Cabozantinib (Cometriq™)

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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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	Cabozantinib is an oral tyrosine kinase inhibitor that targets three relevant pathways in medullary thyroid carcinoma (MTC): MET, VEGFR2 and RET.
Indication(s) Under Review in this document	Treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).
Dosage Form(s) Under Review	20 mg and 80 mg capsules
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements
Pregnancy Rating	Category D

Executive Summary	
Efficacy	• Cabozantinib was approved through the expedited FDA Priority Review process. • The FDA approval of cabozantinib was based on a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients documented radiographic progression of metastatic medullary thyroid cancer (MTC). • All pre-specified patient subgroups appeared to benefit from treatment. These subgroups included age, previous TKI therapy, presence of bone metastases at baseline, hereditary or sporadic forms of MTC. • Overall survival (OS) was not different between groups at the interim analysis. • Quality of life was not evaluated.
Safety	• Boxed Warning notes risk of GI perforations and fistulas, as well as risk of severe and sometimes fatal hemorrhage in cabozantinib-treated patients. • Patient education about Palmar-Plantar Erythrodysesthesia Syndrome (PPES) will be necessary to safely manage this common toxicity. • Careful consideration of patient history and comorbidities, particularly with regard to potential toxicities consistent with VEGF inhibition (i.e. risk of bleed, HTN, impaired wound healing). • Risk of ONJ – providers should perform an oral examination prior to the start of therapy; good oral hygiene practices should be stressed to the patient.
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 interim analysis, median 14 months: PFS 11.2 vs. 4 mos (cabozantinib vs. placebo); OS not different At 1 year: PFS 47.4 vs. 7.2%
Effect Size	PFS HR 0.28[99% CI: 0.19-0.40; p<0.001] OS HR 0.98 [95% CI, 0.63-1.52]
Potential Harms	≥ Gr 3: HTN (8%), diarrhea (16%), PPES (13%),

		hypocalcemia (12%), lymphopenia (16%), fatigue (9%)
	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 cabozantinib 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. • Patient convenience. Blister-packaging may ease concern about taking the proper combination of dosage strengths. • Dispensing a full 30-day supply may result in excess drug waste if daily dose needs to be modified.	

Background

Purpose for review

Recent FDA approval (2012)

Issues to be determined:
Does cabozantinib 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**
Vandetanib	FDA-approved for medullary thyroid cancer (MTC); MTC data: P3 (vs. PBO), PFS 30.5 vs. 19.3 mos; HR 0.46, 95% CI 0.31-0.69; ORR 45 vs. 13% (n=331) Oral agent; REMS for risk of QT prolongation, torsades and sudden death
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 cabozantinib and Cometriq. 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

Cabozantinib vs. Placebo in locally advanced or metastatic MTC

Study design	Inclusion/Demographics	Intervention	Outcomes
Elisei, et al.[3] P3, R, DB, PC, MC N=330 (C 219; P 111) 23 countries	Inclusion Adult patients, histology confirmed MTC; unresectable, locally advanced or metastatic disease; ECOG PS 0-2; PD on radiologic scan at screen compared to image 14 mos prior;ANC $\geq$ 1500/mm^3; platelets $\geq$ 100,000/mm^3; hemoglobin $\geq$ 9 g/dL; bilirubin $\leq$ 1.5 x ULN (unless Gilbert's syndrome), SCr $\leq$ 1.5 mg/dL; ALT, AST $\leq$ 2.5 x ULN Exclusion Prior systemic therapy in 4 weeks prior; radiation $\geq$ 25% of bone marrow; brain mets or spinal cord compression allowed if stable without steroid or anti-convulsant for $\geq$ 10 days; hemoptysis; urine protein/creatinine ratio $\geq$ 1; pregnant or breastfeeding; active infection requiring treatment; HTN despite treatment; unhealed surgical wounds; cardiac arrhythmias; CHF or unstable angina in past 3 months; MI, CVA, TIA in past 6 months	Cabozantinib (C) 140 mg PO daily vs. placebo (PBO) daily until PD or intolerable toxicity R 2:1 Stratified by age, prior TKI (yes/no) No crossover from PBO to C arm Tumor assessments every 12 weeks	Cabozantinib (C) 140 mg PO daily vs. placebo (PBO) daily until PD or intolerable toxicity Primary endpoint: PFS Secondary: OS, ORR Median follow-up 13.9 mos; Cabozantinib vs. PBO PFS 11.2 vs. 4 mos HR 0.28 [95% CI, 0.19-0.40; p<0.001] Benefit maintained in all pre-specified subgroups. PFS at 1 yr: 47.4 vs. 7.2% (C vs. PBO) ORR 28 vs. 0%; p<0.001 DOR 14.6 mos (11.1-17.5 mos) OS at interim analysis: no diff HR 0.98 [95% CI, 0.63-1.52] Grade 3, 4 AEs 69 vs. 33% Most common AEs diarrhea (16%), PPE (13%), fatigue (9%), HTN (70%) Dose-reductions 79 vs. 9% Due to diarrhea, PPE, nausea Dose-interruptions 65 vs. 17% AEs led to DC of tx: 16 vs. 8% SAEs: 42.1 vs. 22.9% Mucosal inflammation (3%), hypocalcemia (3%), PE (2.3%), HTN (2.3%)

- Cabozantinib was approved through the expedited FDA Priority Review process.
- The FDA approval of cabozantinib was based on a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients documented radiographic progression of metastatic medullary thyroid cancer (MTC).
- All pre-specified patient subgroups appeared to benefit from treatment. These subgroups included age, previous TKI therapy, presence of bone metastases at baseline, hereditary or sporadic forms of MTC.

- At the planned interim analysis (after 44% of deaths) there was no difference in OS; an unplanned analysis at the 120-day update at the FDA's request (after 75% of deaths), there was no significant difference in OS noted. Median survival was 26 vs. 20.3 months (cabozantinib vs. placebo, respectively).[2]
- Upon FDA review, there was question about the studied dose with respect to the adverse effect profile and lack of exposure-response relationship noted by the Clinical Pharmacology reviewers. A post-marketing trial is required to evaluate a lower dose.[2]

Potential Off-Label Use

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

- Cholangiocarcinoma
- Castrate-resistant metastatic prostate cancer
- Merkel-cell carcinomas
- In combination with erlotinib for NSCLC
- Hepatocellular carcinoma post-sorafenib therapy
- In combination with gemcitabine for pancreatic cancer

Safety

	Comments
Boxed Warning	• **Risk of perforations and fistulas**: GI perforation occurred in 3% and fistula formation in 1% of cabozantinib-treated patients. • **Severe, sometimes fatal hemorrhage** including hemoptysis and GI hemorrhage occurred in 3% of treated patients.
Contraindications	• None
Warnings/Precautions	• **Perforations and Fistulas.** Perforation were reported in 3% and fistulas reported in 1%; all events were serious; one GI fistula was fatal (<1%). Non-GI fisulas (including tracheal/esophageal) were reported in 4% of patients with 2 (1%) resulting in fatality. • **Hemorrhage.** Serious and fatal hemorrhage has occurred. The incidence of Grade ≥ 3 bleed events was higher with cabozantinib vs. placebo (3 vs. 1%, respectively). Do not administer in patient with recent history of hemorrhage or hemoptysis. • **Thrombotic events.** Increased incidence of thrombotic events have been reported in cabozantinib vs. placebo-treated patients: VTE 6 vs. 3%; ATE 2 vs. 0%, respectively. Discontinue therapy in patients who develop acute MI or any other clinically significant arterial thromboembolic complication. • **Wound complications** have been reported. Stop treatment with cabozantinib at least 28 days prior to scheduled surgery. Resume treatment post-surgery based upon clinical judgement of adequate wound healing. Withhold therapy if dehiscence or healing complications requiring medical intervention. • **Hypertension (HTN).** Therapy has resulted in treatment-emergent hypertension (stage 1 or 2 per modified JNC criteria) in 61 vs. 30% of cabozantinib vs. placebo-treated patients. Monitor blood pressure prior to initiation of therapy and at regular intervals during treatment. Hold drug for HTN that is not adequately controlled with medical management; resume at reduced dose when BP is controlled. Discontinue drug for severe HTN that cannot be controlled with antihypertensive therapy. • **Osteonecrosis of the Jaw (ONJ).** ONJ occurred in 1% of cabozantinib-treated patients and can manifest as jaw pain,

	osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral exam prior to initiation of therapy and periodically during therapy. Advise patients regarding good oral hygiene practice. For invasive dental procedures, withhold therapy for at least 28 days prior to scheduled surgery, if possible. • **Palmar-Plantar Erythrodysesthesia Syndrome (PPES).** PPES occurred in 50% of patients treated with cabozantinib and was severe (≥ Grade 3) in 13%. Withhold therapy in patients who develop intolerable Grade 2 PPES or Grade 3-4 PPES until improvement to Grade 1; resume cabozantinib at a reduced dose. • **Proteinuria.** Proteinuria was noted in 4 (2%) patients receiving cabozantinib, including one with nephrotic syndrome vs. none who received placebo. Monitor urine protein regularly during treatment; discontinue treatment in patients who develop nephrotic syndrome. • **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** RPLS was reported in one (< 1%) patient. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue therapy in patients who develop RPLS. • **Drug Interactions**. Avoid administration of cabozantinib with drugs that are strong CYP3A4 inducers or inhibitors. • **Hepatic Impairment.** Cabozantinib is not recommended for use in patients with moderate or severe hepatic impairment. • **Embryo-fetal toxicity.** Cabozantinib can cause fetal harm. If used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Safety Considerations

- Patient education and diligent monitoring is necessary to ensure safe use.
- Careful consideration of patient history and comorbidities, particularly with regard to potential toxicities consistent with VEGF inhibition (i.e. risk of bleed, HTN, impaired wound healing).
- Risk of ONJ – providers should perform an oral examination prior to the start of therapy; good oral hygiene practices should be stressed to the patient.
- Fistula formation is rare but potentially life-threatening. Upper airway fistulas that develop while on antiangiogenic tyrosine kinase inhibitor therapies have been associated with prior external beam radiotherapy and large tumors invading neck structures[14].

Adverse Reactions

Common adverse reactions	Incidence ≥ 25%: diarrhea, stomatitis, PPES, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, HTN, abdominal pain, constipation Incidence of lab abnormalities ≥ 25%: increased AST, increased ALT, lymphopenia, increased ALP, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, hyperbilirubinemia
Death/Serious adverse reactions	Grade 3,4 events: diarrhea, PPES, lymphopenia, hypocalcemia, fatigue, HTN, asthenia, increased ALT, decreased weight/appetite, stomatitis Fatal reactions in 6%: hemorrhage, pneumonia, septicemia, fistulas, cardiac arrest, respiratory failure
Discontinuations due to adverse reactions	Dose-reductions: 79 vs. 9% (cabozantinib vs. placebo, respectively) DC due to adverse reactions: 16 vs. 8% (cabozantinib vs. placebo, respectively) Reactions leading to DC: hypocalcemia, increased lipase, PPES, diarrhea, fatigue, HTN, nausea, pancreatitis, fistula formation, vomiting

Drug Interactions

Drug-Drug Interactions

- Effect of CYP3A4 Inhibitors. Administration of a strong CYP3A4 inhibitor (ketoconazole) to healthy subjects increased single-dose plasma cabozantinib exposure ($AUC_{0\text{-}inf}$) by 38%. Avoid taking a strong CYP3A4 inhibitor when taking cabozantinib.
- Effect of CYP3A4 Inducers. Administration of a strong CYP3A4 inducer (rifampin) to healthy subjects reduced single-dose plasma cabozantinib exposure ($AUC_{0\text{-}inf}$) by 77%. Avoid chronic co-administration of strong CYP3A4 inducers.

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
Cabozantinib 20, 80mg cap	Axitinib Bosutinib Cabazitaxel Crizotinib Dasatinib Imatinib Nilotinib Regorafenib Ruxolitinib Vandetanib Vemurafenib	None	None	Carfilzomib
Cometriq	None	None	None	Myrbetriq Pristiq

- 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 interim analysis, median 14 months: PFS 11.2 vs. 4 mos (cabozantinib vs. placebo); OS not different At 1 year: PFS 47.4 vs. 7.2%
Effect Size	PFS HR 0.28[99% CI: 0.19-0.40; p<0.001] OS HR 0.98 [95% CI, 0.63-1.52]
Potential Harms	≥ Gr 3: HTN (8%), diarrhea (16%), PPES (13%), hypocalcemia (12%), lymphopenia (16%), fatigue (9%)
Net Clinical Benefit	Minimal (low chance benefit; low chance harm)

Dosing and Administration

- Recommended dose is 140 mg orally, once daily. Dose should consist of 3 x 20 mg caps plus 1 x 80 mg cap.
- Cabozantinib is an oral formulation that is available in two dosage strengths that are blister packed. The capsules are supplied in cartons of 4 cards. Each card is a 7-day blister card. The drug can be purchased as a 28-day supply of the following daily strengths: 140 mg, 100 mg and 60 mg. The reduced doses correspond to the recommended dose modifications provided by the manufacturer. Due to the rate of dose interruptions and reductions by study patients, there is a potential for drug waste as patients change dosage.
- Dose should be taken on an empty stomach; instruct patients not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib.
- Refer to prescribing information for dosage adjustments due to adverse reactions or drug interactions.

Special Populations (Adults)

	Comments
Elderly	• No data identified
Pregnancy	• Category D. Fetal harm can result if administered to a pregnant woman. Animal studies indicate that cabozantinib is embryolethal at very low doses (less than 1% of human exposure by AUC at the recommended dose). 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	• No dose adjustment is recommended for mild or moderate renal impairment; there is no experience in severe renal impairment
Hepatic Impairment	• Not recommended for use in moderate or severe hepatic impairment as safety and efficacy have not been established.
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.
- Cabozantinib has not been directly compared to vandetanib. 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.

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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.