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[C2H2113] Summary of cost-effectiveness evaluation of selpercatinib (Retevmo®)

1. Indications

- locally advanced or metastatic non-small cell lung cancer (NSCLC) with a RET gene fusion
- advanced or metastatic thyroid cancer (TC) with a RET gene fusion
- advanced or metastatic medullary thyroid cancer (MTC) with a RET mutation

2. Price of the drug

Selpercatinib has been reimbursed since November 2021 at JPY 3,680 for 40 mg and JPY 6,984.5 for 80 mg (as of August 2023). The prices are calculated based on the similar efficacy comparison method, with a usefulness premium of 5%. This product is designated as an H1 cost-effectiveness evaluation item.

3. Scope of cost-effectiveness evaluation

The scope of evaluation agreed upon at the first session of the Expert Committee of Cost-Effectiveness Evaluation (ECCEE) is described below. This product is used to treat NSCLC with a RET gene fusion, TC with a RET gene fusion, and MTC with a RET mutation. However, MTC with a RET mutation is out of the scope because the number of patients with MTC and the proportion of the patients having MTC with a RET mutation in the overall patients treated with selpercatinib are limited.

Population	【NSCLC】 NSCLC with a RET gene fusion 【TC】 Adults with advanced or metastatic TC with a RET gene fusion

Comparator	【NSCLC】 Platinum*+pemetrexed+pembrolizumab *The less expensive of carboplatin and cisplatin 【TC】 Lenvatinib

4. Evaluation of additional benefits

【NSCLC】The manufacturer estimated the difference in the efficacy between selpercatinib and platinum+pemetrexed+pembrolizumab using the network meta-analysis which utilized the results from a comparison based on the propensity score matching between individual participant data (IPD) from LIBRETTO-001, a single-arm trial for selpercatinib, and IPD from KEYNOTE-189, a randomized controlled trial for pembrolizumab. The result suggested that selpercatinib was more effective than the comparator regarding overall survival and progression-free survival, and thereafter, the manufacturer insisted on the additional benefits of selpercatinib over the comparator in this population. The academic group performed the network meta-analysis using the latest data from KEYNOTE-189 and obtained results as below table. The third ECCEE session concluded that the results of the academic group were more appropriate. Based on the discussion, selpercatinib has additional benefits for this population. However, it should be noted that this conclusion is accompanied with a high uncertainty as only single-arm trial data were available for selpercatinib during this evaluation process. An ongoing randomized controlled trial (LIBRETTO-431), which compares selpercatinib and platinum+pemetrexed+pembrolizumab, will provide important information for more robust evaluation.

Endpoint	Hazard ratio [95% confidence interval] (ref, comparator)
Progression-free survival	0.33 [0.16 to 0.66]
Overall survival	0.40 [0.22 to 0.71]

【TC】The manufacturer performed the naïve indirect comparison using IPD from LIBRETTO-001, a single-arm trial for selpercatinib, and pseudo-IPD from SELECT, a randomized controlled trial for lenvatinib. The result suggested that

selpercatinib was more effective than the comparator regarding overall survival and progression-free survival, and thereafter, the manufacturer insisted on the additional benefits of selpercatinib over the comparator in this population. The academic group performed the naïve indirect comparison using the latest data from SELECT and confirmed results similar to those by the manufacturer. The third ECCEE session concluded that the results of the academic group were more appropriate. Based on the discussion, selpercatinib has additional benefits for this population. However, it should be noted that this conclusion is accompanied with a high uncertainty as only single-arm trial data were available for selpercatinib during this evaluation process.

5. Results of the cost-effectiveness analysis

The manufacturer performed the cost-effectiveness analysis using the partitioned survival model which consisted of three health statuses, "progression-free survival," "survival after progression," and "death" in both populations. The manufacturer used the data in the evaluation of additional benefits for calculating transition probability. The academic group recalculated the transition probability using the latest data in analogy with the process in the evaluation of additional benefits. Moreover, the academic group pointed out that there were issues in the data for quality of life and that there were several minor errors in the analysis. The ECCEE accepted the following results.

Population	Comparator	ICER (JPY/QALY)
NSCLC with a RET gene fusion	Cisplatin+pemetrexed +pembrolizumab	6,996,198
Adults with advanced or metastatic TC with a RET gene fusion	Lenvatinib	9,295,124