U.S. FOOD & DRUG ADMINISTRATION

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

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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 Presentation

Jamie Brewer, MD

Oncologic Drugs Advisory Committee Meeting

December 17, 2019

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..."

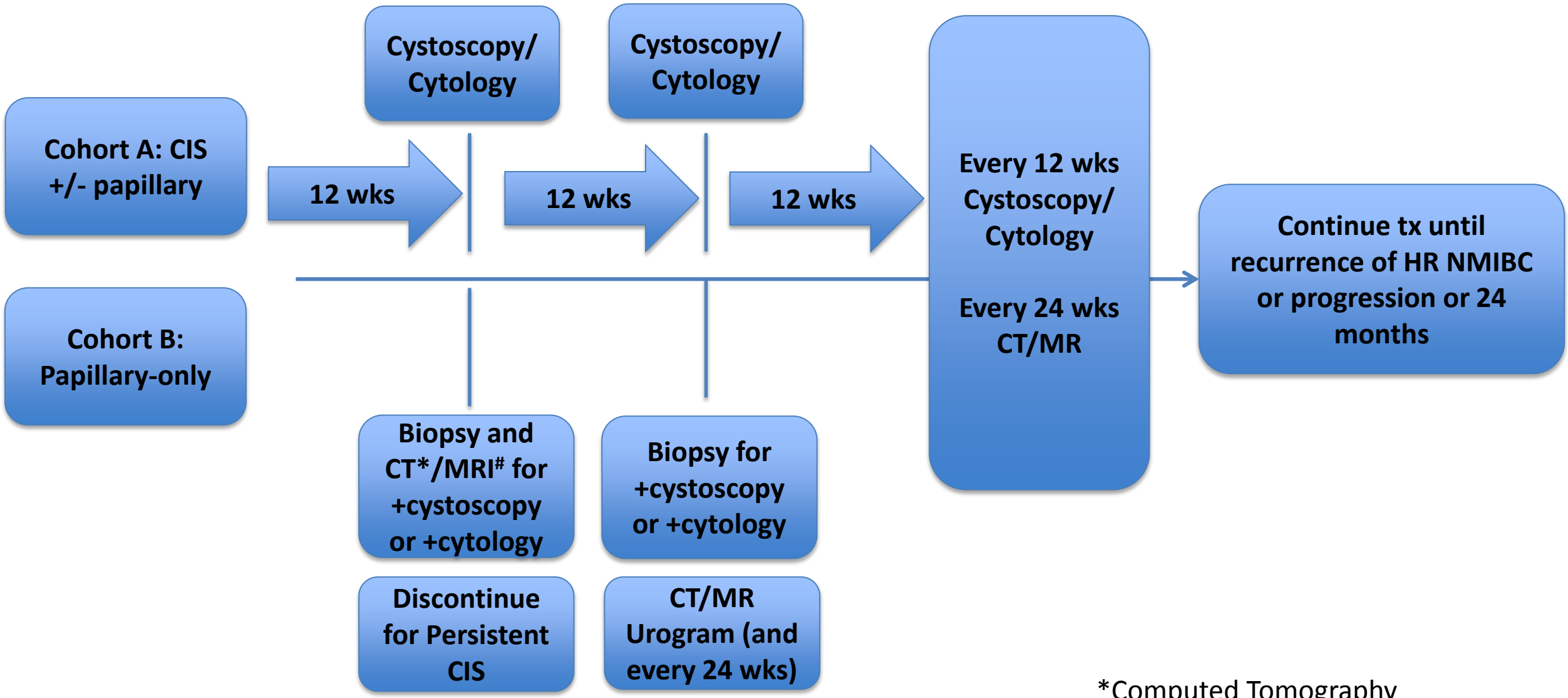
- Recommendations from International Bladder Cancer Group†
  - "For patients with BCG-unresponsive CIS, we recommend an initial complete response rate of 50% at 6 months and durable response rates of 30% at 12 months and 25% at 18 months as clinically meaningful."

*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



*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

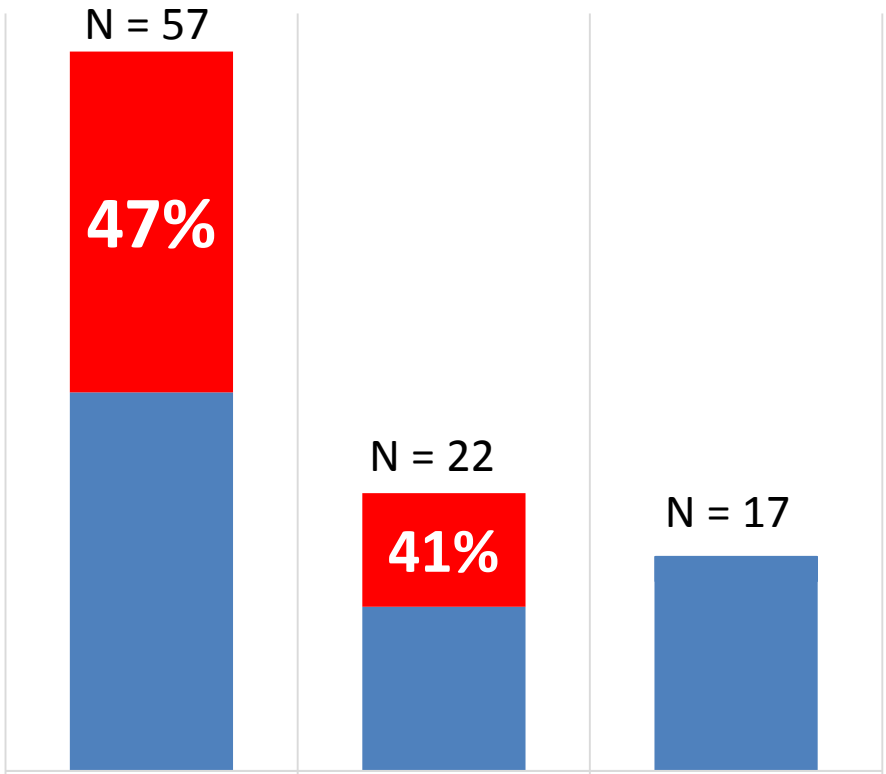
*Tumor invading lamina propria
#Tumor confined to urothelium

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



	Never-responder	CR with recurrence	Ongoing CR
Cystectomy	27	9	0
No Cystectomy	30	13	17

– 8% (3/36*) had MIBC on cystectomy

*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?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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