Positive Quality Intervention: Trifluridine and Tipiracil (Lonsurf®) for Metastatic Colorectal Cancer

Description: This PQI will highlight strategies for appropriate dosing and management of adverse effects related to trifluridine-tipiracil treatment in metastatic colorectal cancer.

Background: Trifluridine and Tipiracil is indicated for the treatment of patients with metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy (anti-EGFR therapy should not be used in right sided tumors).1 This has been designated as a category 2A by NCCN.2 The RECOUERSE trial showed a survival benefit of 7.1 months (trifluridine and tipiracil) versus 5.3 months (placebo).3 Grade 3 and greater adverse effects occurred due to neutropenia (38%), decreased appetite (4%), diarrhea (3%) and nausea/vomiting (2%). Trifluridine and Tipiracil in combination with bevacizumab has also been studied in the non-first-line setting in the C-TASK FORCE study. After a 10 month median follow-up, median progression free survival was 2.6 months with trifluridine and tipiracil alone, compared to 4.6 months in combination with bevacizumab.4 Toxicities were similar between with two groups. The SUNLIGHT trial investigated the efficacy and safety of trifluridine/tipiracil plus bevacizumab versus trifluridine/tipiracil alone in patients with refractory mCRC following disease progression or intolerance on two prior chemotherapy regimens. Results from the main analysis demonstrated that the investigational combination provided a statistically significant and a clinically meaningful improvement in OS of 3.3 months compared to trifluridine/tipiracil alone (10.8 months vs. 7.5 months, hazard ratio [HR]: 0.61, 95% confidence interval [CI]: 0.49-0.77, p<0.001).5 A total of 29.3% of patients in the trifluridine/tipiracil plus bevacizumab and 19.5% trifluridine/tipiracil alone received G-CSF support. All patients, regardless of their baseline disease characteristics, sidedness of tumor, RAS mutational status, stratification factors or prior exposure to bevacizumab benefitted from trifluridine/tipiracil plus bevacizumab therapy vs trifluridine/tipiracil monotherapy. Trifluridine and Tipiracil is indicated for the treatment of patients with gastric cancer (see Trifluridine and Tipiracil (Lonsurf®) for Treatment of Gastric Cancer PQI).

PQI Process: Upon receiving a prescription for trifluridine and tipiracil

- Verify the correct dose
  - 35 mg/m² based on trifluridine component (maximum 80 mg or 160 mg/day) orally twice daily within 1 hour of a meal on days 1-5, and days 8-12, repeated every 28 days until disease progression or unacceptable toxicity
    - Round to the nearest 5 mg increment
    - Absence of food does not affect AUC but can cause CMAX spike and adverse effects
    - It is not recommended to start at a lower dose to prevent dose limiting toxicities
  - Bevacizumab 5 mg/kg on days 1 and 15 (if applicable)
- Obtain complete blood counts prior to Day 1 and on Day 15 of each cycle
  - Make sure platelets are ≥75,000/mm³ and ANC > 1500mm³ prior to the start of each cycle
- Check liver function
  - Do not initiate therapy in patients with moderate to severe hepatic impairment (Bilirubin >1.5 ULN and any AST elevation)
- Check renal function
  - CrCl 15-29: Reduce to 20 mg/m² orally two times daily
    - Consider reduction to 15 mg/m² orally two times daily if further reduction is needed
- Withhold trifluridine and tipiracil for any of the following

IMPORTANT NOTICE: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. Updated 2.12.24
o Absolute neutrophil count (ANC) less than 500/mm$^3$ or febrile neutropenia
o Platelets less than 50,000/mm$^3$ or Grade 3 or 4 non-hematological adverse reactions
o After recovery, resume after reducing the dose by 5 mg/m$^2$/dose from the previous dose level for the following only if there is more than a week delay of the next cycle
  ▪ Febrile neutropenia
  ▪ Uncomplicated Grade 4 neutropenia (recovered to ≥1,500/mm$^3$) or thrombocytopenia

- Timing of presentation of adverse events
  o Cycles 1-3 are the cycles with the highest incidence of adverse events
  o Neutropenia
    ▪ Dose holidays are preferred for neutropenia
    ▪ Retrospective data shows neutropenia at the 1-month mark showed trend towards overall survival benefit$^2$

**Patient-Centered Activities:**
- Provide **Oncology Chemotherapy Education (OCE)** sheet and counsel on potential side effects
- Counsel patient on dosing schedule and administration
  o Consider starting on a Monday to complete days 1-5 from Monday to Friday, break on the weekend (days 6-7), and resume Monday to Friday for days 8-12; no medication on days 13-28
  o Notify the patient that dose delays may be beneficial when managing adverse effects, and should not interfere with their ability to receive treatment or achieve benefit
- Provide medication calendar and clinic appointments calendar
- Ensure patient has access to at home antiemetic and antidiarrheal medications
- Counsel patient on safe storage, handling, and disposal of cytotoxic drugs (wear gloves)
- Provide **Lonsurf® Starter Kits** contain patient and caregiver brochures, pillboxes, and thermometer
- Patient Assistance: **NCODA Financial Assistance Tool**

**References:**
1. Lonsurf® (trifluridine/tipiracil) [package insert].
2. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®) for colon cancer.

**Supplemental Information:**
**Dosing According to Body Surface Area$^1$:** (dosage calculator and calendar creator)

<table>
<thead>
<tr>
<th>BSA (m$^2$)</th>
<th>Total daily dose (mg)</th>
<th>Dose (mg) administered twice daily</th>
<th>Tablets per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 mg</td>
</tr>
<tr>
<td>&lt;1.07</td>
<td>70</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>1.07 – 1.22</td>
<td>80</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>1.23 – 1.37</td>
<td>90</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>1.38 – 1.52</td>
<td>100</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>1.53 – 1.68</td>
<td>110</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>1.69 – 1.83</td>
<td>120</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>1.84 – 1.98</td>
<td>130</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>1.99 – 2.14</td>
<td>140</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>2.15 – 2.29</td>
<td>150</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>≥ 2.30</td>
<td>160</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>