An Oncology Mouthful: Updates and Pearls for Oral Oncolytics

Peter Campbell, PharmD, BCOP
Clinical Pharmacy Manager
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center
Disclosures

• No financial conflicts to disclose
Pharmacist Objectives

• Discuss the role of oral oncolytics in the treatment of cancer

• Identify recently approved oral oncolytics and updates in approved indications

• Recognize common adverse events and management strategies for select oral oncolytics
Technician Objectives

• Recognize oral oncolytics used in the treatment of cancer

• Identify recently approved oral oncolytics and updates in approved indications

• Recall common adverse events associated with oral oncolytics
Brief History of Cancer Treatment

Radiation- pre-1940’s
Nitrogen mustards- 1943
Antifolates- 1948
Thiopurines- 1951
5-fluorouracil- 1957
Methotrexate- 1958
Antitumor antibiotics- 1959
Vinca alkaloids- 1963
Imatinib- 2001
Rituximab- 1997

What Happened?
Oncology Drug Approval Explosion

New Drug Approvals

Traditional Chemotherapy Mechanism

- Reactive Oxygen Species
  - Platinums
  - Anthracyclines

- Microtubule Inhibition
  - Vinca alkaloids
  - Taxanes

- Immune Activation
  - Immunotherapy
  - Biologics

- DNA Replication
  - Platinums
  - Alkylating agents

Oral Chemotherapy

- TKI’s
- Enzyme Inhibitors
- Chemotherapy
- Hormonal Agents
Tyrosine Kinase Inhibitors

ATP

Cell growth, proliferation, survival, differentiation

Phosphorylated tyrosines

TKI’s block ATP-binding sites

Locked in an activated and autophosphorylated state

Phosphorylated tyrosines

Cell growth, proliferation, survival, differentiation

Oral Chemotherapy Easier to Stomach?

Cytotoxic Chemotherapy

- Nausea
- Vomiting
- Myelosuppression
- Infections
- Bleeding
- Hair loss

Oral Agents

- Nausea
- Vomiting
- Handfoot syndrome
- Rash
- Hypertension
- Thrombosis
Wrong Site, Unwanted Effect

Sorafenib

- BRAF: Rash, photosensitivity, hyperkeratosis
- VEGF-R: Hypertension, proteinuria, impaired wound healing, bleeding
- FLT3: FLT3+ Acute Myeloid Leukemia
- C-Kit: Cytopenias, hair pigmentation changes
Drug Interactions

Oral oncology drug = screen for drug interactions (especially CYP3A4)
Management of Drug-Interactions

• Complete a full medication review
  • Complete a medication reconciliation with the patient (including over the counter and herbals/supplements)
  • Call patient’s pharmacy for a complete medication list
  • Review patient’s medical records and clinic/hospital notes if available
    • Lab values, EKGs

• Consider patient specific factors
  • Bleeding risks, procedures, cancer type, underlying health conditions or anatomical abnormalities

• Complete a drug interaction analysis
  • Use multiple databases when possible
    • Be mindful of recent drug approvals not being added to databases

Financial Toxicity of Oral Oncology Agents

• Oral oncology agents may reduce the overall healthcare resource utilization
  • Patient’s required to visit infusion center less frequently, freeing up resources for other patients

• Costs for oral oncology agents is steadily increasing
  • From 2009 to 2010 costs of oral oncology agents increased ~17%

• Patient out-of-pocket cost can present a large financial burden
  • Approximately 10% of patients chose not to fill oral oncology prescriptions due to high-costs
  • Utilization of manufacturer copay cards can help bridge the cost of what insurance does not cover

Mancini R. Oncology. 2013;27(8).
Quality of Life and Patient Preference

• Limited data exists to directly analyze patient quality of life while receiving intravenous vs. oral oncology treatments
  • Small studies suggest improved quality of life measures

• Adherence to oral regimens may be decreased as compared to intravenous regimens
  • More frequent administration or “on-off” cycles (administered 14 days our of a 21 day cycle) result in patients forgetting to take medication as prescribed

• Conflicting data on patient preferences of oral vs. intravenous regimens
  • Small studies suggest patient prefer oral treatments over intravenous treatments
  • Completion of treatment in 1 day, convenience of not going to infusion center

Trial Design- Beyond the Abstract
Oncology Clinical Trial Design

Umbrella

Mutation A → Cancer A → Drug A
Mutation B → Cancer A → Drug B
Mutation C → Cancer A → Drug C

Mutation A → Cancer B
Mutation B → Cancer B
Mutation C → Cancer B

Mutation A → Drug A

Mutation A → Cancer C
Mutation B → Cancer C
Mutation C → Cancer C

Drug A
Drug B
Drug C

Basket

## Progression Free Survival or Overall Survival?

<table>
<thead>
<tr>
<th></th>
<th><strong>Overall Survival</strong></th>
<th><strong>Progression Free Survival</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Use</strong></td>
<td>Considered the gold standard endpoint</td>
<td>Emerging as a common endpoint in oncology</td>
</tr>
<tr>
<td><strong>Definition</strong></td>
<td>Time from random assignment to death</td>
<td>Time from assignment to disease progression</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Provides a clear-cut efficacy of the study drug in question</td>
<td>Allows for faster trial completion, and submission for drug-approval</td>
</tr>
<tr>
<td><strong>Pitfalls</strong></td>
<td>If a modest benefit is gained, it may take very large sample sizes or years of study duration to prove statistical significance</td>
<td>Has proven to be a valid surrogate endpoint in some tumor types, but not all</td>
</tr>
<tr>
<td><strong>Takeaway</strong></td>
<td>• Progression free survival has become a widely used endpoint in oncology clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Although it has proven to be a valid surrogate for overall survival in some disease states, the same has not been proven for others</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Some targeted and biological therapies have shown low progression free survival, but prolonged overall survival</td>
<td></td>
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</tbody>
</table>

Solid Tumors
Relugolix

Orgovyx (relugolix) [prescribing information]. Brisbane, CA: Myovant Sciences Inc; December 2020.
# Relugolix

|------|--------------------------|
| **Patient population** | • n=622  
• Patients with advanced prostate cancer |
| **Intervention** | 2:1 randomized to 120 mg relugolix once daily vs. leuprolide injection every 3 months for 48 weeks |
| **Primary endpoint** | • Sustained testosterone response to castration levels (<50 ng/dL) 96.7% relugolix vs. 88.8% leuprolide (p<0.001) |
| **Secondary endpoints: efficacy** | • Castration at day 4: 56% relugolix vs. 0% leuprolide  
• Castration at day 12: 98.7% relugolix vs. 12% leuprolide  
• FSH levels at week 24: 1.72 IU/L relugolix vs. 5.95 IU/L leuprolide |
Relugolix

• Administered as 360 mg on day 1, followed by 120 mg once daily on subsequent days
  • Trial specifically reported a 99% adherence rate

• Drug interactions:
  • Substrate of CYP2C8 (minor) & CYP3A4 (minor)
  • Qtc prolonging agents should be avoided

• Adverse reactions:
  • Hot flashes, diarrhea, arthralgia, fatigue, hypertension
  • Cardiovascular events (important factor in prostate cancer)

Orgovyx (relugolix) [prescribing information]. Brisbane, CA: Myovant Sciences Inc; December 2020.
Tyrosine Kinase Inhibitors- Entrectinib

Neurotrophic tyrosine receptor kinase (NTRK)

Cell growth, proliferation, survival, differentiation

## Entrectinib

<table>
<thead>
<tr>
<th></th>
<th>N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>(95% CI) 57% (43, 71)*</td>
</tr>
<tr>
<td>Complete Response</td>
<td>7.4%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Duration of Response</strong></td>
<td>N = 31</td>
</tr>
<tr>
<td>Range (months)</td>
<td>2.8, 26.0+</td>
</tr>
<tr>
<td>% with duration ≥ 6 months</td>
<td>68%</td>
</tr>
<tr>
<td>% with duration ≥ 9 months</td>
<td>61%</td>
</tr>
<tr>
<td>% with duration ≥ 12 months</td>
<td>45%</td>
</tr>
</tbody>
</table>

*53% ORR in patients who previously received therapy for metastatic disease
+ongoing response at study cutoff

Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; August 2019.
## Entrectinib

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>N=54</th>
<th>Overall Response Rate</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>13</td>
<td>46</td>
<td>12%, 75%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>10</td>
<td>70</td>
<td>35%, 93%</td>
</tr>
<tr>
<td>Salivary</td>
<td>7</td>
<td>86</td>
<td>42%, 100%</td>
</tr>
<tr>
<td>Breast</td>
<td>6</td>
<td>83</td>
<td>36%, 100%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Colorectal</td>
<td>4</td>
<td>25</td>
<td>NA</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>3</td>
<td>PR</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>3</td>
<td>PR</td>
<td>NA</td>
</tr>
<tr>
<td>Gynecological</td>
<td>2</td>
<td>PR</td>
<td>NA</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1</td>
<td>PR</td>
<td>NA</td>
</tr>
</tbody>
</table>

Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; August 2019.
Entrectinib

• FDA-approved for ROS1-positive metastatic non-small cell lung cancer and solid tumors with NTRK gene fusion
  • Dosed at 600 mg once daily until disease progression
  • Avoid grapefruit juice while taking entrectinib

• Substrate of CYP3A4 (major)
  • Avoid moderate CYP3A4 inhibitors or reduce dose to 200 mg daily
  • Avoid strong CYP3A4 inhibitors or reduce dose to 100 mg daily is BSA >1.5m²

• Adverse reactions:
  • Fatigue, constipation, edema, diarrhea, nausea, increased weight, arthralgia, fevers
  • Congestive heart failure, CNS effects (cognitive impairment, dizziness, mood disorders, sleep disorders), fractures, hepatotoxicity, hyperuricemia, QTc prolongation

Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; August 2019.
Tyrosine Kinase Inhibitors- Erdafitinib
# Erdafitinib

<table>
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<tbody>
<tr>
<td>• N=99</td>
<td></td>
</tr>
<tr>
<td>• Locally advanced and unresectable or metastatic urothelial carcinoma</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Phase 2, multicenter, international, open-label study</td>
<td></td>
</tr>
<tr>
<td>• 28-day cycles of:</td>
<td></td>
</tr>
<tr>
<td>• 10 mg/day, 7 days on 7 days off</td>
<td></td>
</tr>
<tr>
<td>• 6 mg per day continuous</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Overall response rate</td>
<td></td>
</tr>
<tr>
<td>• 70%</td>
<td></td>
</tr>
<tr>
<td>• 3% complete response</td>
<td></td>
</tr>
<tr>
<td>• 37% partial response</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Response in patients having received previous immunotherapy</td>
<td></td>
</tr>
<tr>
<td>• 59%</td>
<td></td>
</tr>
<tr>
<td>• Duration of progression-free survival</td>
<td></td>
</tr>
<tr>
<td>• 13.8 months</td>
<td></td>
</tr>
</tbody>
</table>
Erdafitinib

• Dosed at 8 mg once daily for 14 – 21 days, assess for serum phosphate
  • Serum phosphate <5.5 mg/dL increase dose to 9 mg once daily
  • Dose adjustments for hyperphosphatemia and ocular toxicity

• Drug interactions
  • Substrate of CYP2C9 (major), CYP3A4 (major), P-glycoprotein (minor)
    • Avoid use with strong or moderate inhibitors of CYP3A4 and CYP2C9, monitor and adjust dose as needed if used together
    • CYP2C9*3/*3 genotype requires ~50% dose reduction

• Adverse reactions
  • Mucositis/stomatitis, electrolyte abnormalities, diarrhea, fatigue, nail bed changes, liver function/kidney function abnormalities, taste changes

Balversa (erdafitinib) [prescribing information]. Horsham, PA: Janssen Products, LP; July 2020.
Tyrosine Kinase Inhibitors- Avapritinib

Activation of downstream signaling and cell proliferation

Tyrosine Kinase Inhibitors- Avapritinib

## Avapritinib

|-------------------|----------------------------------------|
| **Patient population** | - N=46  
- Unresectable PDGFRA D842V-mutant GIST regardless of previous therapy or GIST with other mutations who progressed on imatinib and ≥ 1 TKI, or only received imatinib previously |
| **Intervention**   | - Phase 1, multi-center, international, open-label, single-arm  
- 300 mg (originally 400 mg) avapritinib orally once daily until disease progression |
| **Primary endpoint** | - Overall response rate  
  - 84% in patients with PDGFR-alpha exon 18 mutation  
  - 7% complete response  
  - 77% partial response |
| **Secondary endpoints** | - Median duration of response  
  - NR (median follow-up 10.6 months)  
  - Response of at least 6 months  
  - 61% |
Avapritinib

• Dosed as 300 mg orally once daily until disease progression
  • Moderate to high emetic potential
  • Must be given on an empty stomach
  • Dose reductions or interruptions for CNS toxicity, intracranial hemorrhage

• Drug interactions
  • Substrate of CYP2C9 (minor), CYP3A4 (major)
  • Avoid use with strong CYP3A4 inhibitors (7-fold AUC increase)
  • Avoid use with moderate CYP3A4 inhibitors, reduce dose to 100 mg if used together

• Adverse effects:
  • Edema, nausea, fatigue, cognitive impairment, decrease appetite, diarrhea, hair color changes, rash, dizziness, myelosuppression

Hematologic Malignancies
Tazemetostat

### Tazemetostat

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>• n=389</td>
</tr>
<tr>
<td></td>
<td>• Relapsed or refractory follicular lymphoma or failed two or more previous lines of therapy</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>• Phase 2, open-label, single-arm</td>
</tr>
<tr>
<td></td>
<td>• 800 mg tazemetostat orally twice daily in continuous 28-day cycles, until disease progression</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>• Objective response rate</td>
</tr>
<tr>
<td></td>
<td>• 69% EZH2 mutant</td>
</tr>
<tr>
<td></td>
<td>• 35% EZH2 wild-type</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>• Duration of response</td>
</tr>
<tr>
<td></td>
<td>• 10.9 months EZH2 mutant</td>
</tr>
<tr>
<td></td>
<td>• 13.0 months EZH2 wild-type</td>
</tr>
<tr>
<td></td>
<td>• Progression-free survival</td>
</tr>
<tr>
<td></td>
<td>• 13.8 months EZH2 mutant</td>
</tr>
<tr>
<td></td>
<td>• 11.1 months EZH2 wild-type</td>
</tr>
</tbody>
</table>
Tazemetostat

• Dosed as 800 mg orally twice daily until disease progression
  • Dose adjustments and interruptions for neutropenia, thrombocytopenia
  • Avoid drinking grapefruit juice while taking tazemetostat

• Drug interactions
  • Substrate of CYP3A4 (major), and P-glycoprotein (minor)
    • Avoid co-administration of strong CYP3A4 inhibitors
    • Avoid co-administration of moderate CYP3A4 inhibitors, reduce to 400 mg (if normal dose taken is 800 mg, further dose reductions if already receiving a reduced dose)

• Adverse reactions
  • Fatigue, nausea, vomiting, cytopenias, electrolyte abnormalities,
  • Development of secondary malignancies (MDS and AML)

Decitabine and Cedazuridine Mechanism

- Un-methylated
- Methylated

Normal Transcription

Silenced Transcription

Decitabine inhibits DNA methyltransferase (hypomethylation)

Inqovi (decitabine and cedazuridine) [prescribing information]. Princeton, NJ: Taiho Oncology Inc; July 2020.
Decitabine and Cedazuridine

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<tbody>
<tr>
<td>n=80</td>
<td></td>
</tr>
<tr>
<td>Intermediate 1/2 – high risk MDS or CMML</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1:1 randomized, crossover study of DEC-C or decitabine for cycle 1, alternate, and then DEC-C subsequent cycles</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Primary endpoint: systemic exposure</th>
<th></th>
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<tbody>
<tr>
<td>93.5% oral vs. 97.6% IV</td>
<td></td>
</tr>
<tr>
<td>DNA demethylation difference &lt;1%</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Secondary endpoints: efficacy</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>CR 21%</td>
<td></td>
</tr>
<tr>
<td>mCR 22%</td>
<td></td>
</tr>
<tr>
<td>HI 15%</td>
<td></td>
</tr>
<tr>
<td>ORR 60%</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Neutropenia 46%; thrombocytopenia 38%; febrile neutropenia 29%</td>
<td></td>
</tr>
</tbody>
</table>
Decitabine and Cedazuridine

- Dosed as decitabine 35 mg & cedazuridine 100 mg once daily for 5 days per cycle
  - Available as 5-tablet blister card for each cycle
  - No food should be consumed 2 hours before or after each dose

- No known drug-interactions at this time

- No dose adjustments for organ impairment
  - Only studied in patients with CrCl >30 mL/min and mild hepatic impairment

- Dose adjustments are made based on myelosuppression experienced during treatment
  - Consider holding for patients with neutropenia and thrombocytopenia if no longer evidence of disease

Inqovi (decitabine and cedazuridine) [prescribing information]. Princeton, NJ: Taiho Oncology Inc; July 2020.
Venetoclax Mechanism

Venetoclax

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>• n=389</td>
</tr>
<tr>
<td></td>
<td>• Relapsed or refractory chronic lymphocytic leukemia</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>• 1:1 randomized to receive Venetoclax plus rituximab (for 6 cycles) for 2 years vs. bendamustine plus rituximab for 6 cycles</td>
</tr>
<tr>
<td></td>
<td>• Standard venetoclax dose-escalation was utilized</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>• Four year PFS 57.3% VenR vs. 4.6% BR (p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>• Four year OS 85.3% VenR vs. 66.8% BR (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>• This response was noted despite patients receiving multiple novel therapies after BR</td>
</tr>
<tr>
<td></td>
<td>• 73.1% of VenR patients who completed 2 years of therapy remained progression free at a median of 22 months post-therapy follow-up</td>
</tr>
</tbody>
</table>
# Venetoclax

|---------|-----------------------------|

## Patient population
- n=431
- Patients aged 18 years or older with acute myeloid leukemia and unable to get intensive chemotherapy

## Intervention
- 2:1 randomized, placebo-controlled study of azacitidine plus venetoclax vs. azacitidine plus placebo
  - Standard AML venetoclax dose-escalation was utilized

## Primary endpoint
- Overall survival 14.7 months AzaVen vs. 9.6 months Aza (p<0.001)

## Secondary endpoints
- Complete remission 66.4% AzaVen vs. 28.3% Aza (p<0.001)
- Median time to first response 1.3 months AzaVen vs. 2.8 months Aza
- Median duration of complete remission 17.5 months AzaVen vs. 13.4 months Aza
Venetoclax

• Requires dose escalation to avoid tumor lysis syndrome
  • CLL: 20 mg week 1, 50 mg week 2, 100 mg week 3, 200 mg week 4, 400 mg week 5 and subsequent
  • AML: 100 mg on day 1, 200 mg on day 2, 400 mg on day 3 and subsequent

• Undergoes metabolism via CYP3A4, CYP3A5, and p-glycoprotein
  • Dose reductions are necessary for strong and moderate inhibitors of CYP3A4 as well as P-glycoprotein

• Adverse reactions
  • Cytopenias, tumor lysis syndrome, fatigue, nausea, vomiting, edema, electrolyte abnormalities, infections (predominantly upper respiratory tract)
# Oral Azacitidine

|----------------|-------------------------|
| **Patient population** | • n=472  
• Patients aged 55 years or older with acute myeloid leukemia in first remission after intensive therapy |
| **Intervention** | • 1:1 randomized, placebo-controlled study of oral azacitidine vs. placebo |
| **Primary endpoint** | • Median overall survival 24.7 months azacitidine vs. 14.8 months placebo (p<0.001) |
| **Secondary endpoints** | • Median relapse-free survival 10.2 months azacitidine vs. 4.8 months placebo (p<0.001)  
  • Azacitidine favored at 6-month and 12-month analysis  
  • Non-inferiority proven for FACIT Fatigue Scales and health-related quality of life analysis |
Oral Azacitidine

• Administered as 300 mg once daily on days 1-14 of a 28 day cycle
  • Antiemetic prophylaxis should be given prior to azacitidine for first 2 cycles
  • Dose modifications and treatment delays for neutropenia, thrombocytopenia, nausea, vomiting, and diarrhea

• Undergoes hydrolysis, no clinically significant drug-interactions

• Adverse reactions:
  • Nausea, vomiting, diarrhea, constipation, fatigue
  • Pneumonia, febrile neutropenia

Onureg (azacitidine) [prescribing information]. Summit, NJ: Celgene Corporation; September 2020.
An Oncology Mouthful: Updates and Pearls for Oral Oncolytics

Peter Campbell, PharmD, BCOP
Clinical Pharmacy Manager
NewYork-Presbyterian Hospital
Columbia University Irving Medical Center