TEST

Different patients. Multiple tumor types [1,2,3]

- SALIVARY GLAND CANCERS[a]
- PEDIATRIC CANCERS[b]
- GI CANCERS[c]
- CNS CANCERS[d]
- THYROID
- LUNG

INDEX

CNS central nervous system
GI gastrointestinal
[a] Mammary analogue secretory carcinoma (masc).
[b] Infantile fibrosarcoma (ifs) and soft tissue sarcoma.
[c] Colorectal, biliary, pancreatic, and appendiceal.
[d] Glioma and glioblastoma.

VITRAKVI® is for ADULT AND PEDIATRIC PATIENTS with solid tumors where an *NTRK* gene fusion has been identified

TREAT

Favorable long-term safety profile has been demonstrated

- AE — majority of AEs were **Grade 1 or 2** in severity [4]
- 2% — **discontinuation rate** due to treatment-related AEs [4]
- 8% — **of patients had a dose reduction** due to AEs [4]

Date cut-off: Feb 18, 2019

TRANSFORM

Fusion Positive. Positive Result.

- 1.8 — **months median time to response** (range: 0.9 – 6.6 months) [5]
- 78% — **Objective response rate:** (95% CI: 71, 84) [5]
- **Survival endpoints at 12 months:** 69% PFS and 90% OS [5]
- 36.8 — **months median PFS** (95% CI: 25.7, NE) with a median follow-up of 13.8 months [5]

Date cut-off: July 15, 2019

VITRAKVI® is available as capsules and oral solutions for both adults and children

Vitrakvi Abbreviated Prescribing Information.
Larotrectinib sulphate capsules 25mg and 100mg, oral solution 20mg/mL. **Indications.** Treatment of adult and pediatric patients with solid tumors that have a Neurotrophic Tyrosine Receptor Kinase (*NTRK*) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options. Confirm *NTRK* gene fusion in a tumor specimen using a validated test before treatment. **Dosage and administration.** Adults: 100 mg orally, twice daily (total dose of 200 mg) until no clinical benefit from therapy or unacceptable toxicity. Pediatrics: Based on body surface area (BSA). For 1 month to 18 years, 100 mg/m^2 orally, twice daily with a maximum of 100 mg per dose (maximum total dose of 200 mg) until no clinical benefit from therapy or unacceptable toxicity. Geriatrics: No dose adjustment is necessary. Patients with Hepatic Impairment: Reduce starting dose of VITRAKVI by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment for patients with mild (Child-Pugh A) hepatic impairment. Patients with Renal Impairment: No dose adjustment is required. **Dose Modifications.** For an adverse reaction ≥ Grade 3, consider interrupting dosing of VITRAKVI and reevaluating regularly at least weekly. VITRAKVI can be withheld for up to 4 weeks to allow recovery to Grade 1 or back to baseline and resumed at the next dosage modification. Permanently discontinue VITRAKVI if an adverse reaction does not resolve within 4 weeks of the start of withholding the dose. 1st dose modification: 75mg twice daily (adult); 75 mg/m^2 twice daily with a maximum of 75 mg per dose (pediatric); 2nd dose modification: 50mg twice daily (adult); 50 mg/m^2 twice daily with a maximum of 50 mg per dose (pediatric); 3rd dose modification: 100mg once daily (adult); 25 mg/m^2 twice daily with a maximum of 25 mg per dose (pediatric). **Contraindications.** Hypersensitivity to this drug or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. **Mechanism of action.** Larotrectinib is an orally-bioavailable, ATP-competitive, potent and highly selective Tyrosine Receptor Kinase (TRK) kinase inhibitor. Larotrectinib targets the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by *NTRK1*, *NTRK2*, and *NTRK3* genes respectively. Larotrectinib has minimal activity with off-target kinases tested. In-frame gene fusion events resulting from chromosomal rearrangements of the human genes *NTRK1*, *NTRK2*, and *NTRK3* lead to the formation of oncogenic TRK fusion proteins. These resultant novel chimeric oncogenic proteins are aberrantly expressed driving constitutive kinase activity subsequently activating downstream cell signalling pathways involved in cell proliferation and survival leading to TRK fusion cancer. Larotrectinib demonstrated potent inhibition of TRK proteins and inhibition of proliferation of cell lines containing *NTRK* gene fusions in a concentration-dependent manner. In TRK fusion-driven mouse xenograft models larotrectinib treatment induced significant tumor growth inhibition. **Warnings and precautions.** Driving and Operating Machinery: Neurologic adverse events and fatigue have very commonly been reported in patients receiving VITRAKVI and may influence the patient's ability to drive and use machines. Hepatic/Biliary/Pancreatic: Treatment-emergent adverse events (TEAEs) of alanine transaminase (ALT) increased and aspartate transaminase (AST) increased of any grade were reported in 26% of patients for each adverse event. The maximum grades observed were Grade 4 ALT increased in < 1% of patients and Grade 3 transaminase elevations in 6% of patients. Monitor for liver function including ALT and AST assessments. VITRAKVI can cause transaminase elevations. Consider baseline assessment of liver function, including transaminase levels, before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withholding, reducing, or permanently discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of the transaminase elevation. Neurologic/Psychiatric: TEAEs of any grade occurred in 65% of patients, including Grade 3 and Grade 4 adverse events in 6% and <2% of patients respectively. Grade 4 encephalopathy, brain edema, and cerebrovascular accident was reported in a single patient. Grade 3 events included dizziness, gait disturbance, paresthesia, dysarthria, syncope, hemiparesis, and loss of consciousness (1% for each). The majority (67%) of neurologic adverse events occurred within the first three months of treatment (range: 1 day to 26.7 months). Dose modification (interruption or reduction) based on neurologic toxicity of all grades occurred in 5% of patients, most commonly for dizziness (3%). Grade 3 TEAEs of delirium and mental status changes were reported in 2% and 1% of patients respectively. Withholding, reducing, or permanently discontinuing VITRAKVI dosing should be considered, depending on the severity and persistence of these symptoms. Reproduction: There may be a risk of fetal harm to a pregnant woman. Fertility: No clinical data on the effect of VITRAKVI on fertility. However, changes to the female reproductive organs in rats were observed in a repeated-dose toxicity study. **Adverse drug reactions.** The safety of VITRAKVI was evaluated in 176 patients. Overall, 98% of patients experienced at least one TEAE. The most commonly reported TEAEs (≥ 20%) were fatigue, nausea, dizziness, vomiting, anemia, ALT increased, AST increased, cough, constipation, and diarrhea. The most common serious adverse events (≥ 2%) regardless of attribution included pyrexia, diarrhea, sepsis, abdominal pain, cellulitis, dehydration, and vomiting. Grade 3 or 4 TEAEs occurred in 51% of patients. Grade 4 events included sepsis (2%), and pyrexia, neutrophil count decreased, lymphocyte count decreased, ALT increased, hypokalemia, hyponatremia, and hypoglycemia (1% for each). Grade 3 events included anemia, hypophosphatemia, fatigue, dizziness, gait disturbance, paresthesia, nausea, vomiting, constipation, myalgia and weight increased. **Drug interactions.** Larotrectinib is a substrate of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Coadministration of VITRAKVI with strong CYP3A inhibitors, P-gp and BCRP inhibitors increases larotrectinib plasma concentrations (e.g. atazanavir, clarithromycin, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, or voriconazole). If coadministration of a strong CYP3A4 inhibitor cannot be avoided, reduce the VITRAKVI dose by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inhibitor. Coadministration of VITRAKVI with strong CYP3A and P-gp inducers decreases larotrectinib plasma concentrations (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin or St John's wort). If coadministration of a strong CYP3A4 inducer cannot be avoided, double the VITRAKVI dose. After the inducer has been discontinued for 3 to 5 elimination half-lives, resume the VITRAKVI dose taken prior to initiating the CYP3A4 inducer. Please refer to full Prescribing information before prescribing. (Updated March 2020 referencing to PI revised on September 2019) MA-LAR-HK-0016-1

References:
1. VITRAKVI Hong Kong Product Information, September 2019.
2. Vaishnavi A, Le AT, Doebele RC. TRKing down an old oncogene in a new era of targeted therapy. *Cancer Discov.* 2015; 5(1): 25 -34.
3. Okimoto RA, Bivona TG. Tracking down response and resistance to TRK inhibitors. *Cancer Discov.* 2016; 6(1): 14-16.
4. Hong DS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol.* 2020;21(4):531-540.
5. McDermott R, et al. Survival benefits of larotrectinib in an integrated dataset of patients with TRK fusion cancer. Poster presented at: European Society for Medical Oncology Virtual Congress; September 17, 2020. Annals of Oncology (2020) 31 (suppl_4): S1034-S1051. 10.1016/annonc/annonc294

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VITRAKVI® (larotrectinib) 25mg/100mg CAPSULES 20mg/mL ORAL SOLUTION

TEST. TREAT. TRANSFORM.

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