CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 April – May

BRAND NAME
Keytruda®

GENERIC NAME
Pembrolizumab

MANUFACTURER
Merck & Co., Inc.

DATE OF APPROVAL
- Non-small cell lung cancer (NSCLC) indication: May 10, 2017
- Urothelial carcinoma indication: May 18, 2017
- Microsatellite instability-high (MSI-H) cancer indication: May 23, 2017

PRODUCT LAUNCH DATE
Currently commercially available

REVIEW TYPE

☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☒ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Keytruda is indicated:
New indications:
- In combination with pemetrexed and carboplatin for the first-line treatment of patients with metastatic non-squamous NSCLC*

- For the treatment of patients with locally advanced or metastatic urothelial carcinoma
    - Who are not eligible for cisplatin-containing chemotherapy*
    - Who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- For the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or mismatch repair deficient (dMMR)*
    - Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
    - Colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

  Limitation of use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

Existing indications:

- For the treatment of patients with unresectable or metastatic melanoma
- As a single agent for the treatment of patients with metastatic NSCLC
    - Whose tumors have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%) as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC
    - Whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda
- For the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy*
- For the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy*

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* This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OFF-LABEL USES

- NCCN recommended uses are: mycosis fungoides, Sezary syndrome, and Merkel cell carcinoma.
- Other uses currently under investigation include, but are not limited to: small cell lung cancer, esophageal cancer, hepatocellular carcinoma, osteosarcoma, cholangiocarcinoma, malignant peripheral nerve sheath tumor, thyroid cancer, anal cancer, penile squamous

cell carcinoma, endometrial cancer, acute myeloid leukemia, breast cancer, pancreatic cancer, renal cell carcinoma, and glioma.

CLINICAL EFFICACY

NSCLC

The efficacy of Keytruda as a first-line treatment in NSCLC was demonstrated in cohort G of KEYNOTE-021, an open-label, multi-cohort, multicenter study. Patients were randomized in a 1:1 ratio to receive either Keytruda in combination with pemetrexed and carboplatin (n=60) or pemetrexed and carboplatin alone (n=63). Pemetrexed and carboplatin were administered on Day 1 of each 21-day cycle for 4 cycles, while Keytruda was administered on Day 1 and every 3 weeks. Maintenance treatment with pemetrexed every 3 weeks was allowed in both arms. Treatment continued until progression of disease, unacceptable toxicity, or a maximum of 24 months. Patients were allowed to receive Keytruda after disease progression if clinically stable and deriving clinical benefit as determined by the investigator.

A total of 123 patients were enrolled. All had locally advanced or metastatic non-squamous NSCLC and had received no prior systemic treatment for metastatic disease. At baseline, the median age was 64 years (range: 37-80 years) with 39% being male and 87% being white. Ninety-seven percent had metastatic disease, and 12% had brain metastases. The majority of patients (97%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1. Thirty-six percent had tumor PD-L1 expression TPS, and none had sensitizing EGFR or ALK genomic aberrations.

Key exclusion criteria included presence of an autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or receipt of more than 30 Gy of thoracic radiation within the prior 26 weeks.

The primary efficacy endpoint was the objective response rate (ORR) as assessed by blinded independent central review (BICR). Secondary efficacy endpoints included duration of response, progression-free survival (PFS) per BICR, and overall survival (OS). Tumors were assessed every 6 weeks through Week 18 and every 9 weeks thereafter. The median follow-up was 10.6 months.

The ORR was higher in patients receiving Keytruda with pemetrexed and carboplatin than in those receiving pemetrexed and carboplatin alone (55% vs 29%, respectively; p=0.0032). No patients achieved a complete response. Ninety-two percent of patients receiving Keytruda with pemetrexed and carboplatin sustained their response for at least 6 months (range: 1.3-13 months) compared to only 81% of patients receiving just pemetrexed and carboplatin (range: 1.4-15.2 months). The median PFS was 13 months (range: 8.3-NE [not estimable]) with the addition of Keytruda versus 8.9 months (range: 4.4-10.3 months) for pemetrexed and carboplatin alone. OS was not reported.

Ten percent of patients discontinued Keytruda therapy due to adverse reactions, and 29% discontinued due to progressive disease. In addition, 32% of patients receiving pemetrexed and carboplatin alone crossed over to receive Keytruda monotherapy at the time of disease progression.

Urothelial carcinoma
The efficacy of Keytruda in locally advanced or metastatic urothelial carcinoma was demonstrated in KEYNOTE-052 and KEYNOTE-045 in cisplatin-ineligible patients and in patients with disease progression on or after platinum-containing chemotherapy, respectively.

KEYNOTE-052: cisplatin-ineligible patients
KEYNOTE-052 was a multicenter, open-label, single-arm trial. A total of 370 patients received Keytruda every 4 weeks until unacceptable toxicity, disease progression, or up to 24 months. Patients with initial radiographic disease progression were allowed to receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

At baseline, the median age was 74 years with 77% being male and 89% being white. Eighty-seven percent had M1 disease, and 13% had M0 disease. Reasons for cisplatin ineligibility were having a baseline creatinine clearance (CrCl) of < 60 mL/min (50%), ECOG PS of 2 (32%; 9% had both CrCl < 60 mL/min and ECOG PS of 2), and other (9%). The majority of patients were treatment-naïve (90%), with only 10% having received prior adjuvant or neoadjuvant platinum-based chemotherapy. Key exclusion criteria included presence of an autoimmune disease or a medical condition that required immunosuppression.

The primary efficacy endpoints were ORR as assessed by independent radiology review and duration of response. Tumors were assessed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The median follow-up time was 7.8 months (range: 0.1-20 months).

The ORR was 29% (95% CI: 24, 34), with 7% achieving a complete response. The duration of response has not yet been reached (ongoing range: 1.4-17.8 months).

Eleven percent of patients discontinued Keytruda therapy due to adverse reactions. The number of patients discontinuing due to lack of efficacy was not reported.

KEYNOTE-045: disease progression on or after platinum-containing chemotherapy
KEYNOTE-045 was a multicenter, randomized, active-controlled trial. A total of 542 patients were randomized in 1:1 ratio to receive either Keytruda or chemotherapy (paclitaxel, docetaxel, or vinflunine as chosen by investigator) until unacceptable toxicity, disease progression, or up to 24 months. Patients with initial radiographic disease progression were allowed to receive

additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

At baseline, the median age was 66 years (range: 26-88 years) with 74% being male and 72% being white. The majority of patients had ECOG PS < 2 (98%). Ninety-six percent had M1 disease, and 4% had M0 disease. Previously received chemotherapy included cisplatin (76%), carboplatin (23%), and other platinum-based regimens (1%). Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Key exclusion criteria included presence of an autoimmune disease or a medical condition that required immunosuppression.

The primary efficacy endpoints were OS and PFS as assessed by BICR. Secondary efficacy endpoints included ORR as assessed by BICR and duration of response. Tumors were assessed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The median duration of follow-up was 14.1 months (range: 9.9-22.1 months).

Both OS and ORR were higher in patients receiving Keytruda than in those receiving chemotherapy (median OS: 10.3 months vs 7.4 months, respectively [HR: 0.73 with 95% CI: 0.59, 0.91; p=0.002]; ORR: 21.1% vs 11.4%, respectively, with 7% vs 3% achieving complete response [p=0.001]). The median duration of response was not reached in the Keytruda arm (ongoing range: 1.6-15.6 months), while it was 4.3 months for the chemotherapy arm (ongoing range: 1.4-15.4 months). There was no statistically significant difference in PFS between Keytruda and chemotherapy.

Five point six percent of patients discontinued Keytruda therapy due to adverse reactions. The number of patients discontinuing due to lack of efficacy was not reported.

MSI-H cancer
The efficacy of Keytruda in unresectable or metastatic, MSI-H or dMMR solid tumors was demonstrated in 5 uncontrolled, open-label, multi-cohort, multi-center, single-arm trials: KEYNOTE-016, KEYNOTE-164, KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158. MSI-H and dMMR status were confirmed using polymerase chain reaction (PCR) and immunohistochemistry (IHC) tests, respectively. KEYNOTE-016 and -164 were prospective studies, while KEYNOTE-012 and -028 were retrospective. KEYNOTE-158 included both prospective enrollment (for MSI-H/dMMR non-CRC) and retrospective identification (for specific rare tumor non-CRC).

A total of 149 patients received Keytruda 200 mg every 3 weeks or Keytruda 10 mg/kg every 2 weeks until unacceptable toxicity, disease progression, or up to 24 months.

At baseline, the median age was 55 years with 56% being male and 77% being white. All patients had ECOG PS < 2. Ninety-eight percent had metastatic disease, and 2% had locally advanced, unresectable disease. All were required to have received at least 1 prior regimen; 84% of patients with metastatic CRC and 53% of patients with other solid tumors received at least 2 (the median). Key exclusion criteria included presence of an autoimmune disease or a medical condition that required immunosuppression.

The primary efficacy endpoints were ORR as assessed by BICR and duration of response. Across all tumor types, the ORR was 39.6% (95% CI: 31.7, 47.9) with 7.4% achieving a complete response. The median duration of response was not reached (range: 1.6+, 22.7+), but 78% of patients had a response for at least 6 months.

The number of patients discontinuing due to adverse reactions and lack of efficacy was not reported.

CONTRAINDICATIONS
None

BLACK BOX WARNINGS
None

DRUG INTERACTIONS
None

ADVERSE REACTIONS
The most common adverse reactions (reported in ≥ 20% of patients) were fatigue, pruritus, diarrhea, decreased appetite, rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation, and nausea.

In addition, Keytruda has warnings for immune-mediated adverse reactions including pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, thyroid disorders, and type 1 diabetes mellitus), nephritis, possible organ rejection, and complications following allogeneic hematopoietic stem cell transplant after treatment. Other warnings are infusion-related reactions and embryofetal toxicity.

DOSAGE AND ADMINISTRATION
The recommended dosage of Keytruda in NSCLC, urothelial carcinoma, and MSI-H cancer is 200 mg (2 mg/kg for pediatric patients with MSI-H cancer, up to a maximum of 200 mg) administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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In NSCLC, Keytruda should be administered prior to chemotherapy (i.e., pemetrexed and carboplatin) when given on the same day.

PRODUCT AVAILABILITY

- Single-dose vial with powder for reconstitution: 50 mg
- Single-dose vial with solution: 100 mg/4 mL

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Pemetrexed (Alimta®) + [**carboplatin** or **cisplatin**]	Non-squamous NSCLC Pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/mL/min IV on Day 1 of each 21-day cycle	• NCCN category 1 recommendation for PS 0-1 • Carboplatin-containing regimen is category 2A recommendation for PS 2
Bevacizumab (Avastin®) + **carboplatin** + **paclitaxel**	Non-squamous NSCLC Various	• NCCN category 1 recommendation for PS 0-1
Bevacizumab (Avastin®) + [**carboplatin** or **cisplatin**] + pemetrexed	Non-squamous NSCLC Various	• NCCN category 2A recommendation for PS 0-1
[**Carboplatin** or **cisplatin**] + [**paclitaxel**, **docetaxel**, **etoposide**, or **gemcitabine**]	Non-squamous NSCLC Various	• NCCN category 1 recommendation for PS 0-1 • Carboplatin-containing regimens are category 2A recommendation for PS 2
Gemcitabine + [**docetaxel** or **vinorelbine**]	Non-squamous NSCLC Various	• NCCN category 1 recommendation for PS 0-1 • NCCN category 2A recommendation for PS 2
Albumin-bound paclitaxel (Abraxane®)	Non-squamous NSCLC Various	• NCCN category 2A recommendation for PS 2
Docetaxel	Non-squamous NSCLC Various	• NCCN category 2A recommendation for PS 2
Gemcitabine	Non-squamous NSCLC Various	• NCCN category 2A recommendation for PS 2
Paclitaxel	Non-squamous NSCLC Various	• NCCN category 2A recommendation for PS 2
Pemetrexed (Alimta®)	Non-squamous NSCLC Various	• NCCN category 2A recommendation for PS 2
Cisplatin	Urothelial carcinoma	• NCCN category 1

	GC (every 21 days for 2-4 cycles): gemcitabine 1000 mg/m^2 on Days 1, 8, and 15, and cisplatin 70 mg/m^2 on Day 2 or DD-MVAC (every 14 days for 4 or more cycles until disease progression or unacceptable toxicity): Methotrexate IV push on Day 1, then vinblastine IV push, doxorubicin IV push, and cisplatin IV infusion on Day 2	recommendation
Carboplatin	Urothelial carcinoma Gemcitabine 1000 mg/m^2 on Days 1 and 8, and carboplatin on Day 1, every 21 days	• Off-label use supported by NCCN category 2A recommendation for cisplatin-ineligible patients
Atezolizumab (Tecentriq®)	Urothelial carcinoma 1200 mg IV every 3 weeks	• Identical mechanism and indication to Keytruda for urothelial carcinoma • Cisplatin-ineligible patients: similar study design to Keytruda (N=119); ORR of 23.5% with 6.7% achieving complete response (CR) • Patients with disease progression on platinum-containing chemotherapy: study was not randomized or controlled (N=310); ORR of 14.8% with 5.5% achieving CR • Similar safety profile to Keytruda with exception of 2 unique warnings for ocular inflammatory toxicity, and immune-related myasthenic syndrome/myasthenia gravis, Guillain-Barré, or meningoencephalitis
Fluoropyrimidine (e.g., **5-**	MSI-H colorectal cancer	• NCCN category 2A

fluorouracil, **capecitabine**), **oxaliplatin**, **irinotecan**	FOLFOXIRI: every 2 weeks: fluorouracil 1600 mg/m^2/d x 2 days continuous infusion starting on Day 1 [or 400 mg/m^2 IV bolus on Day 1 then 1200 mg/m^2/d x 2 days], and oxaliplatin 85 mg/m^2 IV and irinotecan 165 mg/m^2 IV on Day 1	recommendation for colon and rectal cancer
Nivolumab (Opdivo®)	MSI-H colon/rectal cancer 3 mg/kg or 240 mg IV every 2 weeks	• Off-label use supported by NCCN category 2A recommendation for MSI-H colon/rectal cancer

Boldface indicates generic availability

Utilization Management Recommendation
o There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcome: • Keytruda can be used as a first-line therapy in metastatic NSCLC without high PD-L1 expression only when given in combination with pemetrexed and carboplatin. • Keytruda can be used as a first-line therapy in urothelial carcinoma only if patients are ineligible for cisplatin-containing chemotherapy. Otherwise, it is a second-line therapy. • In addition to its indications for specific cancers, Keytruda is FDA approved as a second-line therapy for all solid tumors with the MSI-H biomarker. • Keytruda is currently undergoing investigation for a number of other uses. ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical program
Product Comparison
Not applicable

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