Vandetanib (Caprelsa®)

Abbreviated National Drug Monograph

May 2015

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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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	Vandetanib is a tyrosine kinase inhibitor that selectively targets RET, VEGFR and EGFR pathway signaling. These targets are important kinases in the pathogenesis of medullary thyroid carcinoma.
Indication(s) Under Review in this document (may include off label)	Treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced or metastatic disease.
Dosage Form(s) Under Review	100 and 300 mg tablets
REMS	☒ REMS ☐ No REMS ☐ Postmarketing Requirements
Pregnancy Rating	Category D

Executive Summary	
Efficacy	• Vandetanib was approved through the expedited FDA Priority Review process. • Approval was based upon a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in unresectable, locally advanced or metastatic MTC. Documentation of radiographic progression was not a part of the trial inclusion, which may reflect the long PFS noted in the placebo arm. • OS data was immature at the data cutoff; final OS analysis is likely to be confounded by crossover design upon progression. • Quality of life was not evaluated.
Safety	• Vandetanib is only available through the REMS Program with Elements to Assure Safe Use, in which only certified prescribers can prescribe and certified pharmacies can dispense vandetanib. Biologics Specialty Pharmacy is the exclusive certified pharmacy to provide drug within the VA. • Boxed Warning notes risk of QT prolongation, Torsades de pointes and sudden death have occurred with vandetanib therapy. • Careful consideration of patient history, comorbidities, concomitant medications and ability to adhere to monitoring parameters are necessary for the safe management of vandetanib therapy.
Other Considerations	• Dose-reductions were made in a significant portion of study patients, therefore would expect reductions will be necessary among the Veteran population. • Impact of therapy on quality of life has not been assessed in a trial population.

Outcome in clinically significant area	At median 24 months: PFS not reached vs. 19.3 mos (vandetanib vs. placebo); Predicted PFS 30.5 mos OS data immature
Effect Size	PFS HR 0.46 [99% CI: 0.31-0.69; p<0.001]]
Potential Harms	≥ Gr 3: HTN (9%), diarrhea (11%), rash (5%), QT prolongation (8%), fatigue (6%)
Net Clinical Benefit	Minimal (low chance benefit; low chance harm)

Potential Impact	• Projected place in therapy. No therapy has shown a survival benefit in locally advanced or metastatic MTC. The benefit of vandetanib is an improvement in PFS in patients who are symptomatic with progressive MTC. Those who are asymptomatic with indolent disease should not be considered due to the risks outweighing potential benefits.

Background

Purpose for review

Recent FDA approval (2011)

Issues to be determined:
Does vandetanib offer advantages to currently available alternatives?
What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives	Other Considerations
Doxorubicin	Only FDA-approved cytotoxic agent; ORR 30% (all PR) as monotherapy; transient effect; no OS benefit; limited role Intravenous therapy
Cyclophosphamide Vincristine Dacarbazine [8]	(n=7); 28% (2) PR of 14 mos and biochemical response (↓ CEA, ↓ calcitonin) 29 mos; Toxicity: BMS, alopecia, GI toxicity Intravenous therapy
Doxorubicin Streptozocin Fluorouracil Dacarbazine[9]	(n=20); 15% (3) PR of 18-28 mos; 50% (10) SD mean 23 mos Toxicity: BMS, N/V, stomatitis, cardiac Intravenous therapy
Non-formulary Alternative (if applicable)	**Other Considerations**
Cabozantinib	FDA-approved for medullary thyroid cancer (MTC); MTC data: P3 (vs. PBO), PFS 11.2 vs. 4 mos; HR 0.28 [(95% CI 0.19-0.40) p<0.001]; ORR 28 vs. 0% (n=330); Oral agent
Sunitinib[11]	FDA-approved for RCC, PNET, GIST; MTC data (off-label): P2, ORR 42%, SD 28% (n=7); Oral agent
Sorafenib	FDA-approved for DTC, RCC, HCC; MTC data (off-label): P2, PR 6%, PFS 18 mos (n=16); Oral agent

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2015) using the search terms vandetanib and Caprelsa. 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. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Vandetanib vs. Placebo in locally advanced or metastatic MTC

Study design	Inclusion/Demographics	Intervention	Outcomes
Wells, et al.[3] P3, R, DB, PC, MC N=331 (V 231; P 100) 23 countries	Inclusion Adults; measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC; WHO PS 0-2, serum calcitonin ≥ 500 pg/ml Exclusion Significant cardiac, hematopoietic, hepatic or renal dysfunction; chemo and/or radiation therapy within 4 weeks of start	Vandetanib (V) 300 mg PO daily vs. placebo (PBO) daily until PD or intolerable toxicity R 2:1 Crossover from PBO to V allowed at PD Tumor assessments every 12 weeks	Vandetanib (V) 300 mg mg PO daily vs. placebo (PBO) daily until PD or intolerable toxicity Primary endpoint: PFS Secondary: OS, ORR, DCR, biochemical response (calcitonin, CEA) Median follow-up 24 mos; Vandetanib vs. PBO PFS Not reached vs.19.3 mos Predicted PFS 30.5 mos HR 0.46 [95% CI, 0.31-0.69; p<0.001] PFS @ 6 mos: 83 vs. 63% OS data immature at cutoff HR 0.89 [95% CI 0.48-1.65] ORR 45 vs. 13%; p<0.001 DCR 87 vs. 71% p=0.001 Calcitonin RR 69 vs. 3%; p<0.001 CEA RR 52 vs. 2%; p<0.001 DOT 90 vs. 40 wks Grade 3, 4 AEs: Diarrhea/colitis (11%), HTN (9%), QT prolonged (8%), fatigue (6%), rash (5%) Most common AEs : Diarrhea/colitis (57%), rash (53%), HTN (33%), nausea (33%), headache (26%), upper resp tract infection, decreased appetite, abdominal pain Dose-reductions 35 vs. 3% AEs led to DC of tx: 12 vs. 3% AEs led to death: 5 vs. 2 patients Causes: asp pna, resp arrest, resp failure, staph sepsis, arrhythmia/acute cardiac failure

DCR Disease Control Rate; DOT Duration of Therapy; CEA Carcinoembryonic antigen; PBO placebo

- Vandetanib was approved through the expedited FDA Priority Review process.
- Approval was based upon a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in unresectable, locally advanced or metastatic MTC. Documentation of radiographic progression was not a part of the trial inclusion, which may reflect the long PFS noted in the placebo arm.
- OS data was immature at the data cutoff; final OS analysis is likely to be confounded by crossover design upon progression.
- All secondary endpoints were met with statistically significant differences compared to the placebo arm.

- Response by *RET* mutational status is inconclusive owing to the small numbers of *RET*-negative and large number of those *RET*-unknown patients with sporadic MTC.
- An ongoing trial is evaluating the safety/efficacy of a lower 100 mg daily dose vs. the approved 300 mg dose.

Potential Off-Label Use

According to www.clinicaltrials.gov website, vandetanib is being actively researched in the following:

- In combination with everolimus for advanced cancers
- In combination with carboplatin for recurrent high-grade gliomas
- In combination with chemotherapy for NSCLC

Safety

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

	Comments
Boxed Warning	• **Risk of QT prolongation, Torsades de pointes and sudden death**: Vandetanib can prolong the QT interval. Torsades de pointes and sudden death have occurred. Do not use drug in patients with hypocalcemia, hypokalemia, hypomagnesemia or long QT syndrome; correct these electrolyte abnormalities prior to therapy; monitor electrolytes; avoid drugs that prolong the QT interval. Only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense vandetanib.
Contraindications	• Avoid use in patients with congenital long QT syndrome.
Warnings/Precautions	• **QT Prolongation and Torsades de Pointes.** Torsades de pointes, ventricular tachycardia and sudden deaths have occurred in patients treated with vandetanib, therefore patients who have a history of Torsades, congenital long QT syndrome, bradyarrhythmias or recent MI should not receive vandetanib. Treatment should not be started in patients whose QTcF interval is greater than 450 ms. The drug has not been studied in patients with ventricular arrhythmias or recent MI. Obtain an ECG and serum potassium, calcium, magnesium and TSH at baseline, 2-4 weeks and 8-12 weeks after starting treatment, and every 3 months thereafter. Monitor electrolytes and ECGs more frequently in patients who experience diarrhea. Following any dose reduction for QT prolongation or any dose interruption greater than 2 weeks, conduct QT assessments as previously described. Maintain serum magnesium and calcium levels within normal ranges to reduce the risk of QT prolongation. Avoid using vandetanib with drugs known to prolong the QT interval. If such drugs are given to patients already receiving vandetanib and no alternative therapy exists, perform ECG monitoring of the QT interval more frequently. Stop vandetanib in patients who develop a QTcF greater than 500 ms until the QTcF returns to less than 450 ms. Dosing can then be resumed at a reduced dose. • **Skin Reactions and Stevens-Johnson Syndrome.** Severe skin reactions, some leading to death, have occurred in patients receiving vandetanib. Consider permanent discontinuation for severe reactions. Photosensitivity reactions can occur during treatment and up to 4 months following treatment discontinuation. • **Interstitial Lung Disease (ILD).** ILD or pneumonitis, including fatal cases, has occurred in patients treated with vandetanib. Consider a diagnosis of ILD in patients presenting with non-specific respiratory signs/symptoms. Interrupt therapy for acute or worsening pulmonary symptoms. Discontinue therapy if ILD is confirmed. • **Ischemic Cerebrovascular Events.** In the MTC trial, ischemic

cerebro-vascular events occurred more often in the vandetanib arm vs. placebo (1.3 vs. 0%, respectively). It is unclear if it is safe to resume vandetanib after such an event. Discontinue therapy in patients who experience a severe ischemic cerebrovascular event.

- **Hemorrhage.** Serious bleeding, including fatalities, have occurred in patients receiving vandetanib. Do not give vandetanib to patients with a recent history of hemoptysis of $\geq$ ½ teaspoon of red blood; discontinue in cases of severe hemorrhage.
- **Heart Failure.** Cases of heart failure, including fatalities, have occurred in patients receiving vandetanib. Monitor for signs/symptoms of heart failure. Consider drug discontinuation in patients with heart failure. Heart failure may not be reversible when therapy is stopped.
- **Diarrhea.** Diarrhea $\geq$ Grade 3 was noted in 11% of patients receiving vandetanib in the MTC study. Monitor serum electrolytes and ECGs, should diarrhea occur, to reduce risk of QT prolongation from dehydration. Interrupt therapy for severe diarrhea. Upon improvement, resume therapy at a reduced dose.
- **Hypothyroidism.** In the MTC study, in which 90% of patients had prior thyroidectomy, increased dosing of thyroid replacement therapy was required in 49% of vandetanib-treated patients vs. 17% of placebo-treated patients. Obtain TSH at baseline, at 2-4 weeks and 8-12 weeks after starting vandetanib treatment, and every 3 months thereafter. If signs/symptoms of hypothyroidism occur, examine thyroid hormone levels and adjust replacement therapy accordingly.
- **Hypertension (HTN).** HTN and hypertensive crisis has occurred in patients treated with vandetanib. Monitor all patients for HTN. Dose reduction or interruption of therapy may be necessary. Do not continue vandetanib if HTN cannot be controlled.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** RPLS has occurred in patients treated with vandetanib. Consider RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. In clinical studies, 3 of 4 patients who developed RPLS also had HTN. Discontinue vandetanib treatment in patients with RPLS.
- **Drug Interactions.** Avoid administration of vandetanib with anti-arrhythmic drugs and other drugs that may prolong the QT interval.
- **Renal Impairment.** Vandetanib exposure is increased in patients with impaired renal function. Reduce starting dose to 200 mg in patients with moderate to severe renal impairment; monitor the QT interval closely. There is no information about patients with end-stage renal disease requiring dialysis.
- **Hepatic Impairment.** Vandetanib is not recommended for use in patients with moderate to severe hepatic impairment, as safety and efficacy have not been established.
- **Embryofetal Toxicity.** Vandetanib can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant while taking this drug, they should be apprised of the potential hazard to the fetus. Advise women of childbearing potential that they must use effective contraception during treatment and for at least 4 months following the last dose.
- **REMS Program.** Vandetanib is only available through a restricted distribution program called the CAPRELSA REMS Program due to the risk of QT prolongation, Torsades de pointes and sudden death. Due to the potential for serious adverse events, vandetanib is only

	available through the Vandetanib Risk Evaluation and Mitigation Strategy (REMS) Program with Elements to Assure Safe Use (ETASU). Under the Vandetanib REMS Program, only program-certified prescribers can prescribe vandetanib and the prescriptions can only be filled and dispensed by program-certified pharmacies. VA pharmacies are <u>not</u> authorized by the program to serve as Vandetanib REMS certified pharmacies and therefore cannot dispense vandetanib. <u>Biologics Specialty Pharmacy is the exclusive certified pharmacy for this medication</u>. The VA prescriber should complete the ***<u>Vandetanib Prescription Form for VA</u>*** and forward the form to the VA pharmacy for review. Once reviewed, the pharmacy should fax the document along with a purchase order number to Biologics Specialty Pharmacy (800) 823-4506. Please only use this VA-specific form as the release of patient information is limited and the operational details are specific to VA.

Safety Considerations

- Vandetanib is only available through the REMS Program with Elements to Assure Safe Use, in which only certified prescribers can prescribe and certified pharmacies can dispense vandetanib. Biologics Specialty Pharmacy is the exclusive certified pharmacy to provide drug within the VA.
- Careful consideration of patient history, comorbidities, concomitant medications and ability to adhere to monitoring parameters are necessary for the safe management of vandetanib therapy.
- Patients experiencing severe diarrhea should have electrolytes and ECG monitoring to reduce risk of potential QT prolongation resulting from dehydration.
- Patient education and diligent monitoring is necessary to ensure safe use.

Adverse Reactions

Common adverse reactions	Incidence $\geq$ 20%: diarrhea/colitis, rash, acneiform dermatitis, HTN, nausea, headache, upper respiratory tract infection, decreased appetite, abdominal pain
Death/Serious adverse reactions	Grade 3, 4 events: diarrhea/colitis, rash, abdominal pain, HTN, fatigue, ECG QT prolonged, decreased appetite, hypocalcemia, ALT increase
Discontinuations due to adverse reactions	Dose-reductions in 83 (36%); dose-interruptions in 109 (47%) DC due to adverse reactions: 12 vs. 3% (vandetanib vs. placebo, respectively) Reactions leading to DC: asthenia, rash, diarrhea, pyrexia, elevated creatinine, QT prolongation, HTN

Drug Interactions

Drug-Drug Interactions

- Strong CYP3A4 inducers can decrease vandetanib plasma concentrations.
- Avoid concomitant use of St. John's Wort, as it can decrease vandetanib exposure unpredictably.
- Vandetanib can increase plasma concentrations of drugs transported by the organic cation transporter type 2 (OCT2), such as metformin. Use caution and closely monitor for toxicities when both are given.
- Use caution and closely monitor for toxicities when administering vandetanib with digoxin, as plasma digoxin levels can be increased.
- Avoid concomitant use of drugs that may prolong the QT interval.

Risk Evaluation

As of May 2015

Comments

Sentinel event advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Vandetanib 100, 300mg tab	Axitinib Cabozantini Dasatinib Erlotinib Gefitinib Imatinib Lapatinib Lenvatinib Nilotinib, Nintedanib Pazopanib Sorafenib Sunitinib Vemurafenib Vismodegib	None	None	Vardenafil
Caprelsa	None	None	None	Carbidopa Celexa

- 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

- American Thyroid Association (ATA) 2015 Guidelines recommend that single or combination cytotoxic chemotherapy should not be given as first-line therapy in patients with persistent or recurrent MTC given the low response rates and advent of promising new treatment options.[ref] Grade D Recommendation (Recommends against based on expert opinion).[6]
- ATA 2015 Guidelines recommend that patients with significant tumor burden and symptomatic or progressive metastatic disease according to RECIST treatment with TKIs targeting both RET and VEGFR tyrosine kinases should be considered as systemic therapy. Vandetanib or cabozantinib can be used as single agent first line systemic therapy in patients with advanced progressive MTC. Grade A Recommendation (Strongly recommends, based on good evidence that the intervention can improve important health outcomes; evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes).[6]
- The European Thyroid Association Task Force developed guidelines in 2012 which includes the recommendation that patients should not be given standard chemotherapy as first-line therapy if they have persistent or recurrent MTC and significant tumor burden, are symptomatic or with progressive disease. Quality of Evidence = ++ (Moderate quality; studies with methodological flaws, showing inconsistent or indirect evidence); Strength of Recommendation: Grade 2 (Weak recommendation; best action may differ depending on circumstances or patient values; benefits and risks or burdens are closely balanced, or uncertain).[7]
- The European Thyroid Association Task Force developed guidelines in 2012 which includes the recommendation that inhibitors of both RET and VEGFR tyrosine kinases appear to be the most effective treatment modality in these MTC patients. Quality of Evidence = +++ (High quality; evidence at low risk of bias, such as randomized trials showing consistent results directly applicable to the recommendation); Strength of Recommendation = Grade 1 (Strong recommendation; applies to most patients in most circumstances; benefits clearly outweigh the risk).[7]
- NCCN Guidelines version 2.2014 list vandetanib and cabozantinib as Category 1 ratings as therapeutic options for recurrent or persistent medullary thyroid carcinoma with distant metastases. Consideration can be given in asymptomatic disease (unless stable or slowly progressive indolent disease) or symptomatic disease or progression. Other TKIs (sunitinib or sorafenib) can be considered if patients progress on vandetanib or cabozantinib or either drug are not available/appropriate.[3]
- NCCN also provides Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer, which points out that several factors should be considered regarding TKI therapy:
    - Therapy is not curative, but can prolong PFS
    - Therapy can be expected to cause significant side effects that can affect quality of life
    - The natural history of DTC and MTC is variable, ranging from months to years
    - Pace of disease progression should be considered as those asymptomatic with indolent disease may not benefit; those with rapidly progressive disease may benefit despite side effect profile
    - Optimal management of kinase inhibitor side effects is essential; guidelines to address dermatologic, hypertensive and GI side effects can be used, as well as dose modification and holding therapy

Outcome in clinically significant area	At median 24 months: PFS not reached vs. 19.3 mos (vandetanib vs. placebo); Predicted PFS 30.5 mos OS data immature
Effect Size	PFS HR 0.46 [99% CI: 0.31-0.69; p<0.001]]
Potential Harms	≥ Gr 3: HTN (9%), diarrhea (11%), rash (5%), QT prolongation (8%), fatigue (6%)
Net Clinical Benefit	Minimal (low chance benefit; low chance harm)

Dosing and Administration

- Recommended dose is 300 mg orally, once daily with or without food until disease progression or unacceptable toxicity.
- Vandetanib is available in two dosage strengths (100 mg, 300 mg), each packaged in bottles of 30 tablets.
- Refer to prescribing information for dose adjustments due to adverse reactions or renal impairment and information about drug administration through nasogastric or gastrostomy tubes.

Special Populations (Adults)

	Comments
Elderly	• No data identified
Pregnancy	• Category D. Vandetanib can cause fetal harm when given to a pregnant woman. Animal studies indicate that vandetanib is embryolethal at exposures less than or equal to those expected at the recommended human dose of 300 mg/day. If used during pregnancy or if the patient becomes pregnant while taking the drug, they should be apprised of the potential hazard to the fetus.
Females and Males of Reproductive Potential	• Use effective contraception during treatment and for up to 4 months after completion of therapy. • There are no data on the effect on human fertility; male and female fertility were impaired in animal studies.
Lactation	• Unknown if excreted in human milk; patient needs to consider either to discontinue nursing or discontinue drug therapy.
Renal Impairment	• Drug exposure is increased with impaired renal function. The starting dose should be reduced to 200 mg in those with moderate renal impairment (CrCl 30-50 ml/min) and severe renal impairment (CrCl < 30 ml/min).
Hepatic Impairment	• There are limited data in patients with liver impairment (Tbili > 1.5x ULN); use in moderate and severe hepatic impairment is not recommended
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Medullary Thyroid Cancer (MTC) is rare. MTC is reported to account for 3-5% of ~56,000 cases of the thyroid gland in 2012. The majority (75%) of cases occur sporadically with the REarranged during Transfection gene (RET) mutated in ~25%. Patients with sporadic MTC typically present in their 50s-60s. Hereditary cases account for the minority (25%), yet RET mutations are found ~95% of these cases. The age onset of hereditary MTCs varies with the specific genetic mutation, but typically presents in early adulthood.[3,4]
- ATA, European Thyroid Association Task Force and NCCN all support the use of cabozantinib and vandetanib as first-line therapeutic options in patients with persistent or recurrent MTC, unless the disease is indolent and the patient is asymptomatic.
- Vandetanib has not been directly compared to cabozantinib. The variation in toxicity profile and comorbid conditions of the individual patient may help guide therapy. Neither therapy is curative. Long-term use of either drug will require aggressive, proactive management of toxicities for safe use. The intensity of management and toxicities may negatively impact quality of life.
- There is no data to support the optimal sequence of these drugs.

References

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	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).
Moderate	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 > 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.
Low	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.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

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

*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.