BC Cancer Protocol Summary of Treatment for Locally Advanced or Metastatic Medullary Thyroid Cancer Using vanDETanib

Protocol Code  
UHNOTVAN

Tumour Group  
Head and Neck

Contact Physician  
Dr. Cheryl Ho

ELIGIBILITY:
- Patients with symptomatic or progressive unresectable, locally advanced, or metastatic medullary carcinoma of the thyroid
- Good performance status
- BC Cancer Compassionate Access Program (CAP) approval
- Registration of the prescribing physician and patients with the CAPRELSA Restricted Distribution Program (www.caprelsa.ca)

EXCLUSIONS:
- History of long QTc syndrome, or QTc interval greater than 500 ms
- Uncorrected hypokalemia, hypomagnesemia, or hypocalcemia
- Uncontrolled hypertension
- Pregnant or lactating women

TESTS:
- **Baseline**: CBC and differential, creatinine, ECG, blood pressure, CEA, calcitonin, TSH, potassium, calcium, magnesium, Bilirubin, ALT, Alkaline phosphatase
- **Prior to each cycle**: potassium, calcium, magnesium, calcitonin, blood pressure
- **At 2 to 4 weeks, 8 to 12 weeks, then every 3 months thereafter**: ECG, blood pressure, potassium, magnesium, calcium, calcitonin, CEA, and TSH levels
- If clinically indicated: ECG, CEA, TSH, Bilirubin, ALT, Alkaline phosphatase

PREMEDICATIONS:
- **NOTE**: dexamethasone, ondansetron, prochlorperazine CANNOT be used with vanDETanib due to risk of increased QTc
- metoclopramide and dimenhydrinate can be used with
- vanDETanib has low emetogenic potential. If antiemetics are needed, avoid agents with potential for interaction (see Precautions).

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>vanDETanib</td>
<td>300 mg</td>
<td>PO once daily</td>
</tr>
</tbody>
</table>

Continue until disease progression, or intolerable side effects.
DOSE MODIFICATIONS: (note: there are no dose modifications for hematology)

1. QTc Prolongation

<table>
<thead>
<tr>
<th>QTc interval</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 500 ms</td>
<td>Hold until QTc is less than 450 ms, then resume at 200 mg/day; may be reduced further to 100 mg/day</td>
</tr>
</tbody>
</table>

2. Hypertension

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCAE Grade 3 or 4</td>
<td>Hold until blood pressure is controlled; then may continue and adjust dose accordingly</td>
</tr>
<tr>
<td>Symptomatic increase greater than 20 mm Hg (diastolic) or greater than 140/90 if previously WNL</td>
<td></td>
</tr>
</tbody>
</table>

3. Renal dysfunction:

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 50</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>30 to less than 50</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Less than 30</td>
<td>Proceed with caution</td>
</tr>
</tbody>
</table>

4. vanDETanib is not recommended for use in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment, as safety and efficacy have not been established

5. Non-hematological toxicity

<table>
<thead>
<tr>
<th>CTCAE Grade</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>100%</td>
</tr>
<tr>
<td>3-4</td>
<td>Delay until less than or equal to Grade 1, then resume at 200 mg/day; may reduce dose further to 100 mg/day</td>
</tr>
</tbody>
</table>

PRECAUTIONS:

1. QT prolongation, leading to Torsade de Pointes and sudden death, has been reported. Serum potassium should be maintained in high normal range (≥ 4 mmol/L) and serum magnesium and calcium levels should be within normal limits to reduce the risk of ECG QT prolongation.
2. **Caution to avoid concomitant use of drugs that prolong QT interval.** If no alternative therapy exists, ECG monitoring of the QTc interval should be done frequently. Drugs that may affect the QT interval include amiodarone, disopyramide, procainamide, sotalol, dofetilide, chloroquine, clarithromycin, dolasetron, granisetron, ondansetron, haloperidol, methadone, MOXifloxacin, pimozide amongst others.

3. **Hypertension, including hypertensive crisis or heart failure,** that may be irreversible, has been observed.

4. **Caution in patients with impaired renal function.** Suggested starting dose of 200 mg for creatinine clearance 30 to 50 mL/min. vanDETanib exposure may be increased up to 2-fold with creatinine clearance less than 30 mL/min.

5. **Caution in patients with impaired hepatic function** with serum bilirubin greater than 1.5 times ULN. Not recommended in patients with moderate to severe impairment (Child-Pugh class B or C).

6. **Intractable diarrhea** may be due to high calcitonin levels. Anti-diarrheal agents are recommended for treatment of diarrhea. Serum electrolytes are to be maintained within normal limits.

7. **Blurred vision or corneal opacities** have been reported.

8. Symptoms of **hypothyroidism** may be managed by monitoring TSH levels and treated with thyroid replacement therapy accordingly.

9. **Mild to moderate skin reactions** (exfoliative rash, photosensitivity reactions, and palmar-plantar erythrodyssæsthesia) may be managed symptomatically, or by dose reduction. More **serious skin reactions** (Stevens-Johnson Syndrome and toxic epidermal necrolysis) may require permanent discontinuation.

10. **Reverse Posterior Leukoencephalopathy syndrome (RPLS)** should be considered in any patient experiencing seizures, headache, visual disturbances, confusion, or altered mental function.

11. **Ischemic cerebrovascular events** have been observed in 1.3% of patients taking vanDETanib. vanDETanib should be discontinued in this setting.

12. **Hemorrhage** can occur with vanDETanib. Patients with greater than 2.5 ml of hemoptysis should not receive this agent.

13. **Interstitial lung disease or pneumonitis** should be ruled out in patients experiencing hypoxia, pleural effusion, cough, or dyspnea.

14. **Strong CYP3A4 inhibitors** may increase vanDETanib serum concentrations.

15. **Strong CYP3A4 inducers** may decrease vanDETanib serum concentrations. Examples include: dexamethasone, phenytoin, rifAMPin, carbamazepine, phenobarbital, St. John’s Wort.

Call Dr. Cheryl Ho or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

**References:**