Introduction

Jeffrey N. Stuart, PhD
Executive Director
Global Regulatory Affairs
Merck & Co., Inc
KEYTRUDA® (pembrolizumab)

- Humanized monoclonal antibody
- Blocks interaction between PD-1 and its ligands (PD-L1 and PD-L2)

KEYTRUDA® (pembrolizumab): FDA-Approved Cancer Types

- Head and neck squamous cell cancer
- Esophageal squamous cell cancer
- Non-small cell lung cancer
- Small cell lung cancer
- Urothelial carcinoma
- Melanoma
- Merkel cell carcinoma
- Gastric cancer
- Hepatocellular carcinoma
- Cervical cancer
- Endometrial carcinoma
- Renal cell carcinoma
- Classic Hodgkin lymphoma
- Primary mediastinal large B-cell lymphoma
- Microsatellite instability-high cancer

Keytruda USPI as of Sep 2019.
Select Studies of Pembrolizumab in Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advanced/Metastatic 2L+</strong></td>
</tr>
<tr>
<td>Failed previous platinum therapy</td>
</tr>
<tr>
<td>KEYNOTE-045: Approved May 2017</td>
</tr>
<tr>
<td><strong>Advanced/Metastatic 1L</strong></td>
</tr>
<tr>
<td>Cisplatin-ineligible&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>KEYNOTE-052: Approved May 2017</td>
</tr>
<tr>
<td>LEAP-011: lenvatinib + pembrolizumab</td>
</tr>
<tr>
<td>All-comers</td>
</tr>
<tr>
<td>KEYNOTE-361: pembrolizumab monotherapy and pembrolizumab plus chemotherapy</td>
</tr>
<tr>
<td><strong>Muscle Invasive Bladder Cancer (MIBC)</strong></td>
</tr>
<tr>
<td>Cisplatin-eligible</td>
</tr>
<tr>
<td>KEYNOTE-866: NeoAdj/Adj pembrolizumab + chemotherapy</td>
</tr>
<tr>
<td>Cisplatin-ineligible</td>
</tr>
<tr>
<td>KEYNOTE-905: NeoAdj/Adj pembrolizumab</td>
</tr>
<tr>
<td><strong>Non-Muscle Invasive Bladder Cancer (NMIBC)</strong></td>
</tr>
<tr>
<td>BCG-unresponsive CIS</td>
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<tr>
<td>KEYNOTE-057: pembrolizumab</td>
</tr>
<tr>
<td>Failed BCG Induction</td>
</tr>
<tr>
<td>KEYNOTE-676: BCG + pembrolizumab</td>
</tr>
</tbody>
</table>

Blue – FDA approval received  
Orange – Ongoing registration study

<sup>a</sup> Resulted in accelerated approval for the treatment of patients who are cisplatin ineligible with CPS>10, or ineligible for platinum-based chemotherapy.
KEYTRUDA is indicated 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.
<table>
<thead>
<tr>
<th>What You Will Hear Today</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmet Medical Need</strong></td>
</tr>
<tr>
<td>• BCG-unresponsive NMIBC with CIS is a serious disease</td>
</tr>
<tr>
<td>• Many patients decline or are medically ineligible for radical cystectomy</td>
</tr>
<tr>
<td>• No well-accepted nonsurgical options for BCG-unresponsive CIS patients</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>• Complete response rate of 41% – exceeds available therapies</td>
</tr>
<tr>
<td>• Complete responses are durable – median DOR 16 months</td>
</tr>
<tr>
<td>• Window of opportunity for radical cystectomy is preserved</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
</tr>
<tr>
<td>• Safety profile of pembrolizumab well characterized: &gt;30,000 patients in clinical trials</td>
</tr>
<tr>
<td>• No new safety concerns in BCG-unresponsive CIS in KEYNOTE-057</td>
</tr>
<tr>
<td>• Immune-related AEs manageable with standard measures</td>
</tr>
<tr>
<td><strong>Benefit-Risk</strong></td>
</tr>
<tr>
<td>• Positive benefit/risk profile in BCG-unresponsive CIS</td>
</tr>
<tr>
<td>• Pembrolizumab is an effective nonsurgical option</td>
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<tr>
<td>Agenda</td>
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<tr>
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</tr>
<tr>
<td>Introduction</td>
</tr>
<tr>
<td>Unmet Need</td>
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<tr>
<td>Efficacy and Safety</td>
</tr>
<tr>
<td>Clinical Perspective</td>
</tr>
<tr>
<td>Benefit-Risk</td>
</tr>
</tbody>
</table>
List of Consultants

Arjun Balar, MD
NYU Langone Health

Jonathan I. Epstein, MD
Johns Hopkins University
Disease Background and Unmet Need

Gary D. Steinberg, MD
Professor and Director
Goldstein Urology Bladder Cancer Program
NYU Langone Health
Bladder Cancer in the United States

- 6th most common cancer
- Approximately 80,000 new diagnoses and 18,000 deaths in 2019
- Prevalence about 600,000 patients
- Median age at diagnosis is 73 years
  - Tobacco smoking-related malignancy
  - Comorbidities (COPD, coronary artery disease, kidney disease, diabetes) are common


Majority of Bladder Cancer at Diagnosis Is Non-Muscle Invasive (NMIBC)

Bladder Cancer

75% NMIBC\(^1,2\)

Carcinoma in Situ (CIS) Represents 10% of All NMIBC

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-muscle invasive</td>
<td>75%</td>
</tr>
<tr>
<td>Tis (CIS) (10%)</td>
<td></td>
</tr>
<tr>
<td>Ta (60%)</td>
<td></td>
</tr>
<tr>
<td>T1 (30%)</td>
<td></td>
</tr>
<tr>
<td>Muscle invasive</td>
<td>20%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>5%</td>
</tr>
</tbody>
</table>

a. Number shown includes patients with CIS only. Publications do not report the percentage of patients with concomitant CIS±Ta, T1.
Standard Diagnosis and Surveillance Approaches for NMIBC

- Cystoscopy: Standard approach for examination of the bladder
- Urine cytology: Done routinely as adjunct to cystoscopy
- Biopsy: Provides definitive diagnosis (stage and grade)
  - Generally performed on “for cause” basis
    - Suspicious lesion on cystoscopy or positive cytology
- Imaging: CT urography
Untreated CIS Has High Risk of Progression

- All CIS is considered high risk by AUA, EUA, NCCN
- Genomic changes similar to muscle invasive bladder cancer (MIBC)
  - MIBC is the most common precursor to metastases
- Can occur in isolation or concomitantly with papillary tumors (Ta, T1)
- CIS is often patchy and diffuse, thus difficult to fully resect
- Has a high tendency for recurrence
- Left untreated, CIS exhibits a high rate of progression to MIBC within 5 years

Standard First-Line Treatment for CIS

- **BCG (Bacillus Calmette-Guerin):** Live attenuated *Mycobacterium bovis* instilled in the bladder via foley catheter
  - Leads to localized immune response
- Intravesical BCG has high initial efficacy:
  - Initial complete response rates (after 1-2 BCG courses) as high as >75%

Many Patients With CIS Will Recur Despite BCG Therapy

- Despite high initial efficacy, responses to BCG are often not durable\(^4,5\)
  - Approximately 50% of patients will recur within 1 year\(^3\)
  - Patients with CIS who recur within 1 year after receiving 2 courses of BCG are considered BCG-unresponsive\(^4\)

BCG-Unresponsive CIS Is at Especially High Risk of Progression

- Definition of BCG-unresponsive CIS only recently standardized
- Historical literature reports in high-risk NMIBC using variable definitions of BCG failure demonstrate
  - 20 to 40% risk of progression to MIBC within 5 years\(^1-4\)
    - About 50% of patients who progress to MIBC subsequently develop metastatic disease
      - Death due to bladder cancer in nearly all of these cases

Recommended Treatment for BCG-Unresponsive CIS

- **Radical cystectomy (curative intent)**
- **Investigational agents**
  - Valrubicin
  - More BCG
- **Alternative therapies not recommended by guidelines**
- **BCG-unresponsive CIS (± papillary)**
- **Radical cystectomy**
Radical Cystectomy Is Major Surgery

- Involves complete removal of the bladder and pelvic lymph nodes plus other gender-specific organs

Male cystectomy removes prostate and seminal vesicles

Female cystectomy removes uterus and ovaries

Left image reprinted from Greene A. Surgery to treat bladder cancer in men (cystectomy). [Graphic 51018 Version 3.0]. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2019.
Right image reprinted from Greene A. Surgery to treat bladder cancer in women (cystectomy). [Graphic 54274 Version 3.0]. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2019.
Radical Cystectomy Is a Highly Morbid Surgery

- Mortality rate (90-day): ~4%¹
- Hospitalization (no complications): 7-10 days²
  - Rehospitalization rate: ~ 30%
- Complication rate: 45% - 70%²
  - Use of intestine major source of complications³
- Recovery period: 6-8 weeks
- Major negative impact on quality of life

Intravesical Valrubicin Only FDA-Approved Therapy for BCG-Refractory CIS

FDA basis of approval

- Single-arm study
- Efficacy population, N=90
  - 70% received ≥2 courses of BCG (timing of courses varies)
    • Not a BCG-unresponsive population!
- Complete response rate (18%, n=16)
- DOR measured from start of treatment
  - Median DOR 13.5 months
Urgent Need for Novel Nonsurgical Therapies for Bladder Preservation

- Limited nonsurgical alternatives to radical cystectomy
- MCNA, docetaxel, BCG + interferon alpha-2b, gemcitabine, and others
- Most studies are retrospective, nonrandomized single-institution series with a heterogeneous patient population
- Few studies measure CR rate and DOR in a homogeneous population with BCG-unresponsive CIS
FDA-AUA Workshop Convened in 2013 to Spur Drug Development in NMIBC

- Framework for clinical trial design in BCG failures was developed
  - Single-arm design deemed appropriate
  - Homogenous population of high-risk patients after BCG treatment
  - Defined efficacy endpoints

- Potential efficacy benchmarks
  - 40% - 50% initial CRR and 30% CRR at 18-24 months\(^1\)
  - 50% initial CRR, 30% CRR at 12 months, and 25% at 18 months (IBCG)\(^2\)
  - In an era when only intravesical therapy was envisioned

Consensus Definition of BCG-Unresponsive NMIBC

- Adequate BCG therapy
  - ≥5 of 6 doses of an initial induction course (adequate induction) PLUS
    - ≥2 of 3 doses of maintenance therapy OR
    - ≥2 of 6 doses of a second induction course

- BCG unresponsive disease includes
  - Persistent or recurrent CIS (with or without recurrent Ta/T1) within 12 months of completion of adequate BCG therapy
  - Recurrent high-grade Ta/T1 within 6 months of completion of adequate BCG therapy
  - T1 high-grade disease at first evaluation following an induction BCG course

Conclusions

- BCG-unresponsive CIS is at high risk for progression to muscle invasive and metastatic disease
- Radical cystectomy is standard of care for BCG-unresponsive CIS
- Many patients elect not to undergo radical cystectomy or are medically ineligible
- No widely accepted treatment options after BCG
- Urgent need for novel nonsurgical/conservative therapies
# Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Jeffrey Stuart, PhD</td>
<td>Merck &amp; Co., Inc.</td>
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<tr>
<td>Unmet Need</td>
<td>Gary Steinberg, MD</td>
<td>NYU Langone Health</td>
</tr>
<tr>
<td>Efficacy and Safety</td>
<td>Ekta Kapadia, MD</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td>Ashish Kamat, MD, MBBS, FACS</td>
<td>MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Benefit-Risk</td>
<td>Scot Ebbinghaus, MD</td>
<td>Merck &amp; Co., Inc.</td>
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</table>
Clinical Development and Summary of KEYNOTE-057 Efficacy and Safety

Ekta Kapadia, MD
Senior Clinical Director, Oncology
Merck & Co., Inc.
**Pembrolizumab Is Approved in Advanced Urothelial Cancer**

- Overall survival benefit in second-line patients
- Meaningful response rates and duration of response in first-line patients

**Response Evaluation**

- **KEYNOTE-045**
  - Objective response rate (95% CI): 29% (24, 34)
  - Complete response: 9%
  - Partial response: 20%
  - Median duration of response: 30.1 (14+ to 35.9+)

- **KEYNOTE-052**
  - Objective response rate (95% CI): 29% (24, 34)
  - Complete response: 9%
  - Partial response: 20%
  - Median duration of response: 30.1 (14+ to 35.9+)

+ Denotes ongoing.

Database Cutoff Dates: 26 OCT 2017 for 045 and 26 SEP 2018 for 052.
KEYTRUDA USPI, September 2019.
Rationale for Pembrolizumab in BCG-unresponsive NMIBC

- Recognized as area with significant unmet medical need for development of nonsurgical therapies
  - Patients have few available alternative options if ineligible for or elect not to undergo radical cystectomy
- NMIBC is amenable to immunotherapies
- Pembrolizumab has shown significant activity in locally advanced/metastatic urothelial carcinoma
Primary objective

- Evaluate antitumor activity of pembrolizumab by evaluating the absence of high-risk NMIBC or progressive disease

Primary hypothesis

- In patients with BCG-unresponsive CIS who are ineligible for or decline radical cystectomy, pembrolizumab monotherapy will result in a complete response (CR) rate that is greater than 20%
KEYNOTE-057: Study Design Consistent With FDA Guidance

Data presented are for Cohort A
Database cutoff: May 24, 2019
Enrollment cutoff: April 1, 2018

**Patient population**:  
- Cohort A: BCG-unresponsive CIS ± papillary disease  
- Ineligible for or declined cystectomy

**Data presented**: for Cohort A

**BCG**=Bacillus Calmette-Guérin; **CIS**=carcinoma in situ; **CR**=complete response; **HR NMIBC**=high risk non–muscle-invasive bladder cancer.

**Key Points**:
- Cohort B: papillary tumors only without CIS—currently enrolling
- Duration of response data are based on database cutoff of September 24, 2019
- Participants with continued CR can electively discontinue pembrolizumab after 18 months
- 1st disease assessment at 12 weeks
- 2nd disease assessment at 24 weeks
- If no recurrence or progression of HR NMIBC at any assessment
- If HR NMIBC present at any assessment
- If no CR, discontinue treatment, enter survival follow-up
- Continue pembrolizumab for up to 2 years and efficacy assessments through year 5, or until recurrent/progressive disease
- Discontinue treatment, enter survival follow-up

28-day screening
Key Inclusion and Exclusion Criteria: A Population With BCG-Unresponsive CIS

**Inclusion**
- Centrally confirmed CIS ± papillary tumor (T1 and/or Ta) of the bladder
- Visually complete resection of all papillary tumor
- Received adequate BCG therapy
- Developed CIS that is unresponsive to BCG therapy
- Elected not to undergo, or was considered ineligible for, radical cystectomy

**Exclusion**
- Muscle invasive (ie, T2, T3, T4), locally advanced non resectable or metastatic disease
- Concurrent extravesical non-muscle invasive disease
  - ie, urethra, ureter, renal pelvis
Key Efficacy Endpoints

- **Primary** – Complete response (CR) rate
  - Proportion of patients free of high-risk NMIBC or progressive urothelial cancer (UC)
  - Evaluated using exact binomial method comparing lower bound of the 95% confidence interval (CI) with historical control rate of 20%
    - Historical control rate based on valrubicin CR rate of 18%

- **Key Secondary** – Duration of response
  - Time from first documented evidence of CR until recurrence of high-risk NMIBC or progressive UC
  - Estimated in responders by Kaplan-Meier method
Disease Assessments

- Central assessment of all urine cytology, TURBTs/Random biopsies, and CTUs required
- Screening
  - Cystoscopy with biopsy confirming CIS, urine cytology, and CTU
- Treatment and Follow-up Phase (up to 5 years or confirmed disease recurrence/progression)
  - Cystoscopies and urine cytology every 3 months × 2 years, then every 6 months through Year 5
  - CTUs every 6 months × 2 years, then yearly (more frequently if suspicious cystoscopy/cytology)
  - Biopsies required to evaluate for recurrence/progression:
    - If positive cystoscopy – directed biopsy
    - If positive cytology only – random biopsies (+ prostatic urethra in males)
- Survival Follow-up
  - General disease status
  - Subsequent therapies
  - Alive/Dead status
  - Efficacy assessment data not collected
KEYNOTE-057
Cohort A (CIS ± Papillary Tumors)
Summary of Efficacy
Analysis Populations (Cohort A)

Treated (safety population)  
N=102

Excluded

Did not meet FDA definition of BCG-unresponsive NMIBC  
n=5

Participant without CIS at baseline  
/vendor transcription error\  
n=1

Efficacy population  
N=96

\textsuperscript{a}Sponsor was notified of transcription error by vendor after Briefing Document was finalized.
Key Baseline Characteristics Are Representative of Patients With High-Risk NMIBC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>73 (44-92)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>30 (31.3)</td>
</tr>
<tr>
<td>≥65 to &lt;75</td>
<td>24 (25.0)</td>
</tr>
<tr>
<td>≥75 to &lt;85</td>
<td>33 (34.4)</td>
</tr>
<tr>
<td>≥85</td>
<td>9 (9.3)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>81 (84.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>15 (15.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64 (66.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>26 (27.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>70 (72.9)</td>
</tr>
<tr>
<td>1</td>
<td>26 (27.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prior BCG instillations, n (range)</td>
<td>12.0 (7.0-45.0)</td>
</tr>
<tr>
<td>Tumor pattern at study entry, n (%)</td>
<td></td>
</tr>
<tr>
<td>CIS with T1</td>
<td>12 (12.5)</td>
</tr>
<tr>
<td>CIS with high-grade Ta</td>
<td>24 (25.0)</td>
</tr>
<tr>
<td>CIS alone</td>
<td>60 (62.5)</td>
</tr>
<tr>
<td>PD-L1 status, n (%)</td>
<td></td>
</tr>
<tr>
<td>CPS ≥10</td>
<td>35 (36.5)</td>
</tr>
<tr>
<td>CPS &lt;10</td>
<td>56 (58.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Reason prior cystectomy not performed, n (%)</td>
<td></td>
</tr>
<tr>
<td>Declined</td>
<td>91 (94.8)</td>
</tr>
<tr>
<td>Ineligible</td>
<td>5 (5.2)</td>
</tr>
</tbody>
</table>
Patient Disposition

Efficacy population 
N=96

Ongoing 
n=7

Completed 
2 years of pembrolizumab 
n=3

Discontinued from treatment n=86
  Persistent disease\(^a\) n=38
  Recurrent high-risk NMIBC or stage progression to T1 n=33
  Adverse event n=9
  Physician decision n=1
  Patient withdrawal n=2

Electively discontinued treatment after 18 mo with continued CR\(^b\) n=3

Median follow-up was 28.0 months (range, 4.6 - 40.5)

- Majority of patients discontinued from study therapy secondary to persistent or recurrent NMIBC
- No progression to muscle invasive or metastatic bladder cancer at time of treatment discontinuation based on study specified disease assessments

\(^a\) Includes patients with CIS at baseline and discontinued from study treatment because they continued to have CIS at the first evaluable efficacy assessment.

\(^b\) Patients who were allowed per protocol to discontinue study treatment after 18 months with continued CR.
The CR Rate Exceeds the Success Criterion for the Primary Hypothesis Test

<table>
<thead>
<tr>
<th>Best Response</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>39 (40.6)</td>
<td>30.7, 51.1</td>
</tr>
<tr>
<td>Non-CR</td>
<td>56 (58.3)</td>
<td>47.8, 68.3</td>
</tr>
<tr>
<td>Persistent</td>
<td>40 (41.7)</td>
<td>31.7, 52.2</td>
</tr>
<tr>
<td>Recurrent</td>
<td>6 (6.3)</td>
<td>2.3, 13.1</td>
</tr>
<tr>
<td>NMIBC stage progression to T1</td>
<td>9 (9.4)</td>
<td>4.4, 17.1</td>
</tr>
<tr>
<td>Progression to T2</td>
<td>0</td>
<td>NA, NA</td>
</tr>
<tr>
<td>Extravesical disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (1.0)</td>
<td>0.0, 5.7</td>
</tr>
<tr>
<td>Non-evaluable (NE)</td>
<td>1 (1.0)</td>
<td>0.0, 5.7</td>
</tr>
</tbody>
</table>

N=96

- Statistically significant CRR – lower bound of 95% CI exceeds the 20% success criterion for the primary hypothesis test

<sup>a</sup> Extravesical disease is defined as the presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. The one patient included in this category developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer, and later scans showed metastases that were most likely from the pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer.
Complete Responses Were Generally Consistent Across Subgroups

<table>
<thead>
<tr>
<th>Protocol-Specified Subgroup</th>
<th>Responses, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>39/96</td>
</tr>
<tr>
<td>Age group, yr</td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>11/30</td>
</tr>
<tr>
<td>≥65 to &lt;75</td>
<td>10/24</td>
</tr>
<tr>
<td>≥75 to &lt;85</td>
<td>14/33</td>
</tr>
<tr>
<td>≥85</td>
<td>4/9</td>
</tr>
<tr>
<td>PD-L1 subgroup</td>
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</tr>
<tr>
<td>PD-L1 CPS &lt;10</td>
<td>27/56</td>
</tr>
<tr>
<td>PD-L1 CPS ≥10</td>
<td>10/35</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6/15</td>
</tr>
<tr>
<td>Male</td>
<td>33/81</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21/64</td>
</tr>
<tr>
<td>Non-White</td>
<td>14/26</td>
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<tr>
<td>Geographic region US</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>10/34</td>
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<tr>
<td>Non-US</td>
<td>29/62</td>
</tr>
<tr>
<td>ECOG status</td>
<td></td>
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<tr>
<td>0</td>
<td>26/70</td>
</tr>
<tr>
<td>1/2</td>
<td>13/26</td>
</tr>
<tr>
<td>Tumor pattern at study entry</td>
<td></td>
</tr>
<tr>
<td>Carcinoma in situ with T1</td>
<td>5/12</td>
</tr>
<tr>
<td>Carcinoma in situ with high-grade TA</td>
<td>7/24</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>27/60</td>
</tr>
</tbody>
</table>
Duration of Complete Response Is Clinically Meaningful

- Of 96 patients, 39 achieved CR at first disease assessment
- Patients not in CR at first disease assessment came off treatment

**Median DOR (range): 16.2 (0.0+ to 30.4+)**

- Of 96 patients, 39 achieved CR at first disease assessment
- Patients not in CR at first disease assessment came off treatment

**12 month DOR landmark:**
- Approximately 15 months from start of therapy
- 57% by Kaplan Meier Estimate
- Number of patients with observed DOR ≥ 12 months was
  - 18/39 (46%) of initial complete responders
  - 19% of all treated patients (n=96)
Duration of Complete Response Is Clinically Meaningful

Median follow-up for patients in CR: 27.0 months (range, 14.6 - 39.6)
### Pembrolizumab Did Not Appear to Limit the Opportunity for Cystectomy or Other Therapies

**Median follow-up was 28.0 months (range, 4.6 - 40.5)**

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>N=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>17 (17.7)</td>
</tr>
<tr>
<td>Non-CR/Recurrent</td>
<td>79 (82.3)</td>
</tr>
<tr>
<td><strong>Cystectomy</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36 (37.5)</td>
</tr>
<tr>
<td><strong>Therapy or procedure excluding cystectomy</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>34 (35.4)</td>
</tr>
<tr>
<td>Local procedure (TURBT, biopsy, fulguration, radiation, other&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>21 (21.9)</td>
</tr>
<tr>
<td>Intravesical therapy (BCG, chemotherapy, vicinium)</td>
<td>27 (28.1)</td>
</tr>
<tr>
<td>Systemic therapy (pembrolizumab)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>No subsequent therapy received</td>
<td>10 (10.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (4.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Subsequent therapy includes any new anticancer therapy, radiation treatment, or surgical procedure performed to treat NMIBC that persisted or recurred after pembrolizumab treatment.

<sup>b</sup> Five patients received both other therapy and cystectomy and are counted in both categories.

<sup>c</sup> Other therapy is photodynamic therapy with TLD-1433 and TLC-3200.

Database cutoff: May 24, 2019; duration of follow-up database cutoff: Sep 24, 2019.
Window of Opportunity for Radical Cystectomy Is Preserved in Most Patients

- Natural history of high-risk NMIBC
  - On average, 20% of patients are upstaged from NMIBC to MIBC as documented in literature
  - Pathological upstaging to MIBC or non-organ confined disease at time of RC may negatively impact potential to undergo curative surgery

- KEYNOTE-057 Data
  - Majority of patients, 33 of 36 (92%), had no pathological upstaging to MIBC at time of RC
    - 3/36 (8.3%) had pT2 or higher disease at RC
      - pT2N0, pT2N1, pT3N1: 60, 86, 457 days post last dose, respectively
  - Window of opportunity for radical cystectomy is generally preserved

Pembrolizumab Offers a Nonsurgical Alternative With Durable Benefit for Patients Who Are Ineligible for or Decline Radical Cystectomy

- KEYNOTE-057: A well-conducted study and consistent with FDA guidelines
- Compelling CR rate: 40.6% (95% CI: 30.7, 51.1)
- Clinically meaningful durability: Median DOR 16.2 months (0.0+ to 30.4+)
  - 12-month DOR landmark: 18/39 (46%) initial complete responders; 19% of all treated patients (n=96)
- Window of opportunity for definitive surgery is generally preserved
  - No progression of NMIBC to MIBC or metastatic bladder cancer while receiving study therapy based on study-specified disease assessments
  - Low rate of upstaging at the time of radical cystectomy
KEYNOTE-057
Summary of Safety
Pembrolizumab Has a Well-Established Safety Profile

- Safety profile is well characterized, based on large clinical program and extensive post marketing experience
  - More than 30,000 patients treated in clinical trials
  - Five years of post-marketing experience – nearly 300,000 patients worldwide have received pembrolizumab

- Pembrolizumab monotherapy Reference Safety Dataset (RSD; n=2799)
  - Advanced melanoma (1567 participants from KEYNOTE-001, KEYNOTE-002, KEYNOTE-006) and
  - Non-small cell lung cancer (1232 participants from KEYNOTE-001 and KEYNOTE-010)
### KEYNOTE-057: Adverse Events Regardless of Causality Consistent with Pembrolizumab Dataset

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Cohort A n=102</th>
<th>Pembrolizumab Reference Safety Dataset n=2799</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>99 (97.1)</td>
<td>2727 (97.4)</td>
</tr>
<tr>
<td>Grade 3-5 AE</td>
<td>30 (29.4)</td>
<td>1273 (45.5)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>26 (25.5)</td>
<td>1042 (37.2)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.0)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>110 (3.9)</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>10 (9.8)</td>
<td>334 (11.9)</td>
</tr>
<tr>
<td>Discontinuation due to serious AE</td>
<td>4 (3.9)</td>
<td>253 (9.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Respiratory failure due to MRSA pneumonia (n=1) and metastatic pancreatic cancer (n=1). Neither of the deaths was deemed related to treatment.
### KEYNOTE-057: Most Common Adverse Events Regardless of Causality

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Cohort A n=102</th>
<th>Pembrolizumab Reference Safety Dataset n=2799</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>22 (21.6)</td>
<td>625 (22.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (20.6)</td>
<td>1044 (37.3)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>21 (20.6)</td>
<td>39 (1.4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 (18.6)</td>
<td>562 (20.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>18 (17.6)</td>
<td>615 (22.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (14.7)</td>
<td>685 (24.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (13.7)</td>
<td>504 (18.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (11.8)</td>
<td>498 (17.8)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (11.8)</td>
<td>162 (5.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12 (11.8)</td>
<td>182 (6.5)</td>
</tr>
<tr>
<td>Immune-Mediated Adverse Events and Infusion Reactions</td>
<td>Cohort A n=102</td>
<td>Pembrolizumab Reference Safety Dataset n=2799</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>----------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Any</td>
<td>21 (20.6)</td>
<td>597 (21.3)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>3 (2.9)</td>
<td>154 (5.5)</td>
</tr>
<tr>
<td>Serious</td>
<td>5 (4.9)</td>
<td>161 (5.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>4 (3.9)</td>
<td>83 (3.0)</td>
</tr>
<tr>
<td>Discontinuation due to serious events</td>
<td>2 (2.0)</td>
<td>68 (2.4)</td>
</tr>
</tbody>
</table>
## KEYNOTE-057: Immune-Mediated Adverse Events and Infusion Reactions

<table>
<thead>
<tr>
<th>Immune-Mediated Adverse Events</th>
<th>Cohort A n=102</th>
<th>Pembrolizumab Reference Safety Dataset n=2799</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>21 (20.6)</td>
<td>597 (21.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8 (7.8)</td>
<td>237 (8.5)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>5 (4.9)</td>
<td>96 (3.4)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (2.9)</td>
<td>94 (3.4)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (1.0)</td>
<td>22 (0.8)</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (1.0)</td>
<td>48 (1.7)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (1.0)</td>
<td>19 (0.7)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1 (1.0)</td>
<td>17 (0.6)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1 (1.0)</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>1 (1.0)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>1 (1.0)</td>
<td>38 (1.4)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1 (1.0)</td>
<td>14 (0.5)</td>
</tr>
</tbody>
</table>

Grade 3-4 AEs included 1 each of Type 1 diabetes, adrenal insufficiency, and severe skin reaction.
KEYNOTE-057 Safety Summary: Consistent With Established Pembrolizumab Monotherapy Safety Profile

- Well-characterized safety profile
  - Large clinical trial program
  - Extensive post marketing experience
- KEYNOTE-057 safety data similar to known safety profile of pembrolizumab in terms of
  - Types and frequencies of AEs overall
  - Low incidence of serious and grade 3-5 immune-mediated AEs
  - Low incidences of treatment discontinuations due to AEs
- No new safety concerns in KEYNOTE-057
- AEs effectively managed by standard clinical practice
# Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Jeffrey Stuart, PhD</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>Unmet Need</td>
<td>Gary Steinberg, MD</td>
<td>NYU Langone Health</td>
</tr>
<tr>
<td>Efficacy and Safety</td>
<td>Ekta Kapadia, MD</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td>Ashish Kamat, MD, MBBS, FACS</td>
<td>MD Anderson Cancer Center</td>
</tr>
<tr>
<td>Benefit-Risk</td>
<td>Scot Ebbinghaus, MD</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
</tbody>
</table>
Clinical Perspective

Ashish M. Kamat, MD, MBBS, FACS
Professor of Urologic Oncology (Surgery)
Wayne B. Duddlesten Professor of Cancer Research
MD Anderson Cancer Center, Houston, Texas
President, International Bladder Cancer Group (IBCG)
Co-President, International Bladder Cancer Network (IBCN)
We Need an Effective Therapeutic Option for Our Patients

To safely avoid, or at least delay, the need for radical bladder removal after BCG has failed
We Need an Effective Therapeutic Option for Our Patients

BCG-unresponsive CIS persists and progresses without effective intervention

Only FDA-approved agent, valrubicin, is seldom used

Patients do not want radical cystectomy
Radical Cystectomy – Effective, but Morbid!

- Typical stay 7-10 days in USA
- 45%-70% complication rate:
  - 15% high-grade complications
- ~30% hospital readmission

Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.
What Are My Patients With Bladder Cancer Worried About?

- Body image
- Sexual function
- Incontinence – bowel or bladder
- Pain
- Quality of life
- Will my clothes fit?
- Will I be able to dance, swim, exercise, play golf … ?
What Are My Patients With Bladder Cancer Worried About?

- Body image
- Sexual function
- Incontinence – bowel or bladder
- Pain
- Quality of life
- Will my clothes fit?
- Will I be able to dance, swim, exercise, play golf … ?

- No effective FDA-approved therapy
- Repeated procedures
- Multiple anesthetics
- Muscle invasive disease
- Risk of metastases
Pembrolizumab Offers an Option for Patients Who Decline or Are Ineligible for Radical Cystectomy

- Upstaging to ≥pT2 in 8.3% of patients

### Best Response

<table>
<thead>
<tr>
<th></th>
<th>n  (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>39 (40.6)</td>
<td>30.7, 51.1</td>
</tr>
<tr>
<td>Non-CR</td>
<td>56 (58.3)</td>
<td>47.8, 68.3</td>
</tr>
<tr>
<td>Progression to T2</td>
<td>0</td>
<td>NA, NA</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>1 (1.0)</td>
<td>0, 5.7</td>
</tr>
</tbody>
</table>

### Median DOR (range)

- Median DOR: 16.2 (0.0+ to 30.4+)

---

**Remaining in Complete Response, %**

- Pembrolizumab
- Censored

**Duration of CR, months (begins from initial CR assessment)**

- Time CR achieved

**At risk, n**

- 39
- 36
- 27
- 18
- 18
- 14
- 10
- 5
- 4
- 2
- 1
- 0
Patient Conversation

BCG-Unresponsive CIS

Evaluate medically and counsel patient for radical cystectomy

If Yes
Radical Cystectomy

If No
Clinical Trial

No agents are currently recommended in medical guidelines
Patient Conversation

BCG-Unresponsive CIS

Evaluate medically and counsel patient for radical cystectomy

If Yes
Radical Cystectomy

If No
Clinical Trial

No agents are currently recommended in medical guidelines

Valrubicin

Off label agents:
- Mitomycin
- Gemcitabine
- Gemcitabine/Docetaxel
- Hyperthermic Chemotherapy
Patient Conversation

BCG-Unresponsive CIS

Evaluate medically and counsel patient for radical cystectomy

If Yes

Radical Cystectomy

If No

Clinical Trial

Our patients are desperate for an effective alternative to cystectomy!

Valrubicin

Hyperthermic Chemotherapy
 Mitomycin
 Gemcitabine

No agents are currently recommended in medical guidelines
Potential to Change the Treatment Algorithm

- **BCG-Unresponsive CIS**
  - Evaluate medically and counsel patient for radical cystectomy
  - **If Yes**: Radical Cystectomy
  - **If No**: Pembrolizumab

**Median DOR (range)**: 16.2 (0.0+ to 30.4+)

19% of all treated patients achieved response lasting at least 1 year
Benefit-Risk Conclusions

Scot Ebbinghaus, MD
Vice President, Clinical Research, Oncology
Merck & Co., Inc.
Favorable Benefit-Risk Balance of Pembrolizumab

- Established anticancer activity in a number of tumor types
- Established anticancer activity in advanced/metastatic urothelial cancer
- Well-understood and acceptable safety profile

### Response Evaluation

**KEYNOTE-045**

- Objective response rate (95% CI): 29% (24, 34)
- Complete response: 9%
- Partial response: 20%
- Duration of response: Median, months (range) 30.1 (14+ to 35.9+)

**KEYNOTE-052**

- Pembrolizumab n=370

Database Cutoff Date: 26 OCT 2017 for 045 and 26 SEP 2018 for 052.
KEYTRUDA USPI, September 2019.
Favorable Benefit-Risk Balance of Pembrolizumab: BCG-Unresponsive CIS (KEYNOTE-057)

- BCG-unresponsive CIS does not resolve on its own ➔ High unmet medical need
- Pembrolizumab has anticancer activity in patients with CIS
  - Compelling CR rate: 40.6% (95% CI: 30.7, 51.1)
  - Clinically meaningful median DOR: 16.2 months (0.0+ to 30.4+)
    - 12-month DOR landmark: 18/39 (46%) initial complete responders; 19% of all treated patients (n=96)
  - Ability to undergo radical cystectomy is preserved
- Safety is manageable and consistent with established pembrolizumab safety profile
- Potential to treat high-risk disease at an early stage for patients
  ➔ Favorable benefit-risk profile of pembrolizumab for the targeted indication
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
Backup Slides Shown
Low Rates of Upstaging to MIBC At Time of Radical Cystectomy in Patients who Discontinued Pembrolizumab

- 33 of 36 (92%) patients did not have upstaging to MIBC

<table>
<thead>
<tr>
<th>Tumor-node classification</th>
<th>Participants, n (N=36)</th>
<th>Maximum T-stage</th>
<th>N-Stage*</th>
<th>Achieved initial CR (Yes/No)</th>
<th>Interval between last dose of pembrolizumab and RC (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tumor</td>
<td>6</td>
<td>pT0</td>
<td>N0=5</td>
<td>Yes=3; No=2</td>
<td>Median (Range): 134.5 (60-149)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nx=1</td>
<td>Yes=1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>pTa</td>
<td>N0=3</td>
<td>No=3</td>
<td></td>
</tr>
<tr>
<td>NMIBC</td>
<td>18</td>
<td>pTis</td>
<td>N0=16</td>
<td>Yes=3; No=13</td>
<td>Median (Range): 77 (42-448)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nx=2</td>
<td>Yes=1; No=1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>pT1**</td>
<td>N0=6</td>
<td>Yes=1; No=5</td>
<td></td>
</tr>
<tr>
<td>MIBC</td>
<td>2</td>
<td>pT2</td>
<td>N0=1</td>
<td>No</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N1=1***</td>
<td>No</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>pT3</td>
<td>N1</td>
<td>No</td>
<td>457</td>
</tr>
</tbody>
</table>

Tumor-node classification based on American Joint Committee on Cancer (AJCC) staging system 8th edition.

* Nx= lymph node dissection not performed.

** 2 participants had concomitant CIS

*** Participant with pT2N1 disease had involvement of a single perivesical lymph node.