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EDITORIAL

Rethinking treatment for *RET*-altered lung and thyroid cancers: selpercatinib approval by the EMA

On 10 December 2020 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended granting a conditional marketing authorisation for selpercatinib (Retevmo) for the treatment of cancers that display a rearranged during transfection (*RET*) gene alterations: *RET* fusion-positive non-small-cell lung cancer (NSCLC), *RET* fusion-positive thyroid cancer and *RET*-mutant medullary thyroid cancer (MTC).[1]

Based on the full indication, Retevmo as monotherapy is indicated for the treatment of patients with:

- advanced *RET* fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
- advanced *RET* fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib
- adults and adolescents 12 years and older with advanced *RET*-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib

The CHMP recommendation for conditional marketing authorisation is the most recent achievement of selpercatinib which was already approved in the United States on 8 May 2020 for the same conditions.[2]

The present CHMP recommendation is based on the analysis of the open-label phase I/II LIBRETTO-001 trial (NCT03157128). In the initial phase I part of the study adolescent and adult patients with any type of solid tumour harbouring an activating *RET* alteration (e.g. fusions or mutations) were eligible for inclusion. Patients were treated with oral selpercatinib in 28-day cycles with the maximal tolerated dose and recommended dose for phase II trials established as 160 mg twice daily.[3] Phase II enrolled patients to one of six cohorts based on tumour type, *RET* alteration and prior therapies. The primary study endpoint was an objective response (a complete or partial response) as determined by an independent review committee. Secondary endpoints included the duration of response, progression-free survival and safety.

The cohort of patients with advanced *RET* fusion-positive NSCLC included patients with advanced or metastatic disease who had progressed on platinum-based chemotherapy [58 of whom had also received prior anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy] and patients with advanced or metastatic NSCLC without prior systemic therapy in separate cohorts.

Selpercatinib demonstrated a substantial antitumour activity, which was long-lasting and observed regardless of previous exposure to platinum-based chemotherapy or immunotherapy or multikinase inhibitors. In the first 105 enrolled patients with *RET* fusion-positive NSCLC treated previously, the percentage of the objective response was 64% with a median duration of response of 17.5 months. Importantly, an objective intracranial response was noted in patients with measurable central nervous system (CNS) metastasis, which was consistent with the efficient brain penetration of selpercatinib.[4]

RET-altered thyroid cancer patients are candidate to systemic therapy in advanced stages. This cohort of patients included patients with *RET*-mutated MTC previously untreated or treated with vandetanib and/or cabozantinib, and patients with previously treated *RET* fusion-positive thyroid cancer.

As in the NSCLC cohort, selpercatinib showed a significant and durable activity in patients with *RET*-mutated MTC with and without previous vandetanib or cabozantinib treatment (objective response 69%; 86% of responses ongoing at 1 year) and in patients with *RET* fusion-positive thyroid cancers treated previously (objective response 79%; 71% of responses ongoing at 1 year). With the limitation of low numbers, efficacy seemed to be confirmed across all *RET* alterations and histologic types of thyroid cancers.[5]

The long-lasting activity of selpercatinib was accompanied by a manageable side-effect profile. The most common grade 3 or 4 adverse events were hypertension (21% of patients), increased serum alanine aminotransferase levels (11%), increased serum aspartate aminotransferase levels (9%), hyponatremia (8%) and diarrhoea (6%). Overall, 30% of patients required a dose reduction because of treatment-related adverse events, and 2% discontinued selpercatinib because of treatment-related adverse events.[3-5]

Several studies have evaluated the activity of different multikinase inhibitors currently used for other indications in *RET* fusion-positive NSCLC (including cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib and regorafenib) and in *RET*-altered thyroid cancers (vandetanib and cabozantinib). Collectively, multikinase inhibitors have been associated with lower activity than that usually observed with targeted therapies in other molecularly selected subgroups with objective response

rates ranging from 16% to 47% and median progression-free survival of 4.54-7.3 months evidencing a differential activity based on RET fusion variants and being associated with substantial treatment-related toxicity.[6-12]

The development of novel RET-selective inhibitors represents a major step forward for the treatment of these group of patients. Another selective RET inhibitor under evaluation by the EMA is pralsetinib (BLU-667),[13] which has recently received the FDA approval for *RET* fusion-positive NSCLC (September 2020) and *RET*-altered thyroid cancer (December 2020).

Selpercatinib represents, so far, the first RET-selective inhibitor granted approval in Europe. Its impressive activity in advanced *RET* fusion-positive NSCLCs and thyroid cancers, regardless of *RET* fusion variants and CNS involvement, and its efficacy against most of the gatekeeper mutations, in addition to the better safety profile, make this selective inhibitor a new valid option for many European patients. To this end, implementation of effective screening approaches in patients with NSCLC and thyroid cancer to identify underlying *RET* fusions or *RET* mutations will be essential for the use of this highly selective *RET* inhibitor.

RET abnormalities will now join other genomic alterations such as *NTRK* fusions, tumour mutational burden and deficient mismatch-repair genes across cancers and *ALK, BRAF, EGFR, MET* and *ROS1* alterations in NSCLC that warrant molecular screening strategies.

Given these promising results, to provide comprehensive clinical data, further studies with a phase III clinical trial design are ongoing for this treatment option. The randomised phase III LIBRETTO-431 (NCT04194944) and LIBRETTO-531 (NCT04211337) trials are evaluating the efficacy of selpercatinib in patients with *RET* fusion-positive NSCLC and treatment-naïve *RET*-mutant MTC, respectively. The phase II LIBRETTO-321 trial (NCT04280081) is underway in China evaluating the efficacy of selpercatinib in patients with advanced solid tumours including *RET* fusion-positive solid tumours, MTC and other tumours with RET activation. LIBRETTO-121 (NCT03899792) is an ongoing multicentre phase I/II dose escalation multicentre trial in patients 6 months to 21 years of age with advanced, RET-altered solid and CNS tumours.

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