Pembrolizumab (KEYTRUDA)

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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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	Pembrolizumab is a first-in-class programmed death receptor-1 (PD-1) blocking antibody. Binding of PD-1 on T-cells to its ligands inhibits T-cell proliferation. Blocking PD-1 with Pembrolizumab releases the inhibition of the immune response of T-cells, including an anti-tumor response.
Indication(s) Under Review in this document (may include off label)	• Treatment of unresectable or metastatic melanoma • Patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patient with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for theses aberrations prior to receiving Pembrolizumab. • These indications are approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Dosage Form(s) Under Review	Pembrolizumab for injection, 50mg single-use vial. Pembrolizumab injection 100 mg/4mL solution in single-use vial
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy	Risk Summary: May cause fetal harm when administered to a pregnant female based on its mechanism of action. In animal models the PD-1/PD-L1 pathway is vital in maintaining pregnancy due to induction of maternal tolerance to fetal tissue. Human IgG4 is known to cross the placenta therefore pembrolizumab could be transmitted from mother to fetus. There is no human data on the risk for embryo-fetal toxicity. Data: Animal reproduction studies have not been conducted with pembrolizumab. Blockade of PD-L1 signaling in murine models of pregnancy disrupts tolerance to fetus and results in an increase in fetal loss. Potential risks of pembrolizumab during pregnancy include abortion or stillbirth. No malformations reported in offspring of animals given pembrolizumab during pregnancy. Based on its mechanism, pembrolizumab may increase the risk of immune-mediated disorders of altering normal immune response. *See Special Populations for additional information*

Executive Summary	
Efficacy	• In advanced melanoma after prior chemotherapy, pembrolizumab significantly improves progression free survival versus ipilimumab [HR for PFS vs ipilimumab:

	HR Pem Q2: 0.58 (95%CI 0.46-0.72); HR Pem Q3: 0.58 (95%CI 0.47-0.72)]. One year OS was 74.1% (HR vs ipi: 0.63) vs 68.4% (HR vs ipi 0.69). • In advanced melanoma after prior ipilimumab plus or minus a BRAF inhibitor or MEK inhibitor or both as indicated, pembrolizumab increased median progression free survival versus chemotherapy. 6 month progression free survival: 34% at 2 mg/kg, 38% at 10 mg/kg, and 16% with chemotherapy. • In a phase I trial in NSCLC, pembrolizumab an overall response rate of 19.4% in both previously treated and previously untreated patients. When restricted to patients by percentage of PD-L1 expression, response rates were highest in those expressing PD-L1 in at least 50% of tumor cells (ORR was 45.2%); patients expressing PD-L1 in 1-49% also responded but at a lower rate (16.5%). Patients expressing PD-L1 in <1% of tumor cells responded at the lowest rates (10.7%).
Safety	• Immune-mediated toxicities are rare but potentially serious. Early recognition and prompt treatment are key to resolution. • Common adverse events: Melanoma (≥20% of patients): fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, diarrhea NSCLC (≥20% of patients): fatigue, decreased appetite, dyspnea, and cough • While the overall percentage of patients with a Grade 3 or 4 adverse event is over 20% in most trials, the incidence of individual Grade 3 or 4 events is small. • Discontinuation rates in the phase 3 melanoma trial were less than the ipilimumab arm.
Other Considerations	

Outcome in clinically significant area	Melanoma: PFS 2.9 vs 2.7 mos (vs chemo after ipi); OS: waiting final analysis NSCLC: Overall response rate: 19.4%; 18% in previously treated; 24.8 in previously untreated
Effect Size	Melanoma: HR PFS: 2mg: 0.57 (95%CI 0.45-0.73) NSCLC: N/A
Potential Harms	Melanoma: 36% NSCLC:38%
Net Clinical Benefit	Melanoma: Moderate NSCLC: Not available

Projected Place in Therapy	• As this is an evolving class of drugs, place in therapy should be limited to FDA indications.

Background

Purpose for review

The purposes of this monograph are to (1) evaluate evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating pembrolizumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational uses in the VA.

Issues to be determined:

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

Other therapeutic options

Unresectable or metastatic melanoma (after ipilimumab [and BRAF inhibitor if indicated])

Formulary Alternatives	Other Considerations
Cisplatin	If not used 1st line and not the same class as 1st line (with vinblastine, dacarbazine, IL-2 and interferon; high incidence of toxicity).
Carboplatin	If not used 1st line and not the same class as 1st line
Vinblastine	If not used 1st line and not the same class as 1st line (see cisplatin)
Carmustine	If not used 1st line and not the same class as 1st line
Imatinib	If c-KIT mutation positive
Paclitaxel	If not used 1st line and not the same class as 1st line
Dacarbazine	If not used 1st line and not the same class as 1st line (see cisplatin)
Carboplatin/paclitaxel	If not used 1st line and not the same class as 1st line
Non-formulary Alternative (if applicable)	**Other Considerations**
Nivolumab	PD-L1 blocker; 1st line or 2nd line
Ipilimumab	Single agent or in combination with nivolumab
Dabrafenib	BRAF mutation positive; 1st line or 2nd line if not used in 1st line; single agent or in combination with trametinib (preferred)
Vemurafenib	BRAF mutation positive; 1st line or 2nd line if not used in 1st line
Temozolomide	
High-dose Interleukin-2`	Limited to good PS and centers experienced with administering in ICU
Nab-paclitaxel	Protein-bound paclitaxel

Non-small cell lung cancer after progression on platinum therapy

Formulary Alternatives	Other Considerations
Erlotinib	With or without EGFR mutation; indirect comparison better OS with nivolumab after chemotherapy
Gemcitabine infusion	PS 0-2
Docetaxel	PS 0-2
Non-formulary Alternative (if applicable)	**Other Considerations**
Nivolumab	PD-L1 blocker
Pemetrexed	Non-squamous histology
Ramucirumab	With docetaxel

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to October 2015) using the search terms Pembrolizumab and KEYTRUDA. The search was limited to the Pub Med Clinical Queries Filter for Therapy (specific/narrow and sensitive/broad) and studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Table 1. Unresectable or metastatic melanoma

Study	Setting	Pts	ECOG PS	Treatment	Response (%)	PFS months	OS months
KEYNOTE 006[1] Merck Sharp & Dohme	Unresectable or metastatic melanoma with no more than 1 previous systemic therapy for advanced disease. Known BRAF mutational status required Previous BRAF inhibitor not required if normal LDH and no tumor-related symptoms or rapidly progressive disease Phase 3 randomized, controlled trial	Age: 61-63 Male: 57.7-62.8% ECOG 0: 68.2-70.3% PD-L1 positive: 80% BRAF V600 mutation: 35% Prev lines of therapy: 0: 66% 1: 34%	0-1	Pembrolizumab 10 mg/kg IV every 2 weeks Pembrolizumab 10 mg/kg IV every 3 weeks Ipilimumab 3 mg/kg IV every 3 weeks for 4 doses	Response rates: Pem Q2: 33.7% (P<0.001 vs ipi) Pem Q3: 32.9% (P<0.001 vs ipi) Ipilimumab 11.9% Complete response 5.0%, 6.1%. 1.4%	Primary 5.5 vs 4.1 vs 2.8 HR for PFS Vs ipilimumab: HR Pem Q2: 0.58 (95%CI 0.46-0.72) HR Pem Q3: 0.58 (95%CI 0.47-0.72) 6 mos PFS: 47.3%, 46.4%, 26.5% Benefit seen I PD-L1 positive and PD-L1 negative subgroups	Primary Med OS not reached in any study group 1yr OS 74.1% (HR 0.63), 68.4% (HR 0.69), 58.2% HR for OS in 18% of pts with PD-L1 negative tumors vs ipi: HR 0.91, Q2 HR 1.02 Q3
KEYNOTE 002[2] Merck Sharp & Dohme	International, randomized, controlled phase 2 pembrolizumab vs chemotherapy Unresectable stage III or IV with confirmed disease progression within 24 weeks of the last ipilimumab dose, previous BRAF or MEK inhibitor therapy or both (if BRAF V600 mutant positive), resolution/improvement in ipi-related adverse events, prednisone dose 10mg/day or less for 2 weeks	Age: 60-62 Male: 58-60% White: 98-99% ECOG 0: 54% $BRAF^{WT}$: 76-78%	0-1	Pem 2mg/kg IV every 3 weeks Pem 10 mg/kg IV every 3 weeks Chemotherapy Choice of paclitaxel + carboplatin, paclitaxel, carboplatin, dacarbazine, oral temozolomide 48% of chemotherapy patients crossed over to pembrolizumab	Overall response rate: 21%, 25%, 4% Complete response: 2%, 3%, 0% Partial response: 19%, 23%, 4%	Primary 2.9, 2.9, 2.7 HR 2mg: 0.57 (95%CI 0.45-0.73) HR 10mg: 0.50 (95%CI 0.39-0.64) PFS 6 mos: 34%, 38%, 16% PFS 9 mos: 24%, 29%, 8%	Interim analysis did not meet superiority; waiting final overall survival

- In the second-line setting of unresectable stage III or IV melanoma, pembrolizumab was evaluated in a phase 3 clinical trial compared to ipilimumab for progression after no more than 1 systemic chemotherapy and in a randomized phase 2 trial compared to investigator's choice of chemotherapy following progression on 1st line ipilimumab.
- In the phase 3 trial, pembrolizumab 10 mg/kg IV every 2 or 3 weeks improved progression free survival with similar hazard ratio's for both pembrolizumab regimens for PFS compared to ipilimumab. Median overall survival had not yet been reached in either study group, but the 1 year overall survival was 74% vs 68% with a hazard ratio for overall survival of 0.69 compared to ipilimumab at 1 year.
- Progression free survival advantage was seen at all PD-L1 expression levels.
- Hazard ratios for overall survival in patients whose tumors were PD-L1 negative were not statistically significantly different than ipilimumab.

- In the randomized phase 2 trial, the hazard ratios for PFS were similar for both pembrolizumab doses and were significantly better than chemotherapy. The interim analysis of overall survival did not show superiority; final analysis of overall survival is awaited.
- 48% of chemotherapy patients in the phase 2 trial crossed over to pembrolizumab.

Table 2. Non-small cell lung cancer after progression

Study	Setting	Pts	ECOG PS	Treatment	Response (%)	PFS months	OS months
KEYNOTE 001[3]	Phase 1 Non-small cell lung cancer cohort Locally advanced or metastatic Squamous or non-squamous PD-L1 expression positive or negative EGFR mutation any ALK translocation Any	Age: 64-68.5 Male: 50.9-66.7% White: 79.4-85.6% ECOG 0: 31.7-50% No. of previous therapies: 0: 15.7-66.7% 1: 12.4-33.3% 2: 0-26.5% 3: 0-22.8% ≥4: 0-21.3%	0-1	Pem 2 mg/kg IV every 3 weeks Pem 10 mg/kg IV every 3 weeks Pem 10 mg/kg IV every 2 weeks	Primary Overall response rate: 19.4% (95%CI 16-23.2); 18% in previously treated patients 24.8% (95%CI 16.7-34.3) in previously untreated patients Best response: stable disease in 21.8% Current/former smokers: 22.5% vs 10.3% never smokers Med duration of response : 12.5 mos 10.4 mos previously treated 23.3 mos previously untreated Biomarker selection: PD-L1 expression in ≥50% of tumor cells Response in PD-L1 ≥50%: 45.2% 43.9 prev treated vs 50.0% prev untreated PD-L1 1-49%: Overall response rate: 16.5% PD-L1 <1%: Overall response rate 10.7%	3.7 all patients 3.0 previously treated 6.0 previously untreated	12 all patients 9.3 previously treated 16.2 previously untreated

- Data for use in NSCLC is from a large Phase 1 trial with multiple disease cohorts.
- The primary outcome was overall response rate.
- The overall response rate was 19.4%; 18% in patients previously treated and 24.8% in patients previously untreated.

- Overall response rate was assessed based on the PD-L1 cut point of ≥50%: ORR was 45.2%; 43.9% in previously treated; 50% in previously untreated.
- Overall response rates for PD-L1 1-49% was 16.5%; for PD-L1 expression <1% overall response rate was 10.7%.
- Pembrolizumab was given accelerated approval for this indication. There are ongoing phase 3 trials continuing to evaluate this in NSCLC.

Potential Off-Label Use

- First-line use in melanoma
- Head and Neck cancer
- Hodgkin's Disease
- Bladder/urothelial cancers
- Triple negative breast cancer
- Gastric Cancer
- Esophageal Cancer
- Hepatocellular carcinoma
- Renal Cell Carcinoma
- Metastatic Colorectal carcinoma with microsatellite instability-high (MSI-H) (FDA breakthrough designation)

Safety

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

	Comments
Boxed Warning	• None
Contraindications	• None

Warnings/Precautions	• Immune-mediated Pneumonitis: including fatal cases. Monitor for signs and symptoms of pneumonitis. For patients with suspected pneumonitis, administer steroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 pneumonitis. Withhold pembrolizumab for moderate (Grade 2) pneumonitis and permanently discontinue for severe (Grade 3) or life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis.
	• Immune-mediated Colitis: Administer steroid (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater. Withhold for moderate (Grade 2) or severe (Grade 3), and permanently discontinue for life-threatening (Grade 4) colitis.
	• Immune-mediated Hepatitis: Administer corticosteroids (initial dose 0.5 mg to 1mg/kg/day [Grade 2] or 1 mg to 2 mg/kg/day [Grade 3 or greater] prednisone or equivalent followed by a taper) and withhold or discontinue pembrolizumab based on severity of liver enzyme elevations.
	• Immune-mediated endocrinopathies:
	  ○ Hypophysitis-Administer corticosteroids and hormone replacement as clinically indicated. Withhold for moderate (Grade 2) and withhold or discontinue for severe (Grade 3) or life-threatening (Grade 4).
	  ○ Thyroid disorders: Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue for severe (Grade 3) or life-threatening (Grade 4).
	  ○ Type 1 Diabetes mellitus: includes diabetic ketoacidosis. Administer insulin for type 1 diabetes. Withhold and administer anti-hyperglycemics for severe hyperglycemia.
	• Other immune-mediated adverse reactions: If severe, withhold and administer corticosteroids. When improved to Grade 1 or less, begin corticosteroid taper and taper over at least 1 month. Resume pembrolizumab when immune-mediated adverse reaction remains at Grade 1 or less

	following taper. Permanently discontinue for severe or Grade 3 immune-mediated adverse reaction that recurs or a life-threatening immune-mediated adverse reaction. • Infusion-related reaction: including severe and life-threatening reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, STOP infusion and permanently discontinue pembrolizumab. • Embryofetal toxicity: Can cause fetal harm based on mechanism of action. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose.

Safety Considerations

- Immune-mediated adverse reactions are the most significant safety concern for this drug. As with other immune-modulators, early recognition and initiation of treatment are key.
- As with other proteins, there is the potential for immunogenicity and anti-pembrolizumab antibody formation.

Adverse Reactions

Common adverse reactions	Melanoma (≥20% of patients): fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, diarrhea NSCLC (≥20% of patients): fatigue, decreased appetite, dyspnea, and cough
Death/Serious adverse reactions	Melanoma: renal failure, dyspnea, pneumonia, cellulitis. NSCLC: pleural effusion, pneumonia, dyspnea, pulmonary embolism, pneumonitis
Discontinuations due to adverse reactions	Melanoma:6% vs 9.4% ipilimumab NSCLC: 14%

Drug Interactions

Drug-Drug Interactions

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.

Risk Evaluation

As of July 2015

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

NME Drug	Lexi-Comp	First	ISMP	Clinical Judgment
Pembrolizumab 50mg inj	Palivizumab, Panitumumab	None	None	Pomalidomide Pazopanib Ponatinib
Keytruda	None	None	None	Kcentra

- 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

Outcome in clinically significant area	Melanoma: PFS 2.9 vs 2.7 mos (vs chemo after ipi) OS: waiting final analysis

	NSCLC: Overall response rate: 19.4% ; 18% in previously treated; 24.8 in previously untreated
Effect Size	Melanoma: HR PFS 2mg: 0.57 (95%CI 0.45-0.73) NSCLC: N/A
Potential Harms	Melanoma: 36% NSCLC:38%
Net Clinical Benefit	Melanoma: Moderate NSCLC: Not available

Definitions

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

- Refer to the package insert for full dosing information and dose modification recommendations.
- Dose: 2 mg/kg administered as an IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity
- For second-line or greater treatment of metastatic non-small cell lung cancer, select patients based on the presence of PD-L1 expression using FDA-approved tests.

Special Populations (Adults)

	Comments
Elderly	• In melanoma trial, 39% were 65 years old or older. No overall differences in efficacy or safety were reported.
Pregnancy	Risk Summary: May cause fetal harm when administered to a pregnant female based on its mechanism of action. In animal models the PD-1/PD-L1 pathway is vital in maintaining pregnancy due to induction of maternal tolerance to fetal tissue. Human IgG4 is known to cross the placenta therefore pembrolizumab could be transmitted from mother to fetus. There is no human data on the risk for embryo-fetal toxicity. Data: Animal reproduction studies have not been conducted with pembrolizumab. Blockade of PD-L1 signaling in murine models of pregnancy disrupts tolerance to fetus and results in an increase in fetal loss. Potential risks of pembrolizumab during pregnancy include abortion or stillbirth. No malformations reported in offspring of animals given pembrolizumab during pregnancy. Based on its mechanism, pembrolizumab may increase the risk of immune-mediated disorders of altering normal immune response.
Lactation	• It is unknown if pembrolizumab is excreted in human breast milk. Because many drugs are excreted in breast milk, instruct women to discontinue breastfeeding during therapy with pembrolizumab and for 4 months after the last dose.
Females and Males of Reproductive Potential	• Based on its mechanism of action, pembrolizumab can cause fetal harm if administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months following the final dose.
Renal Impairment	• Based on population pharmacokinetics, no dose adjustment is needed for patients with renal impairment.
Hepatic Impairment	• Based on population pharmacokinetics, no dose adjustment necessary

	for patients with mild hepatic impairment prior to starting therapy (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1 to 1.5 times the ULN and any AST). Pembrolizumab has not been studied in moderate (total bilirubin 1.5 to 3.0 times the ULN and any AST) or severe (total bilirubin greater than 3 times the ULN and any AST) hepatic impairment.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy (this section may be edited prior to final approval of document and web posting)

- Metastatic melanoma: Current FDA approved choices for therapy for metastatic melanoma that is refractory to ipilimumab and/or BRAF inhibition if BRAF V600 mutation positive, include dacarbazine and interleukin-2, both providing limited benefit and considerable toxicity, and nivolumab.
- Lung cancer is one of the top 2 cancers in the VA.
- In non-squamous non-small cell lung cancer that has progressed on a platinum based chemotherapy regimen, there are a number of drugs available for use in this setting. Subsequent therapy in the context of platinum failure may depend on the tumor molecular profile.
- In squamous non-small cell lung cancer that has progressed on 1 prior platinum based chemotherapy, choices for subsequent therapy are more limited.
- Clinical Practice Guidelines
    - Melanoma: NCCN gives pembrolizumab a Category 2A recommendation for first-line single agent treatment of metastatic disease. For second-line therapy pembrolizumab has a Category 2A recommendation.
    - Melanoma: ESMO recommends PD-1 inhibitors as a reasonable 1st line approach, especially in patients with BRAF wild type disease. For 2nd line therapy, PD-1 inhibitors are recommended after 1st line ipilimumab and have favorable efficacy compared to ipilimumab in this setting.
    - Non-small cell lung cancer: NCCN recommends pembrolizumab in 2nd-line or subsequent therapy with a Category 2A recommendation and a note that it is approved by the FDA for patients with tumors that express PD-L1 as determined by and FDA approved test. Pembrolizumab has not yet been incorporated into ASCO or ESMO guidelines.
- The quality of the evidence is Moderate due to the fact the pembrolizumab was approved under accelerated approval for both indications. While some of the confirmatory data for melanoma has now been published, the confirmatory data for NSCLC has not.
- An ongoing issue with this drug is use in NSCLC based on PD-L1 expression. While the FDA approved it for use in NSCLC in patients whose tumors express PD-L1 they did not specify a particular cut point for expression. In the phase 1 trial, the cut point validated was 50%, although patients with PD-L1 expression 1-49% also responded, although at a lower level than those at or above 50%. Compared indirectly to docetaxel in this setting, pembrolizumab at any PD-L1 expression level has better overall response rates; whether this translates into a clinical benefit (PFS or OS) is unknown at this time.
- The place in therapy for pembrolizumab should be restricted to FDA labeled indications until more clinical data is available.

References

[1] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521-32.
[2] Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomized, controlled, phase 2 trial. Lancet Oncol 2015:16:908-918.
[3] Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med 2015;372:2018-28.

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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.