Obinutuzumab (Gazyva) Update: Follicular Lymphoma Indication

National Drug Monograph Addendum

April 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 comprehensive 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.

This Addendum highlights the latest FDA-approved indication (Follicular Lymphoma).
Refer to Obinutuzumab (GAZYVA) Drug Monograph for data regarding the Chronic Lymphocytic Leukemia (CLL) indication.

FDA Approval Information

Description/Mechanism of Action	Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the cell surface of B-lymphocytes; binding to CD20 results in B-cell death via (1) engagement of immune effector cells (2) direct cell death and/or (3) activation of complement cascade
Indication(s) Under Review in this document (may include off label)	Obinutuzumab is approved • in combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen
Dosage Form(s) Under Review	Available as a 1000 mg/40 ml (25 mg/ml) single-use vial
REMS	☐ REMS ☒ No REMS *See Other Considerations for additional REMS information*
Pregnancy Rating	Likely to cause fetal B-cell depletion; may harm unborn baby

Executive Summary

Efficacy	• Obinutuzumab received FDA-approval based upon demonstration of improvement in Progression-Free Survival (PFS) among patients with FL who had no response or disease progression during or within 6 months of a rituximab-containing regimen [HR 0.48 (95% CI 0.34-0.68); p<0.001] • Patients were randomized to obinutuzumab + bendamustine or bendamustine alone for 6 cycles, followed by obinutuzumab monotherapy for up to 2 years. • Secondary endpoints of ORR and OS were not different between groups at time of analysis.
Safety	• Boxed warning highlights risk of HBV reactivation and risk of PML. • Infusion-related reactions can be severe and life-threatening, especially with the initial dose; premedication and monitoring are necessary. • Bone marrow suppression can be severe and prolonged; Antimicrobial prophylaxis may be considered. • Grade ≥ 3 neutropenia and infusion-related reactions were noted in the obinutuzumab + bendamustine arm, compared to bendamustine alone; more Grade ≥ 3 thrombocytopenia and pneumonia were noted in the bendamustine alone arm
Other Considerations	• Prior to initiating therapy, patients should be evaluated for risk of Tumor Lysis Syndrome (TLS) and risk for bleeding, due to expected thrombocytopenia

Outcome in clinically significant area	O+B vs. B: PFS 29.2 vs. 13.7 mos
Effect Size	O+B vs. B: HR 0.48; 95% CI 0.35-0.67; p<0.001
Potential Harms (Grade ≥ 3)	O+B vs. B

		Neutropenia 33 vs. 26% IRR 8.8 vs. 3.5% Thrombocytopenia 11 vs. 16% Anemia 8 vs. 10% Pneumonia 2.6 vs. 5.6%
	Net Clinical Benefit	n/a (expedited review)
	Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%) Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)	
Potential Impact	• Obinutuzumab + bendamustine, followed by maintenance obinutuzumab x 2 years is a therapeutic option for patients with FL for whom rituximab-based therapy is not an option	

Background

Purpose for review

FDA-approval 2/2016

Issues to be determined:

- ✔ Evidence of need
- ✔ Does obinutuzumab offer advantages to currently available alternatives?
- ✔ What safety issues need to be considered?
- ✔ Does obinutuzumab have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options[2-7]

Formulary Alternatives	Other Considerations
None	

Non-formulary Alternative (if applicable)	Other Considerations
Idelalisib	Dose: 150 mg PO twice daily FDA approval: relapsed FL s/p at least 2 prior therapies P2 trial in 125 adults (median age 64 yrs) with indolent NHL (FL 58%); relapsed/refractory to rituximab; Median 4 prior therapies Results after follow-up at 9.7 months: ORR 57% (CR 6%), median DOR 12.5 mos; PFS 11 mos: OS 20 mos; est'm 1-yr survival 80% Toxicity, all: diarrhea 43%; fatigue 30%; nausea 30% Grade 3, 4 tox: neutropenia 27%; AST/ALT ↑ 13%; diarrhea 13%; pneumonia 7% Boxed warning: Risk of hepatotoxicity, severe diarrhea/colitis, pneumonitis, GI perforation FDA warning: SAEs and death reported in trials of idelalisib in combo with other anticancer therapies
Ibritumomab tiuxetan (Zevalin)	Radioimmunotherapy; a murine anti-CD20 MoAb conjungated to Yttrium-90 ORR 65-83%; CR 20-37% Median duration of CR ~47 months Toxicity: prolonged cytopenias Requires clinical expertise and logistics for radiolabeled therapy

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2016) using the search terms obinutuzumab and Gazyva. 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

Efficacy Measures (see Appendix B: Approval Endpoints)

The following outcomes are commonly evaluated in the NHL trial setting:

Objective Response Rate (ORR)
Complete Response (CR), Partial Response (PR),
Stable Disease (SD), Progressive Disease (PD)
Progression-Free Survival (PFS)
Overall Survival (OS)
Duration of Response (DOR)

Summary of efficacy findings

- The FDA approved obinutuzumab in combination with bendamustine, followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen.
- This approval is based upon interim results from the phase 3 GADOLIN study, which is available in abstract form.
- In summary, GADOLIN was an international, open-label phase 3 trial that included 413 rituximab-refractory, CD20-positive patients with indolent NHL.
- Rituximab-refractory was defined as:
  - Patient did not respond to rituximab as monotherapy or rituximab in combination with chemotherapy OR
  - Patient progressed within 6-months of completion of last dose of a rituximab-containing regimen (after at least 4 doses of monotherapy or 4 cycles of rituximab + chemotherapy)
- Patients were randomized 1:1 to receive either of the following:
  - Obinutuzumab 1000 mg IV on days 1, 8 and 15 of cycle #1, then on day 1 of cycles #2-6 plus bendamustine 90 mg/m2/day IV on days 1 and 2 of cycles #1-6; after CR, PR or SD patients received obinutuzumab maintenance 1000 mg IV every 2 months for 2 years or until PD
  - Bendamustine 120 mg/m2/day on days 1 and 2 of cycles #1-6
- Response was monitored via CT scan post-induction, then every 3 months x 2 years, then every 6 months
- Demographics: Median age 63 years; with median 2 prior therapies; ECOG PS not reported

	Obinutuzumab + bendamustine (n=194)	Bendamustine (n=202)
Prior R + chemotherapy	80.4%	77.7%
Prior R monotherapy	19.6%	22.3%
Follicular lymphoma	79.9%	82.2%
Marginal zone lymphoma	13.9%	9.4%
Small lymphocytic lymphoma	6.2%	7.9%

- Results at median follow-up of 21 months; study unblinded as primary endpoint had been reached

	Obinutuzumab + bendamustine (n=194)	Bendamustine (n=202)	Stratified HR (95% CI); p value
IRF-assessed PFS			
Events	71 (37%)	104 (51%)	
Median PFS, months (95% CI)	NR (22.5-NR)	14.9 (12.8-16.6)	0.55 (0.40-0.74); p=0.0001
Investigator-assessed PFS			
Median PFS, months (95% CI)	29.2 (20.2-NR)	14 (11.7-16.0)	0.52 (0.39-0.70); p<0.0001
Median OS	NR	NR	0.82 (0.52-1.30); p=0.4017
End-of-induction ORR	69.2%	63%	NS
Best ORR at 12 months	78.7%	76.7%	NS

Potential Off-Label Use

Studies listed in www.clinicaltrials.gov include:

- Obinutuzumab in combination with fludarabine/cyclophosphamide or bendamustine in the first-line CLL setting
- Ibrutinib plus obinutuzumab in previously untreated and relapsed, refractory CLL setting
- Obinutuzumab plus CHOP in diffuse large B-Cell NHL
- Obinutuzumab plus CHOP or FC in relapsed/refractory follicular NHL

Safety

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

	Comments
Boxed Warning	• Risk of Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death • Progressive Multifocal Leukoencephalopathy (PML) resulting in death
Contraindications	• None
Warnings/Precautions	• **HBV reactivation.** HBV reactivation has been reported in patients who are hepatitis B surface antigen positive and also in patients who are HBsAg negative but are hepatitis B core antibody positive and those who appear to have resolved hepatitis B infection. All patients should be screened for HBV infection prior to starting treatment with obinutuzumab. Screening should include measuring HBsAg and anti-HBc. For patients with evidence of HBV infection, a physician with Hepatitis B expertise should be consulted regarding monitoring and consideration for antiviral therapy. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with obinutuzumab. If HBV reactivation occurs while receiving obinutuzumab, immediately stop drug with any concomitant chemotherapy and institute appropriate treatment. Insufficient data exist regarding safety of resuming therapy in those who develop HBV reactivation. • **Progressive Multifocal Leukoencephalopathy (PML).** PML has been observed in patients treated with obinutuzumab. Discontinue obinutuzumab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. • **Infusion Reactions.** Severe and life-threatening infusion reactions can occur with obinutuzumab. Overall, 69% of indolent NHL patients experienced an infusion-related reaction (IRR). During cycle #1, the incidence of IRR was 55% (all grades) with 9% (Grades 3, 4). The highest incidence was on day 1 at 38% and decreased with subsequent infusions: day 2 (25%), day 8 (7%) and day 15 (4%). During cycle #2 the incidence of IRR was 24%. Premedicate patients with acetaminophen, antihistamine and a glucocorticoid. Provide medical management as needed. Closely monitor patients during the entire infusion. Reactions can occur within 24 hours of receiving obinutuzumab. Stop obinutuzumab for any Grade 4 infusion reaction. Permanently discontinue obinutuzumab therapy. For patients with Grades 3 infusion reactions, interrupt obinutuzumab until resolution of symptoms. For Grade 1 or 2 reactions, interrupt or reduce the rate of infusion and manage symptoms. Monitor patients with pre-existing cardiac or pulmonary conditions more frequently as they may be at greater risk of experiencing more severe reactions. Hypotension can present as part

of an infusion reaction, therefore consider withholding antihypertensive treatments for 12 hours prior to, during and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider risk vs. benefits of withholding antihypertensive medications.

- **Tumor Lysis Syndrome (TLS).** TLS, including fatal cases, has been reported with obinutuzumab. Those with high tumor burden, high circulating lymphocyte count (>25 x 10^9/L) or renal impairment are at greatest risk for TLS and should receive appropriate TLS prophylaxis with antihyperuricemics and hydration prior to obinutuzumab infusion. During the initial days of treatment, monitor laboratory parameters of those at risk for TLS. Treatment of TLS may include the correction of electrolyte abnormalities, monitor renal function, fluid balance, supportive care, including dialysis as indicated.
- **Infections.** Serious bacterial, fungal and new or reactivated viral infections can occur during and following obinutuzumab therapy. The incidence of infection was 66% (Grade 3,4: 16%) in the obinutuzumab + bendamustine vs. 56% (Grade 3,4: 14%) in the bendamustine alone arm. Fatal infections have been reported. Do not administer to patients with an active infection. Those with a history of recurring or chronic infections may be at increased risk of infection.
- **Neutropenia.** Severe and life-threatening neutropenia, as well as febrile neutropenia has been reported during treatment with obinutuzumab. The incidence of neutropenia was higher in the obinutuzumab + bendamustine arm at 38% vs. bendamustine alone at 32%. Those with Grade 3-4 neutropenia need frequent monitoring until resolution. Monitor for signs/symptoms of infection. In those with Grade 3-4 neutropenia, granulocyte colony-stimulating factors can be considered. Neutropenia can be late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days). Delaying treatment should be considered in cases of Grade 3 or 4 neutropenia. Antimicrobial prophylaxis is strongly recommended in patients with severe and long-lasting neutropenia during treatment. Antiviral and antifungal prophylaxis should be considered.
- **Thrombocytopenia.** Severe and life-threatening thrombocytopenia has been reported during treatment with obinutuzumab + bendamustine, although the incidence was lower in the combination arm (15%) vs. bendamustine arm (24%). The incidence of hemorrhagic events in the combination arm was 11% vs. 10% with bendamustine alone. Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. Monitor platelet counts more frequently in patients with Grade 3 or 4 thrombocytopenia until resolution. Consider subsequent dose delays of obinutuzumab and chemotherapy or dose reductions of chemotherapy. Platelet transfusions may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.
- **Immunization.** Safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy has not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-cell recovery.

Safety Considerations

- Boxed warnings highlight risk of HBV reactivation. All patients should be screened for HBV infection before starting therapy. HBV-positive patients should be monitored during and after treatment.
- Boxed warning highlighting the risk of PML should alert providers to monitor and consider this diagnosis in patients presenting with new onset or changes to baseline neurological status.
- Infusion-related reactions (IRR) can be severe and occur with higher frequency with the initial doses. For all doses of obinutuzumab, ensure appropriate premedication is provided, necessary adjustments are made to the infusion rate and patient is monitored throughout infusion and for 24-hours thereafter.
- Assess patient for potential risk of TLS and prophylaxis with hydration and anti-hyperuricemics. Continue monitoring during risk period.
- Anticipate neutropenia and potential risk for infection. Note that neutropenia can have a late onset and can be prolonged. Consider use of granulocyte colony-stimulating factors, as appropriate, based upon risk of febrile neutropenia and patient characteristics. Consider antimicrobial, antiviral and antifungal prophylaxis.
- Evaluate concomitant therapies that can put patient at increased risk of bleed due to thrombocytopenia, especially during the first cycle.

Adverse Reactions

Common adverse reactions	Most common adverse reactions (≥10%) were IRR, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia and urinary tract infection.
Death/Serious adverse reactions	Grade 3 or 4 reactions (≥10%): neutropenia, thrombocytopenia, IRR
Discontinuations due to adverse reactions	Infusion related reactions caused discontinuation in 2% of patients

Musculoskeletal Disorders. Adverse events related to musculoskeletal disorders were reported with a higher incidence in the obinutuzumab +bendamustine vs. bendamustine alone arm (41 vs. 29%).

Liver Enzyme Elevations. Elevated liver enzymes have occurred in the clinical trial CLL setting. Most events occurred within 24-48 hours of the first infusion. Overall hepatotoxicity events were similar between all arms. Monitor liver function tests during treatment, especially during the first cycle. Consider interruption or discontinuation for hepatotoxicity. No data is available in the indolent NHL setting at this time.

Gastrointestinal (GI) Perforation. Cases of GI perforation have been reported among NHL patients receiving obinutuzumab.

Drug Interactions

Drug-Drug Interactions

- No formal drug interaction studies have been conducted.

Risk Evaluation

As of December, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	See table below

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Obinutuzumab 25 mg/ml Inj	Blinatumomab Dinutuximab Ofatumumab Omalizumab	None	None	None
Gazyva	None	None	None	Genvoya Xgeva

- (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Supporting evidence is available in abstract form only. Evidence presented in a peer-reviewed publication is anticipated.
- The FDA application was granted Priority Review as rituximab-refractory patients have limited treatment options.
- Trial was stopped at interim analysis, when primary endpoint of PFS was reached, yet this did not equate to a difference in OS between the arms.
- No advantage, in terms of ORR, was noted in the obinutuzumab + bendamustine arm compared to bendamustine alone.
- The toxicity profile of obinutuzumab + bendamustine is not benign as there is more Grade 3, 4 neutropenia and IRR compared to bendamustine alone.

Outcome in clinically significant area	O+B vs. B: PFS 29.2 vs. 13.7 mos
Effect Size	O+B vs. B: HR 0.48; 95% CI 0.35-0.67; p<0.001
Potential Harms (Grade ≥ 3)	O+B vs. B Neutropenia 33 vs. 26% IRR 8.8 vs. 3.5% Thrombocytopenia 11 vs. 16% Anemia 8 vs. 10% Pneumonia 2.6 vs. 5.6%
Net Clinical Benefit	n/a (expedited review)

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

Recommended Dosage Regimen

- Premedicate before each infusion
- Provide prophylactic hydration and anti-hyperuricemics to patients at high risk for tumor lysis syndrome
- Administer as an intravenous infusion through a dedicated line; do not administer as IV push or bolus
- Monitor blood counts at regular intervals
- Administer by healthcare professional with appropriate medical support to manage severe infusion reactions should they occur.

Recommended Dose for Follicular Lymphoma

- Obinutuzumab 1000 mg, intravenously
- Cycle #1 (loading doses): day 1 (1000 mg), day 8 (1000 mg), day 15 (1000 mg)
- Cycles #2-6: day 1 (1000 mg)
- Maintenance: 1000 mg every 2 months for 2 years
- Refer to package insert for full dosing information that includes recommendations for:
    - Rate of infusion
    - Infusion adjustments based upon experience of infusion reaction
    - Premedication to reduce infusion-related reactions (IRR)
    - Premedication for antimicrobial prophylaxis
    - TLS prophylaxis
    - Treatment interruption for toxicity
    - Preparation and administration

Special Populations (Adults)

	Comments
Elderly	• Of 194 NHL patients: 44% > 65 years; 14% > 75 years • Among >65 years: 52% had SAEs; leading 26% to treatment withdrawl • Among < 65 years: 28% had SAEs; leading 12% to treatment withdrawl • No differences in efficacy were noted
Pregnancy	• Drug is likely to cause fetal B-cell depletion based upon mechanism of action and findings from animal studies. There is no data with the use of obinutuzumab in pregnant women to inform a drug-associated risk. No embryo-toxic or teratogenic effects were observed in monkeys, but opportunistic infections and immune responses against the drug were noted. Consider the potential risk to the fetus when prescribing to a pregnant woman.
Lactation	• Benefits of breastfeeding should be considered along with the mother's clinical need for obinutuzumab, along with any potential adverse effects on the breastfed infant.
Renal Impairment	• PK analysis indicates a baseline CrCl $\geq$ 30 ml/min does not affect PK of obinutuzumab. Drug has not been studied in CrCl < 30 ml/min.
Hepatic Impairment	• Drug has not been studied in patients with hepatic impairment.
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Rituximab is a key component to those with follicular lymphoma. Given as part of a chemoimmunotherapy regimen for aggressive disease, or as monotherapy for those unable to tolerate the chemotherapy component, rituximab has been shown to improve ORR, PFS and OS.
- Patients who are no longer responsive to rituximab have limited treatment options. Stem cell transplant may be an option for select, fit individuals. Use of radioimmunotherapy may be an option in facilities with nuclear medicine expertise.
- Obinutuzumab + bendamustine, followed by obtinutuzumab monotherapy, is a treatment option in patients refractory to rituximab-based therapy

References

1. Gazyva (obinutuzumab) Prescribing Information. Genentech, Inc. South San Francisco, CA. February 2016

2. Sehn L, Chua N, Mayer J, Dueck G, Treny M, Bouabdallah K, et al. GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma. J Clin Oncol 33: LBA8502.

3. Gabellier L, Cartron G. Obinutuzumab for relapsed or refractory indolent non-Hodgkin's lymphomas. Therapeutic Advances in Hematology 2016; 7: 85-93.

4. Sehn L, Goy A, Offner F, Martinelli G, Caballero M, Gadeberg O, et al. Randomized phase II trial comparing obinutuzumab with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: Final Analysis of the GAUSS study. J Clin Oncol 2015; 33.

5. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015; 33.

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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.