Trifluridine-tipiracil Drug Monograph

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**Trifluridine-tipiracil (LONSURF®)**

**National Drug Monograph**

**February 2016**

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

### FDA Approval Information

**Description/Mechanism of Action**

Trifluridine-tipiracil is a combination of a nucleoside metabolic inhibitor, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil, which are used together for treatment of patients with metastatic colorectal cancer. Tipiracil increases thymidine exposure by inhibiting its metabolism by thymidine phosphorylase.

**Indication(s) Under Review in this document (may include off label)**

Treatment of patients with metastatic colorectal cancer who have been previously treated with the following:

- Fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy
- Anti-VEGF biological therapy
- Anti-EGFR therapy, if KRAS wild-type

**Dosage Form(s) Under Review**

Oral tablets packaged in 2 strengths.

- 15mg trifluridine/6.14mg tipiracil
- 20mg trifluridine/8.19mg tipiracil

**REMS**

☐ REMS  ☒ No REMS  ☒ Post-marketing Requirements

**Pregnancy Rating**

Fetal harm can occur. Women should be advised of the potential risk to a fetus. See Special Populations for additional information

### Executive Summary

#### Efficacy

- In a phase three trial study participants who had metastatic colorectal cancer (mCRC) which had previously been treated with at least 2 other forms of chemotherapy received trifluridine-tipiracil + Best Supportive Care (BSC) or placebo + BSC. The median age in the study was 63 years with 61% males. 58% were white and all patients had an ECOG performance status of 0 or 1.
- Overall survival (OS) rates were 7.1 vs 5.3 months, respectively, when comparing trifluridine-tipiracil to placebo. (HR 0.68; 95% CI, 0.58 to 0.81; P<0.001). Progression Free Survival (PFS) rates were 2.0 vs 1.7 months (HR 0.48; 95% CI 0.41-0.57; P<0.001).
- Disease control rate (DCR) was achieved in 44% of tipiracil-trifluridine subjects and 16% of placebo subjects (P<0.001)
- Median length of transition from baseline ECOG score(0 or 1) to 2 or higher was 5.7 vs 4.0 months in the tipiracil-trifluridine vs placebo groups respectively (HR 0.66 (95% CI, 0.56 to 0.78; P<0.001)

#### Safety

- Adverse events of grade 3 or higher occurred in 69% of the trifluridine-tipiracil patients vs 52% of the placebo patients
- Adverse events led to dose reduction in 14% of patients receiving trifluridine-tipiracil
- Adverse events led to 4% of Trifluridine-tipiracil patients withdrawing from the study vs 2% of placebo patients,
- No clinically meaningful differences with regards to hepatic or renal dysfunction, anorexia, stomatitis, hand-foot syndrome, or cardiac events between the two study arms
Other Considerations

- Drug is available in two strengths of an oral tablet formulation which are considered cytotoxic and will require special handling and disposal procedures.
- Dose is based upon BSA and may require use of both tablet strengths. Doses are to be taken on a twice daily schedule for 5 days (Days 1-5), followed by 2 days of rest, then another 5 days of treatment (Days 8-12) followed by 15 days of rest. One cycle = 28 days.
- Table 1: Determination of benefit in mCRC

| Outcome in clinically significant area | Median OS: 7.1 vs 5.3 months |
| Effect Size | HR 0.68; 95% CI 0.58 to 0.81; P<0.001 for OS |
| | HR 0.48; 95% CI 0.41-0.57; P<0.001 for PFS |
| Potential Harms | Grade 3−4 toxicity including neutropenia (38 vs 0%); leukopenia (21 vs 0%); anemia (18 vs 3%); and febrile neutropenia (4% vs 0%) |
| Net Clinical Benefit | Minimal (modest benefit, high toxicity) |

Projected Place in Therapy

- Last line/salvage therapy for mCRC after adequate trials of fluoropyrimidine agent, oxaliplatin, irinotecan, anti-VEGF therapy and, if KRAS wild type, an anti-EGFR agent.
- Determination of trifluridine-tipiracil role in relation to regorafenib is still under investigation

Background

Purpose for review

Recent FDA approval

Issues to be determined:

✓ FDA approval September 2015
✓ What is the evidence of need for trifluridine-tipiracil
✓ Does trifluridine-tipiracil offer advantages to currently available alternatives?
✓ Does trifluridine-tipiracil offer advantages over current VAFN agents?
✓ What safety issues need to be considered?
✓ Does trifluridine-tipiracil have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Non-formulary Alternative (if applicable)

Regorafenib

- Oral formulation, taken with food:
  - Once daily dosing x 21 days of 28-day cycle;
  - P3 (CORRECT trial): Regorafenib vs. placebo results:
    - OS: 6.4 vs 5 months, (HR 0.77; 95% CI 0.64-0.94; p=0.0052)
    - PFS: 1.9 vs 1.7 months (HR 0.49; 95% CI 0.42-0.58; p<0.0001)
- Indication: Regorafenib is approved for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with a fluoropyrimidine agent, oxaliplatin, irinotecan, anti-VEGF therapy and, if KRAS wild type, an anti-EGFR agent.
- Toxicity: Adverse events (all grades):
  - 93 vs 61%: Most common AE: fatigue, HFSR, diarrhea, hypertension and rash.
  - Grade 3−51 vs 12%; included fatigue 15 vs. 9%, HFSR 17 vs. 0%, diarrhea 8 vs. 2%, HTN 8 vs. 1%, Rash 6 vs. <1% AE led to dose modification: 67 vs 23%

CPU Inclusion Criterion

- Inclusion:
  - Life expectancy ≥ 3 months;
  - ECOG PS 0 or 1;
  - Adequate bone marrow, liver and renal function;
  - Diagnosis of mCRC and received all the following regimens unless not a candidate:
    - Fluoropyrimidine-based;
    - Oxaliplatin-based;
    - Irinotecan-based;
    - Anti-VEGF agent;
    - If KRAS WT, anti-EGFR agent, if medically eligible

- OR

Diagnosis of GIST and received prior imatinib ≥ 6 months

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Efficacy (FDA Approved Indications)

Literature Search Summary
A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms <Trifluridine Tipiracil> and <LONSURF>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer’s AMCP dossier were searched for relevant clinical trials. There was a single phase 3 trial evaluated for approval by the FDA which leads to a Moderate GRADE for quality of evidence for this medication.

Review of Efficacy
- The FDA approval of Trifluridine-tipiracil was largely based on a single, international, phase 3, randomized, double-blind, placebo-controlled study that was conducted in patients with previously treated metastatic colorectal cancer
- Trifluridine-tipiracil is FDA-approved for the treatment of patients with mCRC who have progressed after receiving adequate trials of a fluoropyrimidine agent, oxaliplatin, irinotecan, anti-VEGF therapy and, if KRAS wild type, an anti-EGFR agent
- The primary endpoint of the phase 3 clinical trial was overall survival which was modestly prolonged compared to placebo

Clinical Trial

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Trial Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer, et al. R, DB, PC</td>
<td>Methods:&lt;br&gt;- Patients with biopsy documented adenocarcinoma of the colon or rectum were eligible if they were ≥18 years old and had received at least 2 prior regimens of standard chemotherapies .&lt;br&gt;- Prior chemotherapies could have included adjuvant chemotherapies if a tumor recurred within 6 months, if they had tumor progression within 3 months after last administration of chemotherapy, or if they had significant adverse events from standard chemotherapies.&lt;br&gt;- Additional patient requirements included Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, KRAS wild-type status, metastatic lesions defined by RECIST criteria and prior treatment with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and -for patients with KRAS wild-type tumors – cetuximab or panitumumab,&lt;br&gt;- The trial was placebo-controlled, patients assigned in a 2:1 ratio to receive trifluridine-tipiracil plus Best Supportive Care (BSC) or placebo plus BSC and were stratified based on KRAS status, time from first diagnosis of metastatic disease, and geographic region,&lt;br&gt;- Trifluridine-Tipiracil or placebo were administered at a dose of 35 mg/m²/dose of trifluridine or placebo twice daily on days 1-5 and 8-12 of each 28 day cycle.&lt;br&gt;  o Dose was rounded to nearest 5mg increment&lt;br&gt;  o Maximum of 80 mg (trifluridine component or placebo) in any one dose regardless of total body surface area&lt;br&gt;  o Regimen was continued until disease progression or unacceptable toxicity&lt;br&gt;- The primary objective was to demonstrate improvement in overall survival with trifluridine-tipiracil + BSC in comparison to placebo + BSC in patients with refractory mCRC&lt;br&gt;- Secondary objectives were determination of progression-free survival, safety, and tolerability endpoints.</td>
</tr>
<tr>
<td>RE COURSE Trial</td>
<td>Results:&lt;br&gt;- The primary and major secondary endpoints for the trial are listed in the table below.&lt;br&gt;- The median age in the study was 63 years with 61% males. 58% were white and all patients had an ECOG performance status of 0 or 1.&lt;br&gt;- Mean duration of therapy: 12.7 ± 12.0 weeks vs 6.8± 6.1 weeks in the trifluridine-tipiracil vs placebo groups, respectively&lt;br&gt;- Delay in ECOG elevation defined as the length of time it took to change from baseline ECOG score of 0 or 1 to ≥2&lt;br&gt;- All patients were started at 35 mg/m²/dose of the trifluridine component or placebo&lt;br&gt;  o Patients received 89 vs 94% of their planned doses in the trifluridine-tipiracil vs placebo groups, respectively&lt;br&gt;  o In the trifluridine-tipiracil group, a total of 73 patients (14%) required a dose reduction&lt;br&gt;    • 53 patients required a single reduction, 18 patients required two reductions, and 2 patients required 3 reductions&lt;br&gt;    • 19 patients stopped treatment due to adverse events</td>
</tr>
</tbody>
</table>
### Trifluridine-Tipiracil Drug Monograph

**干预措施**

<table>
<thead>
<tr>
<th>干预措施</th>
<th>总体生存期（第1个端点）</th>
<th>进展自由生存期</th>
<th>ECOG升高延迟</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifluridine-Tipiracil + BSC</td>
<td>7.1个月 (95% CI 6.5-7.8)</td>
<td>2.0个月 (95% CI 1.9-2.1)</td>
<td>5.7个月</td>
</tr>
<tr>
<td>Placebo + BSC</td>
<td>5.3个月 (95% CI 4.6-6.0)</td>
<td>1.7个月 (95% CI 1.7-1.8)</td>
<td>4个月</td>
</tr>
</tbody>
</table>

**危害比率**

<table>
<thead>
<tr>
<th>比较方法</th>
<th>对比危害比率</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>杜腐定-他培利</td>
<td>0.68 (95% CI 0.58-0.81)</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 for all comparisons*

- **患者**根据KRAS状态和首次诊断后的时间被分组
  - **患者**KRAS野生型更可能有总体生存期的增加，而KRAS突变型则不
  - **患者**≥18个月的总体生存期有改善，而<18个月的无改善
  - **患者**以前接受过4次或4次以上的化疗，总体生存期有显著改善

**评论**

- **患者**之前接受过regorafenib的不完全样本，难以确定regorafenib的治疗是否有效
- **患者**1.8个月与安慰剂相比，总体生存期的改善可能与高药物相关毒性有关，可能不具有成本效益

**潜在非标签用途**

- **目前正在进行的研究包括**
  - **患者**转移性实体瘤
  - **患者**胃癌
  - **患者**小细胞肺癌

*最新的版本可在www.pbm.va.gov或PBM INTRAnet查看*
**Safety**

(for more detailed information refer to the product package insert)

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boxed Warning</strong></td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
</tr>
<tr>
<td><strong>Warnings/Precautions</strong></td>
</tr>
<tr>
<td><strong>Embryo-fetal toxicity</strong>: Based on animal studies and its mechanism of action, embryo-fetal lethality and toxicity may occur even at doses lower than required for treatment. Advise females of reproductive potential to use effective contraception. Advise pregnant women of the risk to the fetus.</td>
</tr>
</tbody>
</table>

**Safety Considerations**
- Myelosuppression with Trifluridine-tipiracil was prominent
- Reproduction:
  - Females: Trifluridine-tipiracil can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment
  - Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with Trifluridine-tipiracil and for a least 3 months after the final dose
- Trifluridine-tipiracil is a cytotoxic drug. Follow applicable special handling and disposal procedures
- Patients 65 years of age or older who received Trifluridine-tipiracil had a higher incidence of myelosuppressive adverse events than those younger than 65 years of age
- Trifluridine-tipiracil should be taken twice daily within 1 hour after completion of morning and evening meals
- Dose is based upon BSA and may require use of both tablet strengths to make up one dose. Dosing schedule may be complicated for some as drug is to be taken twice daily for non-consecutive days (5-days on, 2-days off, then 5-days on, followed by a rest period). Patient education and understanding will be very important for successful use of this therapy.

**Adverse Reactions**
- Common adverse reactions: Incidence ≥ 10%: anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.
- Death/Serious adverse reactions (Gr ≥ 3: Drug vs. placebo): Grade ≥ 3: Any event 69 vs. 52%:
  - Neutropenia (38 vs. 0%)
  - Leukopenia (21 vs. 0%)
  - Anemia (18 vs. 3%)
  - Febrile neutropenia (4 vs. 0%)
  - Infections were more common in the trifluridine-tipiracil vs. placebo arm: 27 vs. 15% and included nasopharyngitis and UTIs
  - Pulmonary emboli was noted with higher incidence: 2 vs. 0%
  - One death each due to sepsis, septic shock, pneumonia, pulmonary embolism, pulmonary edema, and liver abscess.
- Discontinuations due to adverse reactions: 4% (vs 2%) in the placebo arm of patients discontinued the medication due to adverse events
  - 14% of patients in the Trifluridine-tipiracil arm required dose reductions
    - Neutropenia, anemia, febrile-neutropenia and decreased neutrophil count accounted for over half of all dose reductions
    - Fatigue, diarrhea, nausea, vomiting and decreased appetite were also significant factors leading to dose reduction

**Drug Interactions**
- No pharmacokinetic drug-drug interaction studies have been conducted with Trifluridine-tipiracil
- Trifluridine is a substrate thymidine phosphorylase and is not metabolized via cytochrome P450(CYP) enzymes
  - It is eliminated via thymidine phosphorylase to inactive metabolite 5-(trifluoromethyl) uracil
- Tipiracil inhibits the metabolism of trifluridine by thymidine phosphorylase and is not metabolized by the liver

**Updated version may be found at** [www.pbm.va.gov](http://www.pbm.va.gov) **or** PBM INTRAnet
Risk Evaluation
As of January 29th, 2016

Sentinel event advisories
- None

Look-alike/sound-alike error potential

<table>
<thead>
<tr>
<th>NME Drug Name</th>
<th>Lexi-Comp</th>
<th>First DataBank</th>
<th>ISMP</th>
<th>Clinical Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trifluridine-tipiracil 15mg-6.14mg tab, 20mg-8.19mg tab</td>
<td>Trifluoperazine</td>
<td>None</td>
<td>None</td>
<td>Tegafur-Uracil</td>
</tr>
<tr>
<td>Lonsurf</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Lorzone Lomustine</td>
</tr>
</tbody>
</table>

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations
- The FDA has required a single post-marketing pharmacokinetic study to determine the appropriate dose in patients with moderate to severe hepatic impairment and severe renal impairment
- Trifluridine-tipiracil initially became available for use in Japan in March 2014
- If stored outside of the original bottle, medication should be discarded after 30 days
- Obtain complete blood counts prior to and on Day 15 of each cycle at a minimum

Outcome in clinically significant area
- Median OS: 7.1 vs 5.3 months
- Median PFS: 2.0 vs 1.7 months

Effect Size
- HR 0.68; 95% CI, 0.58 to 0.81; P<0.001 for OS
- HR 0.48; 95% CI 0.41-0.57; P<0.001 for PFS

Potential Harms
- Grade 3-4 toxicity including neutropenia (38 vs 0%); leukopenia (21 vs 0%); and anemia (18 vs 3%)

Net Clinical Benefit
- Minimal (modest benefit, high toxicity)
Dosing and Administration

Dosing:
- 35 mg/m²/dose of trifluridine component orally twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.
  - Round dose to nearest 5mg increment
  - Maximum of 80 mg (trifluridine component) in any one dose regardless of total body surface area
  - Continue regimen until disease progression or unacceptable toxicity
- CBC should be obtained prior to and on Day 15 of each cycle.
- Dose Modifications
  - Do not initiate cycle of Trifluridine-tipiracil until:
    - ANC ≥ 1,500/mm³ or febrile neutropenia resolved
    - Platelets ≥ 75,000 /mm³
    - Grade 3 or 4 non-hematological reactions are resolved to Grade 0 or 1
  - Within a treatment cycle withhold Trifluridine-tipiracil if:
    - ANC ≤ 500/mm³ or febrile neutropenia
    - Platelets ≤ 50,000/mm³
    - Grade 3 or 4 non-hematological adverse reactions
  - Once blood counts have recovered, reduce dose by 5mg/m²/dose from the previous dose level if the following occur:
    - Febrile neutropenia
    - Uncomplicated Grade 4 neutropenia (recovered to ANC ≥ 1500) or thrombocytopenia (recovered to > 75,000) that results in more than 1 week delay in start of next cycle
    - Non-hematologic Grade 3 or Grade 4 adverse reaction except for N/V responsive to antiemetic therapy or diarrhea responsive to anti-diarrheal therapy
  - Maximum of 3 dose reductions are permitted to a minimum dose of 20mg/m² twice daily
  - Do not escalate dose after it has been reduced
- Refer to package insert for full dosing information

Administration:
- Take Trifluridine-tipiracil within 1 hour after completion of morning and evening meals
- Trifluridine-tipiracil is a cytotoxic drug. Follow applicable special handling and disposal procedures

Special Populations (Adults)

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
</tr>
<tr>
<td>No differences in overall survival were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of Trifluridine-tipiracil based on age.</td>
</tr>
<tr>
<td>Patients 65 years of age or older who received Trifluridine-tipiracil had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Based on animal data and its mechanism of action, Trifluridine-tipiracil can cause fetal harm. Trifluridine-tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. There are no available data on Trifluridine-tipiracil exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.</td>
</tr>
<tr>
<td>Lactation</td>
</tr>
<tr>
<td>It is not known whether Trifluridine-tipiracil or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of Trifluridine-tipiracil or its metabolites on the breastsed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with Trifluridine-tipiracil and for one day following the final dose.</td>
</tr>
<tr>
<td>Females and Males of Reproductive Potential</td>
</tr>
<tr>
<td>Females: Trifluridine-tipiracil can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment.</td>
</tr>
</tbody>
</table>
| Males: Because of the potential for genotoxicity, advise males with female
partners of reproductive potential to use condoms during treatment with Trifluridine-tipiracil and for at least 3 months after the final dose.

**Renal Impairment**
- Patients with moderate renal impairment had a higher incidence of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function.
- No dose adjustment is recommended to the starting dose of Trifluridine-tipiracil in those with mild or moderate renal impairment, but these patients may require dose modification due to toxicity; No data exist in patients with severe renal disease.

**Hepatic Impairment**
- No dose adjustments are needed in patients with mild to moderate hepatic dysfunction. No data exist in patients with severe liver disease.

**Pharmacogenetics/genomics**
- No data identified.

**Ethnicity**
- Primary study was conducted in both the United States and Japan.
- No significant differences in incidence of adverse events were noted between the Western and Asian study populations.
- Racial Distribution
  - 57% White
  - 35% Asian
  - 1% Black
  - 7% Missing

**Projected Place in Therapy**
- Trifluridine-tipiracil (LONSURF®) is FDA approved for the treatment of metastatic colorectal cancer in patients who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if KRAS wild-type, an anti-EGFR therapy.
- It is estimated that approximately 134,000 new cases of colon and rectal cancer will be diagnosed in the U.S. in 2016 and will result in 49,000 deaths. This makes it the 4th most frequently diagnosed and 2nd deadliest type of cancer.
- The evidence GRADE for trifluridine-tipiracil is moderate based on one large and well-designed clinical trial. The patient population was composed of mostly white males over the age of 60 which does correlate well with the VA population however there was limited ethnic and racial diversity in the study population.
- Currently regorafenib is the only medication which falls in a similar line of therapy and it currently holds a non-formulary status with criteria for use within the VA. Aside from regorafenib, best supportive care (BSC) is recommended in these patients.
- Trifluridine-tipiracil may be useful for patients who are required to take medications that are inhibitors/inducers of CYP3A4 that could interact with regorafenib.

*Updated version may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or PBM INTRAnet*
References


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Contact person: Berni Heron, Pharm.D., BCOP
National PBM Clinical Pharmacy Program Manager, Department of Veterans Affairs, Pharmacy Benefits Management
Appendix A: GRADEing the Evidence

<table>
<thead>
<tr>
<th>Quality of evidence designation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with &gt; 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.</td>
</tr>
<tr>
<td>Low</td>
<td>Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.</td>
</tr>
</tbody>
</table>

### Appendix B: Approval Endpoints (use for oncology NMEs)

#### Table 1. A Comparison of Important Cancer Approval Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Regulatory Evidence</th>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>Clinical benefit for regular approval</td>
<td>• Randomized studies essential</td>
<td>• Universally accepted direct measure of benefit</td>
<td>• May involve larger studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinding not essential</td>
<td>• Easily measured</td>
<td>• May be affected by crossover therapy and sequential therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Precisely measured</td>
<td>• Includes noncancer deaths</td>
</tr>
<tr>
<td>Symptom Endpoints (patient-reported outcomes)</td>
<td>Clinical benefit for regular approval</td>
<td>• Randomized blinded studies</td>
<td>• Patient perspective of direct clinical benefit</td>
<td>• Blinding is often difficult</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Data are frequently missing or incomplete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Clinical significance of small changes is unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Multiple analyses</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>• Lack of validated instruments</td>
</tr>
<tr>
<td>Disease-Free Survival</td>
<td>Surrogate for accelerated approval or regular approval*</td>
<td>• Randomized studies essential</td>
<td>• Smaller sample size and shorter follow-up necessary compared with survival studies</td>
<td>• Not statistically validated as surrogate for survival in all settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinding preferred</td>
<td></td>
<td>• Not precisely measured; subject to assessment bias, particularly in open-label studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinded review recommended</td>
<td></td>
<td>• Definitions vary among studies</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>Surrogate for accelerated approval or regular approval*</td>
<td>• Single-arm or randomized studies can be used</td>
<td>• Can be assessed in single-arm studies</td>
<td>• Not a direct measure of benefit in all cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinding preferred in comparative studies</td>
<td>• Assessed earlier and in smaller studies compared with survival studies</td>
<td>• Not a comprehensive measure of drug activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinded review recommended</td>
<td>• Effect attributable to drug, not natural history</td>
<td>• Only a subset of patients with benefit</td>
</tr>
<tr>
<td>Complete Response</td>
<td>Surrogate for accelerated approval or regular approval*</td>
<td>• Single-arm or randomized studies can be used</td>
<td>• Can be assessed in single-arm studies</td>
<td>• Not a direct measure of benefit in all cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinding preferred in comparative studies</td>
<td>• Durable complete responses can represent clinical benefit</td>
<td>• Not a comprehensive measure of drug activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinded review recommended</td>
<td>• Assessed earlier and in smaller studies compared with survival studies</td>
<td>• Small subset of patients with benefit</td>
</tr>
<tr>
<td>Progression-Free Survival (all deaths)</td>
<td>Surrogate for accelerated approval or regular approval*</td>
<td>• Randomized studies essential</td>
<td>• Smaller sample size and shorter follow-up necessary compared with survival studies</td>
<td>• Not statistically validated as surrogate for survival in all settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinding preferred</td>
<td>• Measurement of stable disease included</td>
<td>• Not precisely measured; subject to assessment bias, particularly in open-label studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blinded review recommended</td>
<td>• Not affected by crossover or subsequent therapies</td>
<td>• Definitions vary among studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Generally based on objective and quantitative assessment</td>
<td>• Frequent radiological or other assessments</td>
</tr>
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<td></td>
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<td>• Involves balanced timing of assessments among treatment arms</td>
</tr>
</tbody>
</table>

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

**Guidance for Industry:** Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.