed a systematic literature review to identify and summarize published evidence for the efficacy and safety of [177Lu]Lu-DOTA-TATE in adult patients with inoperable or advanced SSTR-positive PPGL, thymic NET, bronchial NET, unknown primary NET, or medullary thyroid carcinoma (MTC).

**Condition being studied:** Adults (as defined by the authors) with any of the following inoperable or metastatic SSTR-positive NETs: PPGL, thymic NET, bronchial NET, NET of unknown primary origin, or MTC. Efficacy and safety outcomes were analyzed.

**METHODS**

**Search strategy:** The search strategy included both Medical Subject Headings terms and free-text terms, and included variants of the terminology for the NETs, such as cancer, carcinoma, carcinoid, tumor, tumour, and neoplasm as well as variants for LUTATHERA®, such as [177Lu]Lu-DOTA-TATE, lutetium Lu 177 dotate, lutetium (177Lu) oxodotreotide, lutetium ox-odotreotide Lu-177, (177Lu-DOTAOTyr3)octreotate, DOTATATE-177Lu, 177Lu-DOTATATE, and (177lutetium-DOTA(O)Tyr3)octreotate.

**Participant or population:** Adults with inoperable or metastatic SSTR-positive PPGL, thymic NET, bronchial NET, NET of unknown primary origin, or MTC.

**Intervention:** [177Lu]Lu-DOTA-TATE as a single agent.

**Comparator:** Not applicable.

**Study designs to be included:** Randomized controlled trials, non-randomized controlled trials, quasi-experimental studies, prospective and retrospective cohort studies, and case series (if the patients were analyzed or analyzable as a group) were included. Studies were excluded where relevant outcome data (response rates, survival time, or safety) were not available for the specific NET types of interest or the specific radioligand treatment of interest. Individual case reports were excluded, as were case series that only reported relevant tumor types in a single patient.

**Eligibility criteria:** Search included studies published up to May 13, 2021. No geographic, language, or age restrictions were applied in the search, but only English-language publications reporting studies in adults were selected for inclusion. Studies that included multiple NET types were only included if the results and baseline characteristics were provided for individual NETs. Studies that included both pediatric and adult patients were retained, if it was possible to extract data for adults only.

**Information sources:** PubMed. In addition, the reference lists of reviews were examined to identify additional studies that had not been detected by the initial search strategy.

**Main outcome(s):** Progression-free survival, time to tumor progression, disease control rate, response rates, overall survival, mortality, and adverse events by organ and type.

**Data management:** Not applicable as only aggregate data as reported in the original publications were used.

**Quality assessment / Risk of bias analysis:** The selection process was performed by two reviewers independently and any differences resolved by consensus.

**Strategy of data synthesis:** Qualitative and quantitative data were extracted from the
studies and descriptive analyses performed.

Subgroup analysis: Efficacy data are presented by NET subtype and safety data are summarized for all NETs analyzed.

Sensitivity analysis: Results are presented as per original publications without any sensitivity analysis.

Language restriction: No language restrictions were applied in the search, but only English-language publications reporting eligible studies were selected for inclusion.

Country(ies) involved: Switzerland, USA.

Keywords: Pheochromocytomas; paragangliomas; bronchial neuroendocrine tumors; unknown origin neuroendocrine tumors; medullary thyroid carcinoma; [177Lu]Lu-DOTA-TATE.

Dissemination plans: Publication in peer-reviewed journal.

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Conflicts of interest: M.H., O.B., I.F., and G.K. are employees of Advanced Accelerator Applications, a Novartis Company. A.C. is an employee of Novartis Pharma AG and B.D.P. is an employee of Novartis Pharmaceuticals. Novartis stock ownership is declared by M.H., A.C., I.F., and B.D.P.