Report KISPLYX® lenvatinib - RCC

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: lenvatinib **Brand Name:** Kisplyx **Originator/licensee:** Eisai GmbH **Classification:** NI **ATC code:** L01EX08 **Orphan Status:** **Eu:** No **Us:** - **Mechanism of action:** Lenvatinib is a RTK inhibitor that selectively inhibits the activities of VEGF receptor kinase VEGFR1, VEGFR2 and VEGFR3, in addition to other RTKs related to proangiogenic and oncogenic agents, including FGF receptors FGFR1, 2, 3, 4, PDGFRα, KIT and RET [1].	**Authorized Indication:** **EMA:** lenvatinib is indicated for the treatment of adult pts with advanced RCC in combination with pembrolizumab, as first-line treatment [2]. **FDA:** lenvatinib is indicated, in combination with pembrolizumab, for the first line treatment of adult pts with advanced RCC.[1] **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 14/10/2021 **FDA M.A. date:** 10/08/2021 **EU Speed Approval Pathway:** Yes **FDA Speed Approval Pathway:** - --- **ABBREVIATIONS:** **AE:** Adverse Events **CHMP:** Commettee for Medicinal Products for Human Use **FGF:** fibroblast growth factor **FGFR**: Fibroblast Growth Factor Receptor **HR:** Hazard Ratio **KIT:** stem cell factor receptor **IMDC**: International Metastatic Renal Cell Carcinoma Database Consortium **INF-α** : Interferon-α **IRC:** Independent Radiologic Review **MA:** Marketing Authorization **MSKCC**: Memorial Sloan Kettering Cancer Center **OS**: Overall Survival **p**: p-value **PDGFRα**: Platelet Derived Growth Factor Receptor Alpha **PFS**: Progression free survival **PD-1**: Programmed Cell Death-1 **PD-L1**: Programmed Cell Death-Ligand1 **PO**: Positive Opinion **pts**: patients **RCC**: Renal Cell Carcinoma **RECIST v1.1**: Response Evaluation Criteria in Solid Tumors version 1.1. **RET:** rearranged during transfection protein receptor **RTK**: Tyrosine Kinase Receptor **SAE**: serious AE **VEGF**: Vascular Endothelial Growth Factor **VEGFR**: Vascular Endothelial Growth Factor Receptor **vs.:** versus	**Summary of clinical EFFICACY:** **KEYNOTE-581 (NCT02811861)** is a multicenter, open-label, randomized trial conducted in adult pts (n=1069) with advanced RCC and no previous systemic therapy. Pts were enrolled regardless of PD-L1 tumor expression status. Pts were randomized to receive: • n=355, pembrolizumab 200 mg IV every 3 weeks up to 24 months + lenvatinib 20 mg orally daily • n=357, lenvatinib 18 mg orally daily + everolimus 5 mg orally daily • n=357, sunitinib 50 mg orally daily for 4 weeks then off treatment for 2 weeks Treatment continued until unacceptable toxicity or disease progression. The primary outcomes were PFS, as assessed by IRC according to RECIST v1.1, and OS. Median PFS was 23.9 months in the lenvatinib + pembrolizumab arm vs. 9.2 months in the sunitinib arm (HR: 0.39; 95% CI: 0.32 to 0.49; p<0.001); median PFS was 14.7 months in the lenvatinib +everolimus arm vs. 9.2 months in the sunitinib group (HR: 0.65; 95% CI, 0.53 to 0.80; p<0.001). Survival rate at 24 months was: 79.2% in the lenvatinib+pembrolizumab arm vs. 66.1% in the lenvatinib+everolimus arm vs. 70.4% in the sunitinib arm. OS was longer with lenvatinib + pembrolizumab than with sunitinib (HR: 0.66; 95% CI: 0.49 to 0.88; p = 0.005). OS with lenvatinib + everolimus was longer than sunitinib (HR: 1.15; 95% CI: 0.88 to 1.50; p = 0.30) [3-5]. **Summary of clinical SAFETY:** Almost all pts in each arm experienced AEs (99.7% in both lenvatinib+pembrolizumab arm and in lenvatinib+everolimus arm and 98.5% in sunitinib arm). Serious AEs occurred in 50.57%of the pts in the lenvatinib+pembrolizumab arm, in 46.20% of the subjects in the lenvatinib+everolimus arm and 33.24% of the pts in the sunitinib arm. SAEs included in the three arms, respectively: hypertension (2.27%, 0.56%, 0.59%), acute kidney injury (2.27%, 2.82%, 1.47%), adrenal insufficiency (2%, 0%, 0%) and myocardial infarction (1.70%, 0.85%, 0.29%). The most common non-serious in the three groups were, respectively: diarrhea (61.4%, 66.5%, 49.4%), hypertension (55.4%, 45.6%, 41.5%), hypothyroidism (47.2%, 26. 8%, 26.5%) [3-5]. **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** Yes **Discontinued studies (for the same indication):** No --- **References:** 1. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-5 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s102lbl.pdf 4. https://clinicaltrials.gov/ct2/show/results/NCT02811861?term=NCT02811861&draw=2&rank=1 5. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021;384(14):1289-1300. doi:10.1056/NEJMoa2035716 6. https://gallery.farmadati.it/Home.aspx 7. https://www.aiom.it/wp-content/uploads/2020/10/2020_Numeri_Cancro-operatori_web.pdf 8. https://www.aiom.it/wp-content/uploads/2021/04/2020_LG_AIOM_Rene.pdf 9.https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=Pembrolizumab&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= 10.https://clinicaltrials.gov/ct2/results?cond=Renal+Cell+Carcinoma&term=&cntry=&state=&city=&dist=&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&type=Intr&phase=2	**Cost of therapy:** In Italy, the cost of lenvatinib is 1,692.07 € for 30 capsules (10 mg) (ex-factory price) [6] One-month treatment costs 3,384.14 € (the recommended dose of lenvatinib is 20 mg orally once daily) [1]. **Epidemiology:** In Italy, in 2020 estimated new diagnosis of RCC were 13,521. In about 25-30% of pts it occurs in the loco-regionally advanced and/or metastatic phase [7]. --- **POSSIBLE PLACE IN THERAPY** Currently, in Italy the available therapeutic options are the following: sunitinib; pazopanib; pembrolizumab + axitinib; cabozantinib (indicated in pts with intermediate-unfavorable risk according to classification IMDC, only); bevacizumab + IFN-α and temsirolimus (with limited indication to pts with unfavorable risk according to MSKCC classification, only) [8]. **OTHER INDICATIONS IN DEVELOPMENT:** advanced hepatocellular carcinoma, hepatocellular carcinoma, differentiated thyroid cancer, head and neck squamous cell carcinoma, malignant melanoma, non-small cell lung cancer, urothelial carcinoma, endometrial neoplasms and other [9] **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:** - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** sorafenib, Pazopanib, Tivozanib+Nivolumab, Nivolumab+Ipilimumab, bempegaldesleukin, Atezolizumab, Sorafenib+Pazopanib, Dovitinib [10] *Service reorganization No *Possible off label use Yes

Issued on: