Keytruda® (pembrolizumab)
For the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy

FDA Opening Remarks

Daniel Suzman, MD
Division of Oncology 1
Office of Oncologic Diseases
December 17, 2019
Non-Muscle Invasive Bladder Cancer (NMIBC): Available Therapies

• High-risk group: Poor prognosis
• No widely accepted non-cystectomy therapies after BCG
• BCG-unresponsive:
  – No approvals in 20+ years
  – Difficulty of randomized trials
  – Adequacy of prior BCG

Van den Bosch and Witjes, Eur Urol 2011
FDA Guidance on BCG-Unresponsive NMIBC

• NMIBC with carcinoma in situ (CIS)
  – Single arm trial acceptable
  – Primary endpoint: Complete response rate
  – Duration of response

• NMIBC without CIS (papillary-only)
  – Cannot be assessed via single-arm trial
KEYNOTE-057 Design

• Design: Single-arm trial of intravenous pembrolizumab
• Eligibility: High-risk NMIBC after failure of prior BCG
  – Cohort A: CIS +/- papillary
  – Cohort B: Papillary-only
• Endpoints:
  – Cohort A: CR rate (evaluated at Month 3, treatment discontinued for persistent disease)
  – Cohort B: Disease-free Survival
KEYNOTE-057 Results

• 96* patients with BCG-unresponsive CIS
  – 41% with complete response (CR) at 3 months
• Maintenance of response (Data Cutoff: Sept 2019):
  – Median duration 16.2 months (range: 0+ to 30.4+)
  – 19% (18/96) of all treated patients one year post-CR
  – 46% (18/39) of responding patients one year post-CR
  – No random biopsies
• Safety of a systemic therapy
  – 3% Grade 3-4 immune-related events, no related deaths
  – No progression events with 14 month min, 24 mo median follow-up

*97 patients in briefing document, 1 patient removed due to misclassification
Issues

• **Risk/Benefit:** Do the observed complete response rate and duration of response represent a favorable risk/benefit profile for patients with BCG-unresponsive high-risk NMIBC with CIS treated with pembrolizumab?
Project Point/Counterpoint

• Oncology Center of Excellence (OCE) initiative
• Oncologic Drugs Advisory Committee (ODAC) briefing document
  – Reduce redundancy
  – Reduce errata
  – Streamline data/analysis presentation
• Please provide feedback
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FDA Review Team

• Clinical: Jamie Brewer, MD and Daniel Suzman, MD
• Statistics: Joyce Cheng, PhD and Shenghui Tang, PhD
• Division Director, DO1: Julia Beaver, MD
• Deputy Division Director, DO1: Amna Ibrahim, MD
• Regulatory Project Manager: Jeannette Dinin
Key Issues for Discussion

- **Risk/Benefit**: Do the observed complete response rate and duration of response represent a favorable risk/benefit profile for patients with BCG-unresponsive high-risk NMIBC with CIS treated with pembrolizumab?
FDA Presentation Outline

• Available treatment for BCG-unresponsive NMIBC
• FDA guidance on trial design
• Efficacy – KEYNOTE-057
• Safety
• Summary
Available Therapies for BCG-Unresponsive NMIBC

• Radical cystectomy
  – ~40% risk of progression to MIBC in BCG-unresponsive patients
    • 20-30% progress to metastatic disease
  – High morbidity/mortality with radical cystectomy
    • 1.5-5% 30-day mortality, up to 10-15% 90-day mortality in SEER* for Age ≥70#

• Limited acceptable bladder-sparing options
  – Valrubicin approved for BCG-unresponsive CIS in 1998
    • 18% complete response rate, median duration of response 13.5 months
  – Sparse off-label data for alternatives

*Surveillance, Epidemiology, and End Results Program
#Schiffmann et al, Eur J Surg Oncol 2014
Expert Opinion on NMIBC Clinical Trials

- FDA and American Urological Association workshop, May 6, 2013, San Diego, CA*
  - “There was broad consensus by the panel that provided results were robust, a single-arm trial could provide sufficient benefit.”
  - “For patients with BCG-refractory CIS, the panel felt than an initial complete response (CR) of 40-50% at 6 months and a durable response rate of at least 30% for 18-24 months...”

- Recommendations from International Bladder Cancer Group†
  - “For patients with BCG-unresponsive CIS, we recommend an initial complete response rate of 50% at 6 months and durable response rates of 30% at 12 months and 25% at 18 months as clinically meaningful.”

*Jarow et al, Urology 2014
†Kamat et al, JCO 2016
FDA Guidance on BCG-Unresponsive NMIBC

- Published February 2018
- Defined BCG-unresponsiveness
- Acceptability of single-arm trial
- Efficacy endpoints in CIS-containing BCG-unresponsive NMIBC
- Lower bound of 95% CI of observed CR rate should rule out a “clinically unimportant CR rate”
- “A high complete response rate is not meaningful if the response duration is short”
- Recommends but does not require random biopsies at specific time points
Study Design KEYNOTE-057

Cohort A: CIS +/- papillary

- 12 wks
- Cystoscopy/Cytology
- Biopsy and CT*/MRI# for +cystoscopy or +cytology
- Discontinue for Persistent CIS

Cohort B: Papillary-only

- 12 wks
- 12 wks
- 12 wks
- Cystoscopy/Cytology
- Biopsy for +cystoscopy or +cytology
- CT/MR Urogram (and every 24 wks)

Every 12 wks Cystoscopy/Cytology
Every 24 wks CT/MR

Continue tx until recurrence of HR NMIBC or progression or 24 months

*Computed Tomography
#Magnetic Resonance Imaging
Efficacy Endpoints: Cohort A

Primary Efficacy Endpoint
• CR rate of High-Risk NMIBC
  – Complete response rate for high-risk NMIBC
  – Treatment discontinued if persistent disease at any assessment
  – Point estimate with confidence intervals using the binomial exact method

Key Secondary Endpoints
• CR rate of Any Disease
  – Includes low-grade disease
• Duration of Response (of High-Risk NMIBC and Any Disease)
  – Kaplan-Meier methods
BCG-Unresponsive Patients

• BCG-Unresponsive CIS per FDA Definition – 94% (N=96*/102)
  – 5 patients with inadequate/unknown exposure
  – 1 patient misclassified as having CIS

• Baseline High-Risk NMIBC Disease Status
  – Persistent high-risk NMIBC – 27% (N=26)
  – Recurrent high-risk NMIBC – 73% (N=70)

*1 patient removed due to misclassification
Primary Efficacy Population

• 95% elected not to have cystectomy
  – 3% medically ineligible
  – 2% “other”

• Tumor pattern at study entry
  – 13% CIS with T1*
  – 25% CIS with high grade Ta#
  – 63% CIS

*Tumor invading lamina propria
#Tumor confined to urothelium
FDA Efficacy Evaluation: Cohort A

• CR rate: 41% (31, 51%) at 3 months, N = 39/96
  – Median Duration of Response: 16.2 months (0+, 30+)

• Duration of follow-up:
  – Minimum: 14 months
  – Median: 24 months

• Responses of ≥ 12 months from CR in:
  – 46% (18/39) of responding patients
  – 19% (18/96) of all treated patients

• Response rate similar across subgroups evaluated
  – Age, concomitant papillary, PD-L1*, gender, race, geographic region, ECOG#,
    persistent vs recurrent

*Programmed Death-Ligand 1
#Eastern Cooperative Oncology Group
Performance Status
Subsequent Cystectomy: Cohort A

- 8% (3/36*) had MIBC on cystectomy

<table>
<thead>
<tr>
<th></th>
<th>Never-responder</th>
<th>CR with recurrence</th>
<th>Ongoing CR</th>
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<tr>
<td><strong>Cystectomy</strong></td>
<td>27</td>
<td>9</td>
<td>0</td>
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<tr>
<td><strong>No Cystectomy</strong></td>
<td>30</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
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*N = 57

*N = 22

*N = 17

*3 of 38 for 102-patient cohort
FDA Efficacy Summary

• 19% of all patients with CR persisting ≥1 year from response

• No random biopsies unless suspicious urine cytology
  – Historically, ~15% disease on random biopsy with negative cytology*

*Subiela et al Actas Urologicas Espanolas 2018
FDA Safety Analysis

• Primary safety population: KEYNOTE-057 Cohort A (N = 102)

• Evaluation of safety included:
  – Adverse events
  – Laboratory assessments
  – Patient narratives
  – Case report forms
FDA Safety Summary

• Generally consistent with experience in other settings
  – 29% Grade 3-4 adverse events
  – 21% of patients with immune-related adverse event (3% Grade 3-4)
  – Two deaths on study due to pneumonia and pancreatic cancer
  – 10% discontinuation rate due to adverse events

• No MIBC progression events prior to cystectomy

• In 36 patients with cystectomy: MIBC in 3 patients on pathology review
  – All patients without CR
Conclusions

• Radical cystectomy is current standard of care
• CR rate of 41% is greater than historical controls
  – Median duration 16.2 months (0+, 30+)
• Durability of one year or greater in 19% (18/96) of all treated patients
  – Limitations: No negative cytology random biopsies, limited evidence of durability beyond ≥18 months
  – No progression events to MIBC or metastatic urothelial cancer prior to cystectomy, 14 month minimum, 24 month median follow up
Voting Question

• Do the observed complete response rate and duration represent a favorable risk/benefit profile in patients with BCG-unresponsive high-risk NMIBC with CIS treated with pembrolizumab?
Back Up Slides Shown
Subsequent Cystectomy: Cohort A

• Cystectomy
  – 41% (9/22) of complete responders with recurrence
    • Median time to cystectomy 11.5 months
  – 47% (27/57) of never-responders
    • Median time to cystectomy 6.1 months
  – 8% (3/36) had MIBC on cystectomy