Introduction

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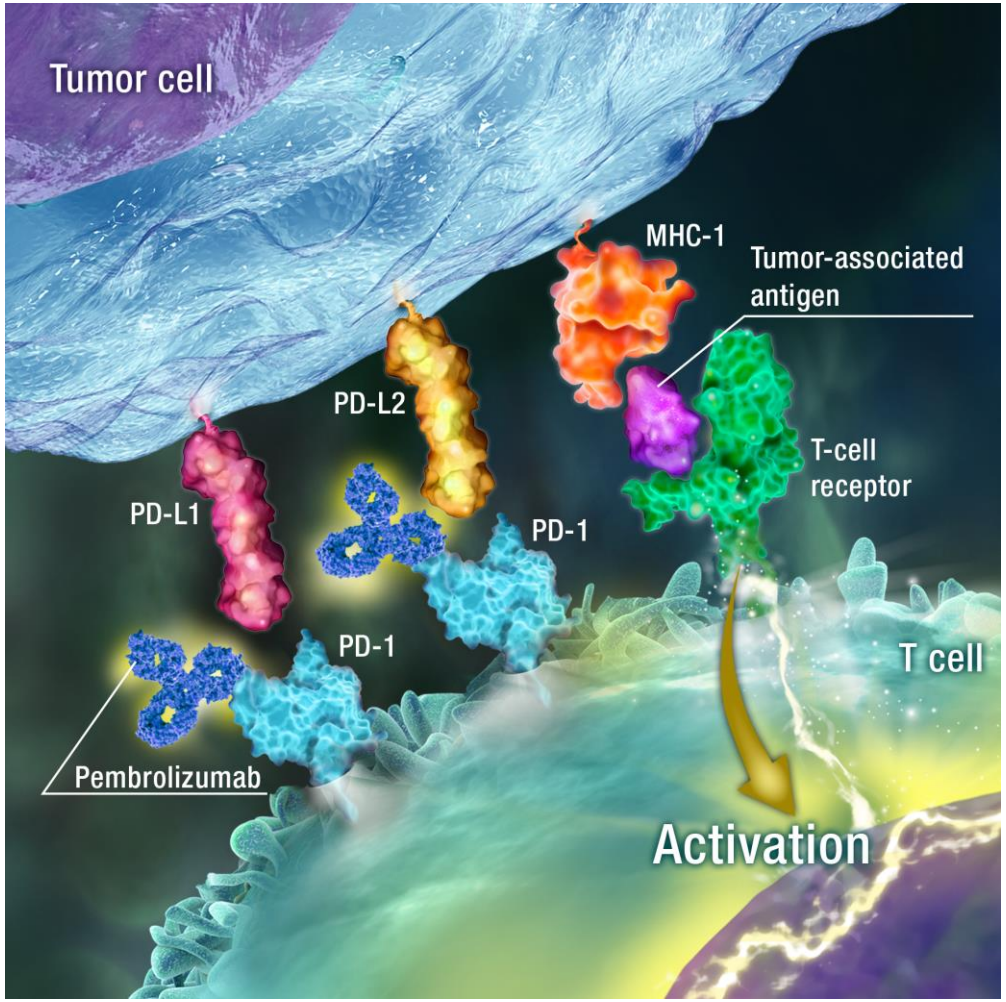
MERCK

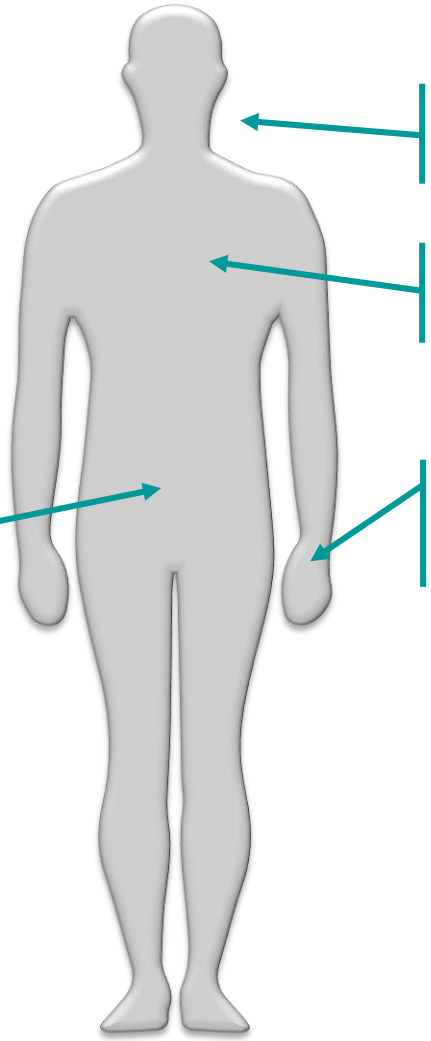
KEYTRUDA® (pembrolizumab)

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



Iwai Y, et al. *Proc Natl Acad Sci USA,* 2002;99:12293-12297.

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

- ✓ Melanoma
- ✓ Merkel cell carcinoma

- ✓ **Urothelial carcinoma**
- ✓ Gastric cancer
- ✓ Hepatocellular carcinoma
- ✓ Cervical cancer
- ✓ Endometrial carcinoma
- ✓ Renal cell carcinoma

Other:

- ✓ 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

Disease progression

Advanced/Metastatic 2L+	Advanced/Metastatic 1L	Muscle Invasive Bladder Cancer (MIBC)	Non-Muscle Invasive Bladder Cancer (NMIBC)
Failed previous platinum therapy KEYNOTE-045: Approved May 2017	**Cisplatin-ineligible**[a] KEYNOTE-052: Approved May 2017 LEAP-011: lenvatinib + pembrolizumab **All-comers** KEYNOTE-361: pembrolizumab monotherapy and pembrolizumab plus chemotherapy	**Cisplatin-eligible** KEYNOTE-866: NeoAdj/Adj pembrolizumab + chemotherapy **Cisplatin-ineligible** KEYNOTE-905: NeoAdj/Adj pembrolizumab	**BCG-unresponsive CIS** KEYNOTE-057: pembrolizumab **Failed BCG Induction** KEYNOTE-676: BCG + pembrolizumab

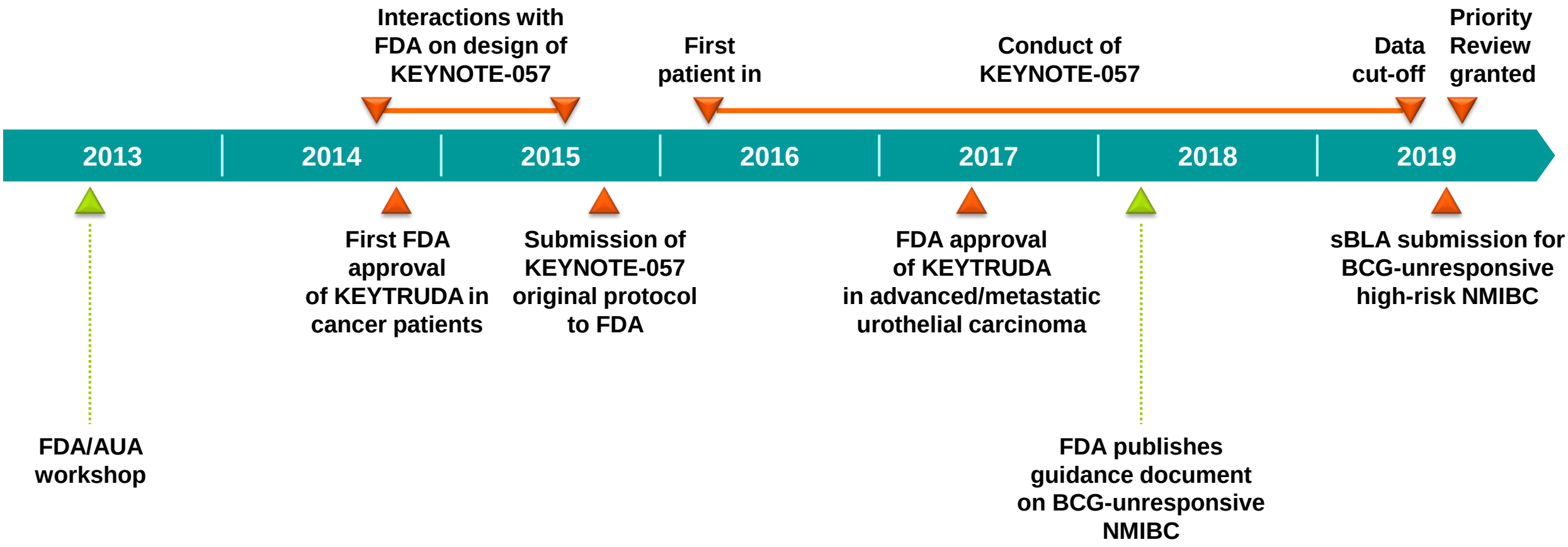
Blue – FDA approval received
Orange – Ongoing registration study

[a] Resulted in accelerated approval for the treatment of patients who are cisplatin ineligible with CPS>10, or ineligible for platinum-based chemotherapy.

Proposed indication

- 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

Regulatory Timeline



What You Will Hear Today

Unmet Medical Need	• BCG-unresponsive NMIBC with CIS is a serious disease • Many patients decline or are medically ineligible for radical cystectomy • No well-accepted nonsurgical options for BCG-unresponsive CIS patients
Efficacy	• Complete response rate of 41% – exceeds available therapies • Complete responses are durable – median DOR 16 months • Window of opportunity for radical cystectomy is preserved
Safety	• Safety profile of pembrolizumab well characterized: >30,000 patients in clinical trials • No new safety concerns in BCG-unresponsive CIS in KEYNOTE-057 • Immune-related AEs manageable with standard measures
Benefit-Risk	• Positive benefit/risk profile in BCG-unresponsive CIS • Pembrolizumab is an effective nonsurgical option

Agenda

Introduction	**Jeffrey Stuart, PhD** Merck & Co., Inc.
Unmet Need	**Gary Steinberg, MD** NYU Langone Health
Efficacy and Safety	**Ekta Kapadia, MD** Merck & Co., Inc.
Clinical Perspective	**Ashish Kamat, MD, MBBS, FACS** MD Anderson Cancer Center
Benefit-Risk	**Scot Ebbinghaus, MD** Merck & Co., Inc.

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

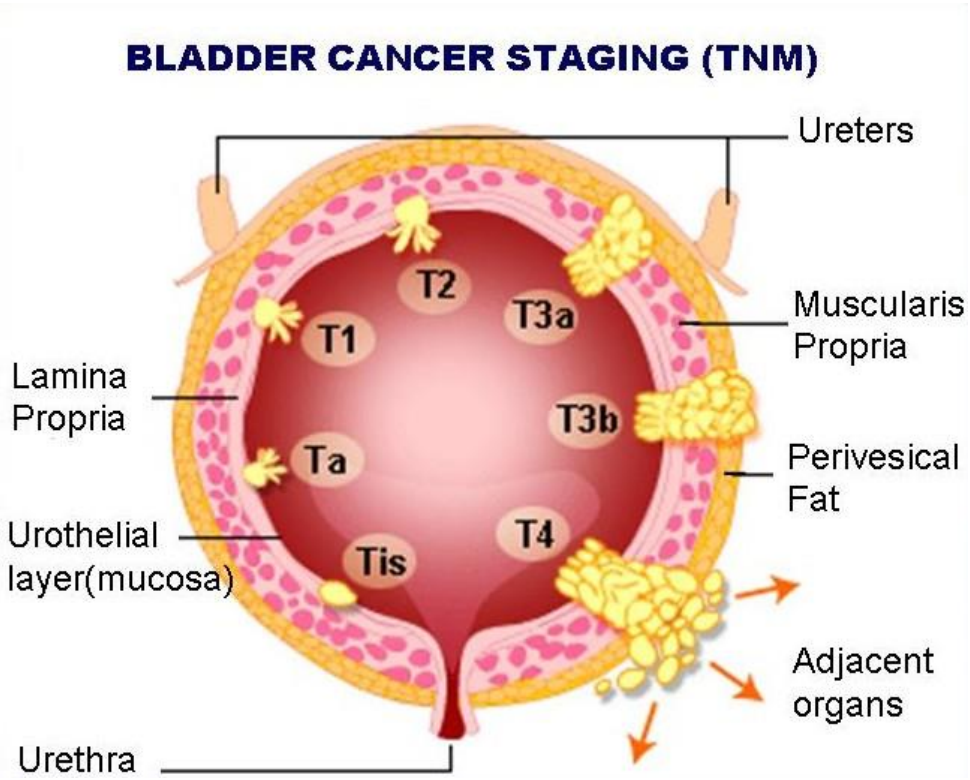
Professor and Director

Goldstein Urology Bladder Cancer Program
NYU Langone Health

MERCK

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



Reprinted from Shah A, Lamke E. J Ady Pract Oncol. 2018; 9:316-320.

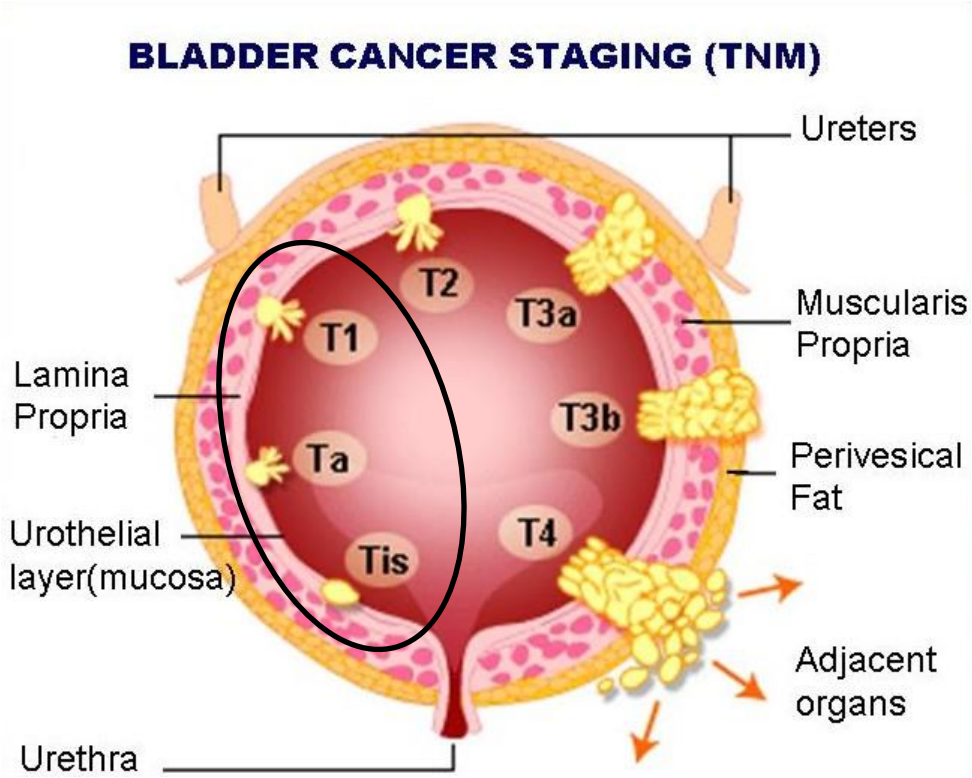
https://seer.cancer.gov/statfacts/html/urinb.html (accessed 04-Dec-2019)

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

Bladder Cancer

↓

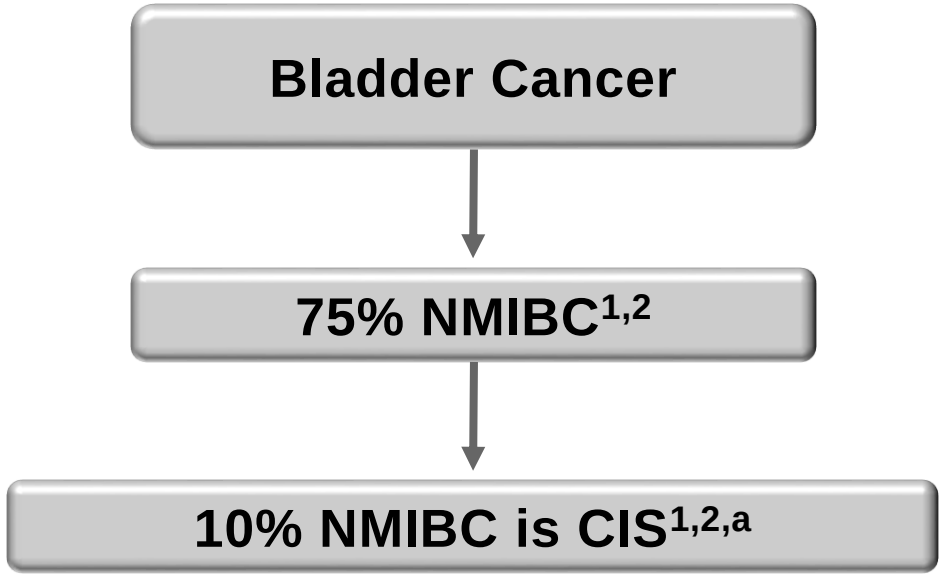
75% NMIBC[1,2]



Reprinted from Shah A, Lamke E. J Ady Pract Oncol. 2018; 9:316-320.

1. Chang SS. AUA/SUO guideline [manuscript]. 2016.
2. Kirkali Z. *Urology*; 2005;66 (6 suppl 1):4-34.

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



Stage at Diagnosis	% of Patients
Non-muscle invasive	**75%**
Tis (CIS) (10%)	
Ta (60%)	
T1 (30%)	
Muscle invasive	20%
Metastatic	5%

1. https://seer.cancer.gov/statfacts/html/urinb.html (accessed 04-Dec-2019).
2. Chang SS. AUA/SUO guideline [manuscript]. 2016.
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

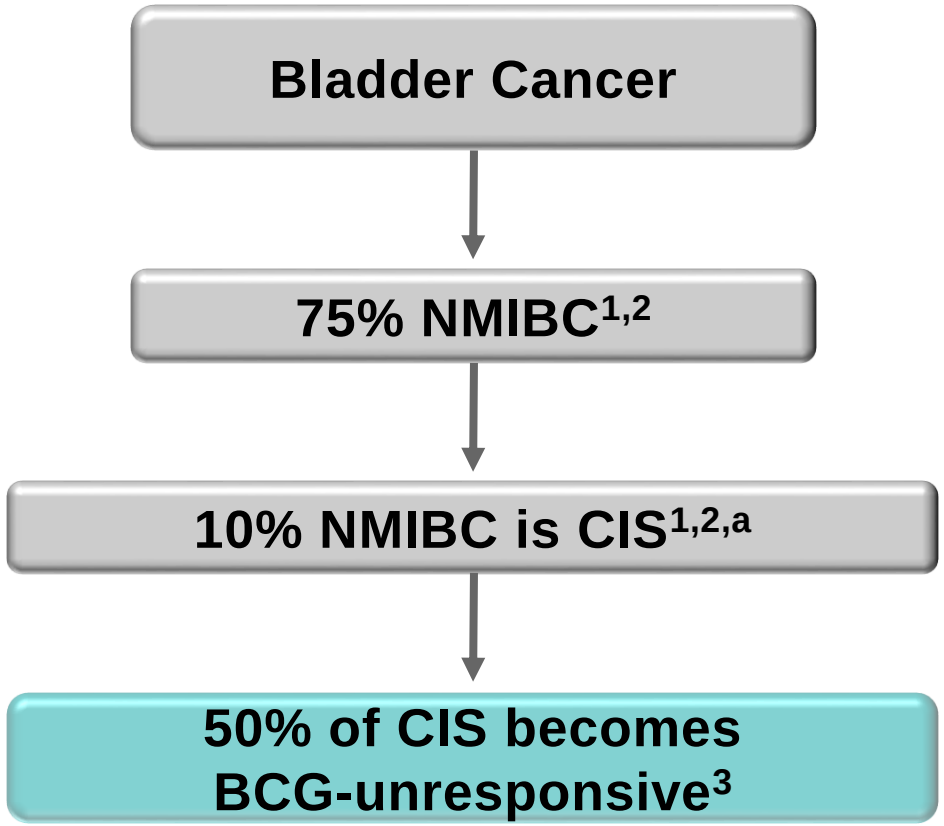
Kamat AM, et al. *Lancet.* 2016;388:2976-2810.

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%[1]

1. Lamm DL, et al. *J Urol.* 2000;163:1124-1129.

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]

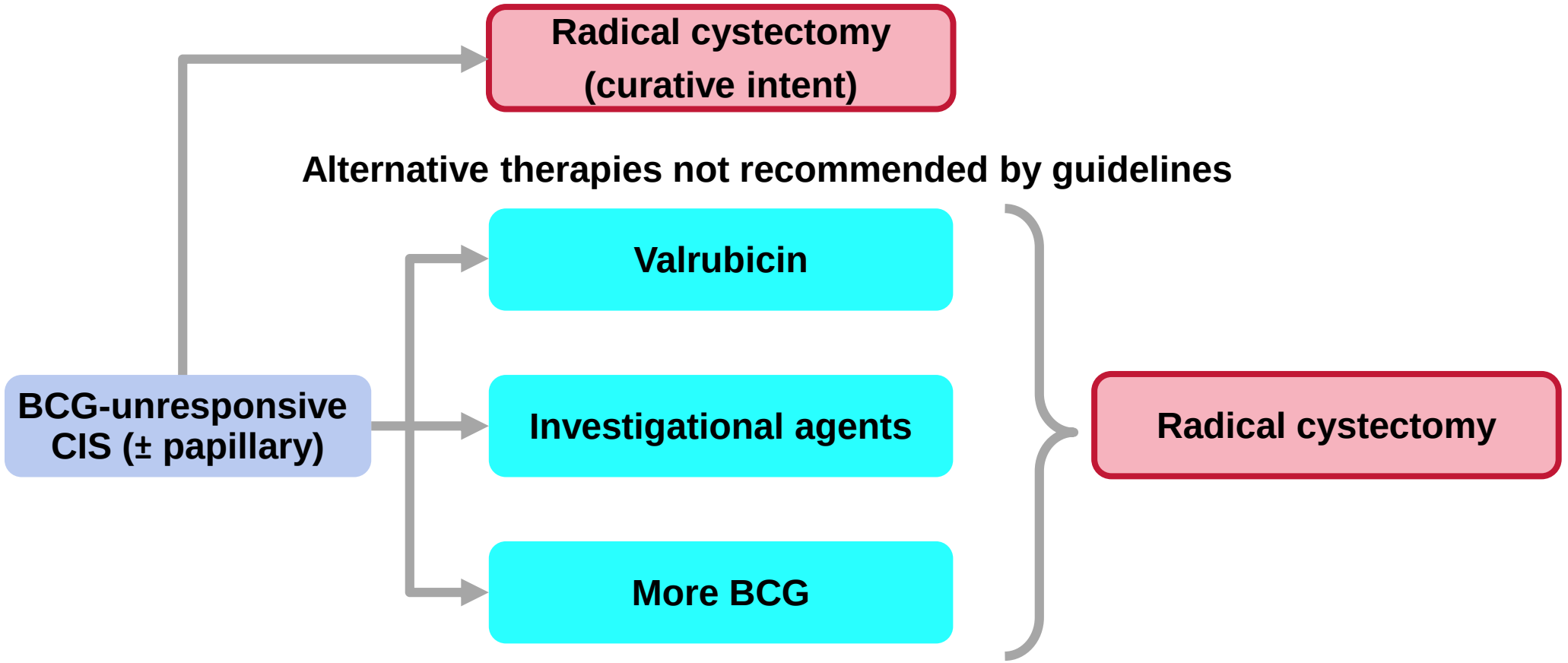
1. https://seer.cancer.gov/statfacts/html/urinb.html (accessed 04-Dec-2019). 2. Chang SS. AUA/SUO guideline [manuscript]. 2016.
a. Number shown includes patients with CIS only. Publications do not report the percentage of patients with concomitant CIS±Ta, T1. 3. Hussain MHA. *J Clin Oncol.* 2009;27:5680-5684. 4. Steinberg RL, et al. *Bladder Cancer* 2015;1:105-126. 5. Nepple KG et al. *J Urol*. 2010 Nov; 184:1915-1919.

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

1. Chang SS. AUA/SUO guideline [manuscript]. 2016. 2 Hussain MHA. *J Clin Oncol*. 2009;27:5680-5684. 3.van den Bosch S. *Eur Urol*. 2011;60:493-500. 4. Kamat AM, et al. *Lancet* 2016;388:2976-2810

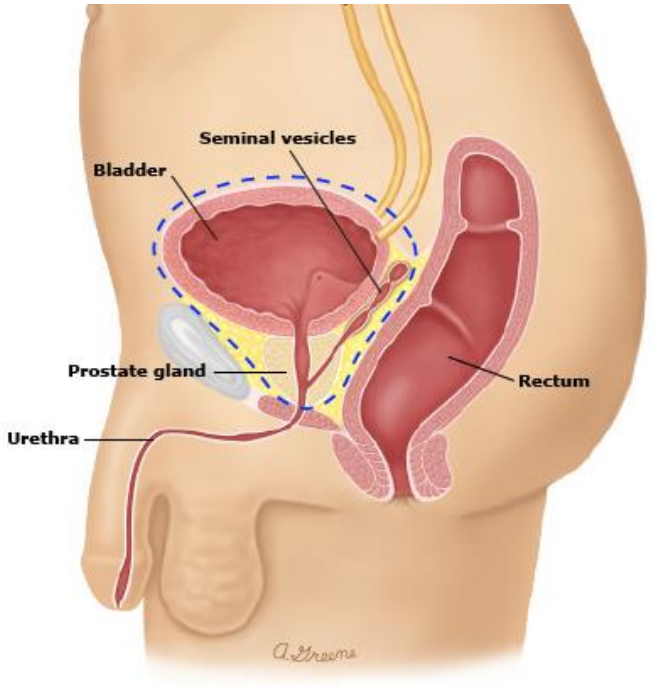
Recommended Treatment for BCG-Unresponsive CIS



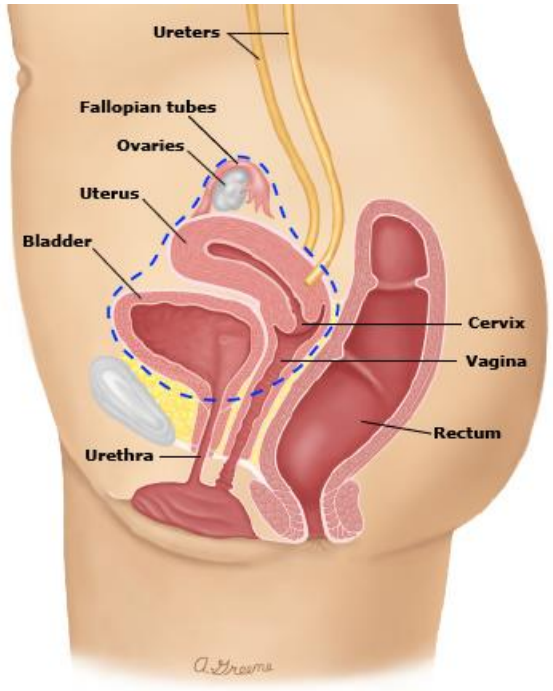
Radical Cystectomy Is Major Surgery

- 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 days[2]
  - Rehospitalization rate: ~ 30%
- Complication rate: 45% - 70%[2]
  - Use of intestine major source of complications[3]
- Recovery period: 6-8 weeks
- Major negative impact on quality of life

All Complications (grades 2-5)

0-90 d after RC

Complication Category, n (%)	N=611
GI	242 (40)
Infection	240 (39)
Cardiac	115 (19)
Bleeding	99 (16)
DVT/PE	92 (15)
Wound	88 (14)
GU	85 (14)
Pulmonary	68 (11)
Neurologic	29 (5)
Miscellaneous	13 (2)
Surgical	7 (1)

1. Liberman D, et al. *Urology*. 2011;77:660-666; 2. Donat SM, et al. *Eur Urol*. 2009;55:177-185.
3. Parekh DJ, Donat SM. *Semin Oncol*. 2007;34:98-109.

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

[1]Jarow JP et al. *Urology.* 2014; [2] Kamat AM, et al. J Clin Oncol. 2016; 34:1935-1944.

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

Kamat AM, et al. *J Clin Oncol*. 2016; Lerner SP, et al. *Bladder Cancer*. 2016; 2:165-201. FDA Guidance Document, 2018

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

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Clinical Development and Summary of KEYNOTE-057 Efficacy and Safety

Ekta Kapadia, MD

Senior Clinical Director, Oncology
Merck & Co., Inc.

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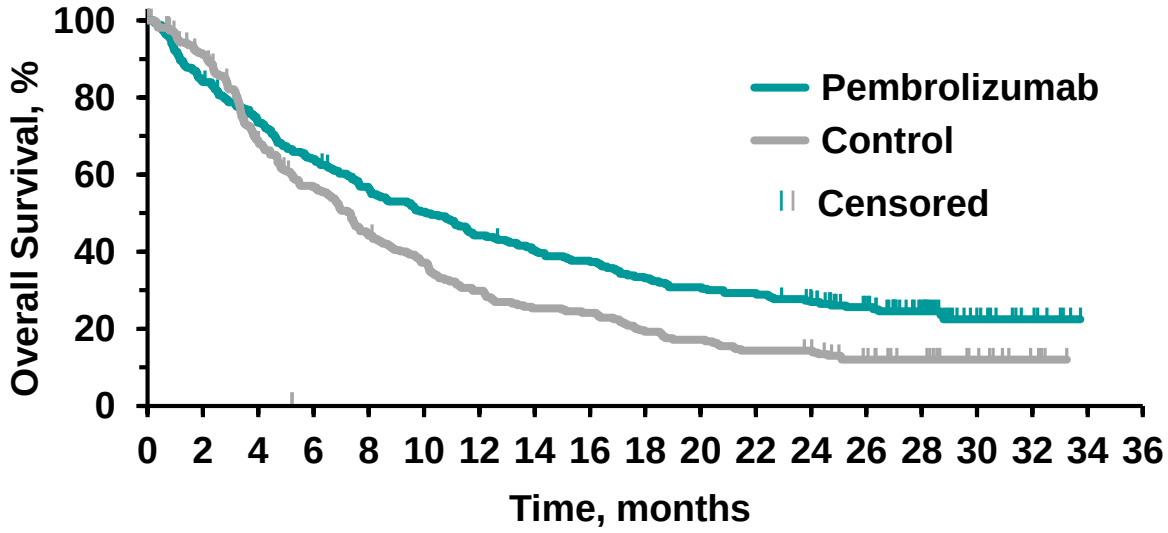
Pembrolizumab Is Approved in Advanced Urothelial Cancer

KEYNOTE-045



KEYNOTE-052

Response Evaluation	Pembrolizumab n=370
Objective response	
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+)**

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

+ 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

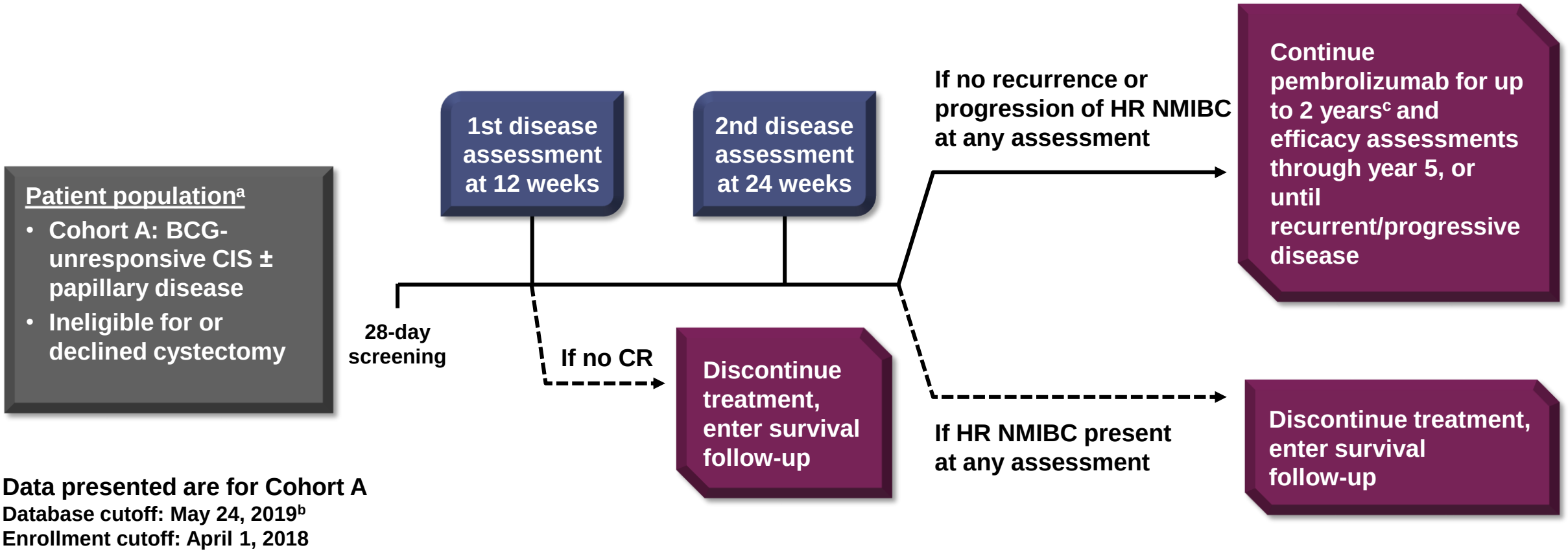
- Recognized as area with significant unmet medical need for development of nonsurgical therapies
  - Patients have few available alternative options if ineligible for or elect not to undergo radical cystectomy
- NMIBC is amenable to immunotherapies
- Pembrolizumab has shown significant activity in locally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

KEYNOTE-057 Primary Objective and Hypothesis

- **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[b]
Enrollment cutoff: April 1, 2018

BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; CR=complete response; HR NMIBC=high risk non–muscle-invasive bladder cancer.
[a] Cohort B: papillary tumors only without CIS - currently enrolling
[b] Duration of response data are based on database cutoff of September 24, 2019
[c] Participants with continued CR can electively discontinue pembrolizumab after 18 months

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

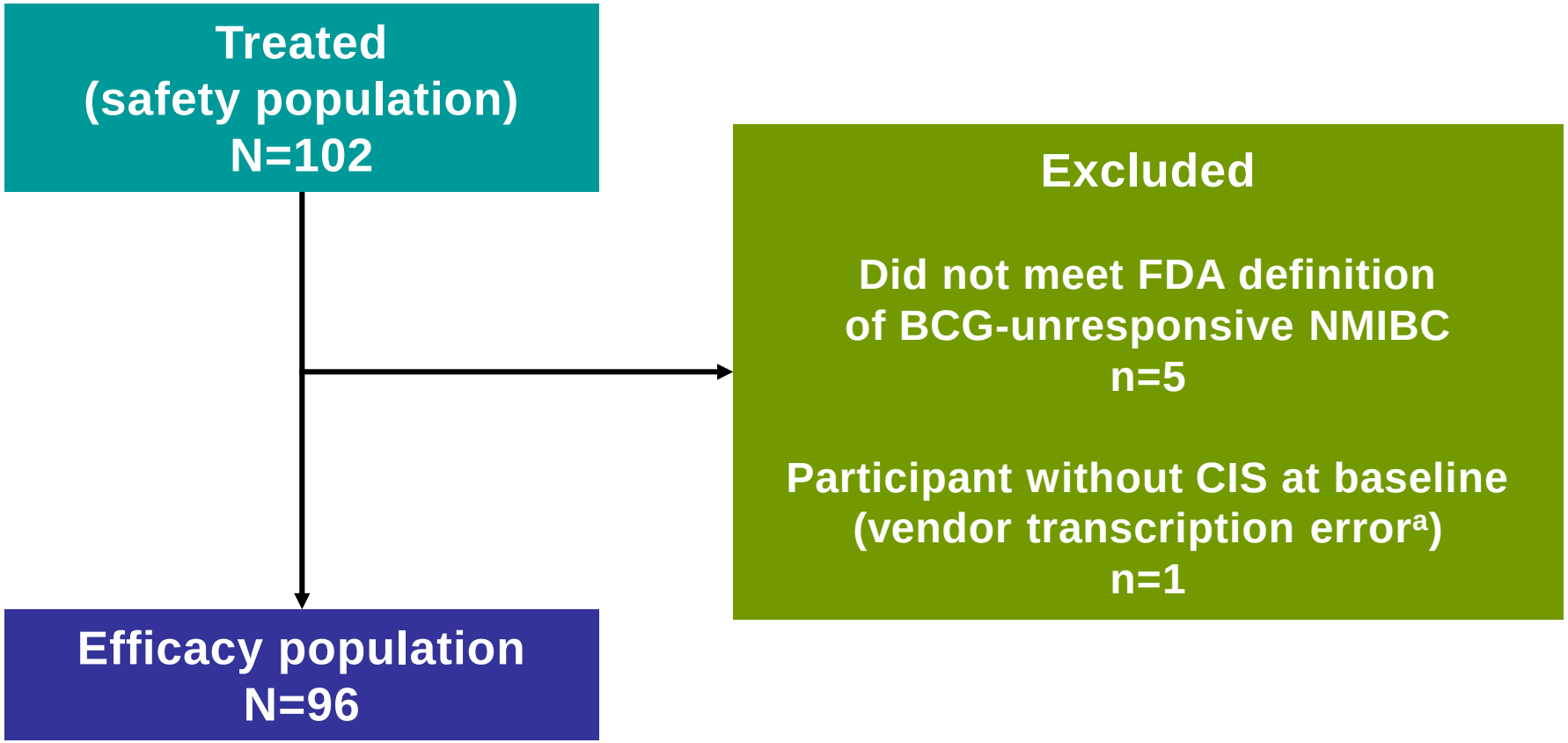
- **Primary** – Complete response (CR) rate
  - Proportion of patients free of high-risk NMIBC or progressive urothelial cancer (UC)
  - Evaluated using exact binomial method comparing lower bound of the 95% confidence interval (CI) with historical control rate of 20%
    - Historical control rate based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



[a]Sponsor was notified of transcription error by vendor after Briefing Document was finalized.

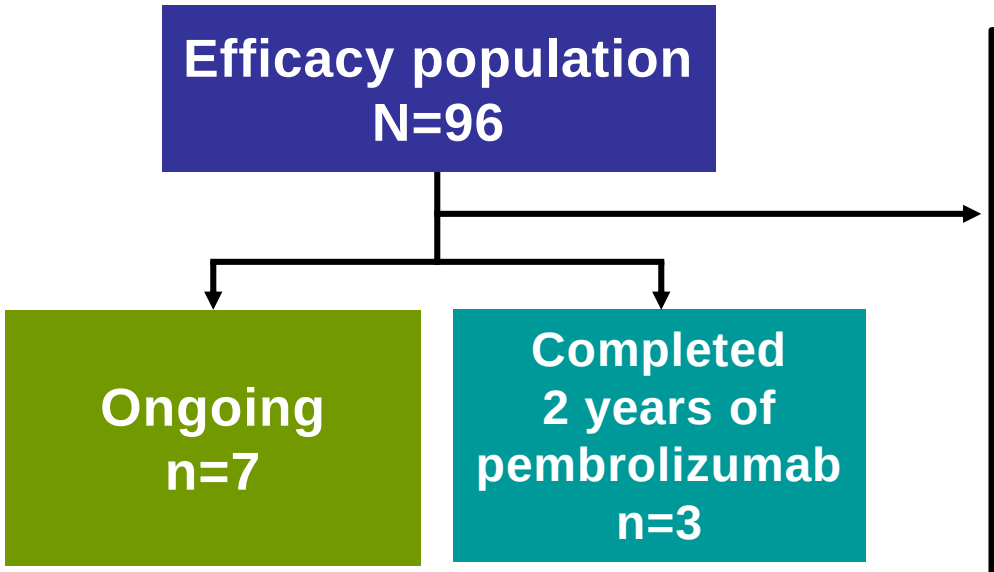
Key Baseline Characteristics Are Representative of Patients With High-Risk NMIBC

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

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

Patient Disposition

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



	n
Discontinued from treatment	86
Persistent disease[a]	38
Recurrent high-risk NMIBC or stage progression to T1	33
Adverse event	9
Physician decision	1
Patient withdrawal	2
Electively discontinued treatment after 18 mo with continued CR[b]	**3**

- 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

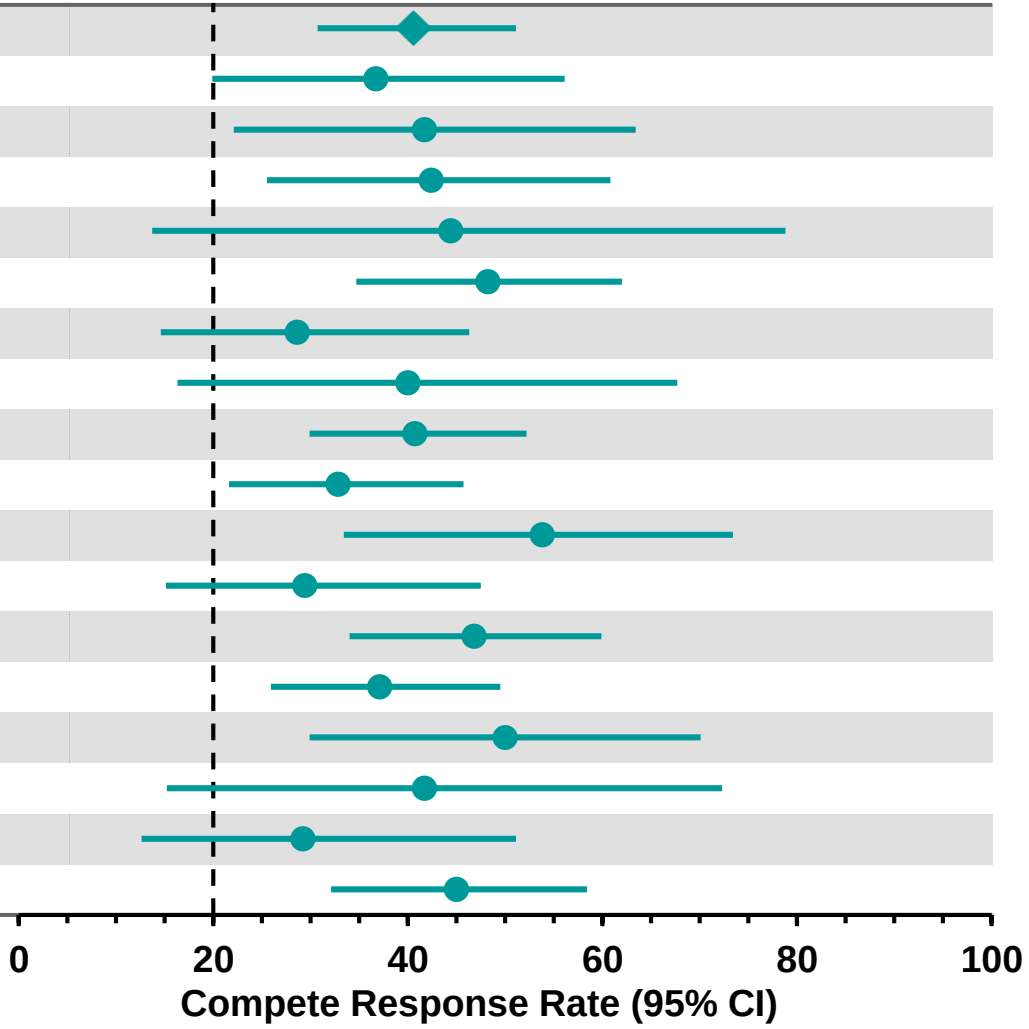
	N=96	
Best Response	**n (%)**	**95% CI**
CR	39 (40.6)	30.7, 51.1
Non-CR	56 (58.3)	47.8, 68.3
Persistent	40 (41.7)	31.7, 52.2
Recurrent	6 (6.3)	2.3, 13.1
NMIBC stage progression to T1	9 (9.4)	4.4, 17.1
Progression to T2	0	NA, NA
Extravesical disease[a]	1 (1.0)	0.0, 5.7
Non-evaluable (NE)	1 (1.0)	0.0, 5.7

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

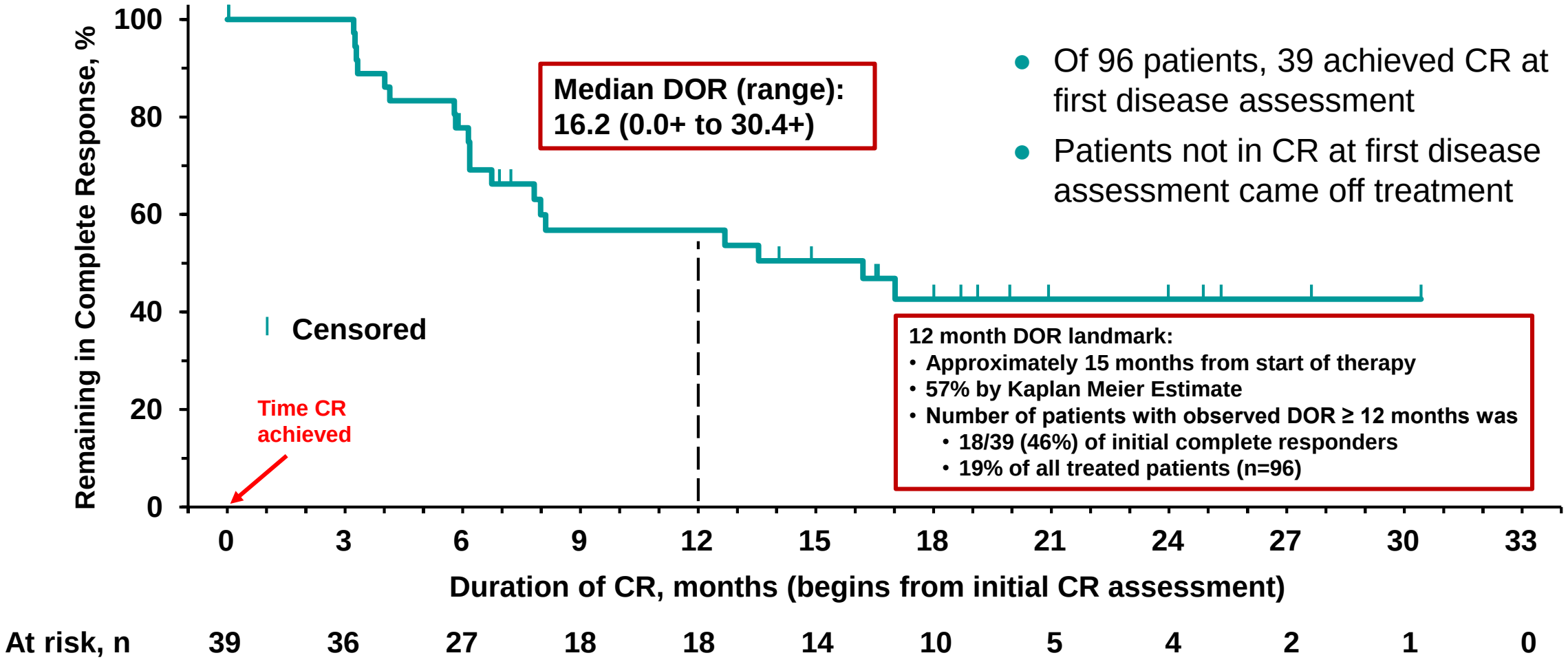
[a] Extravesical disease is defined as the presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. The one patient included in this category developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent 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

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

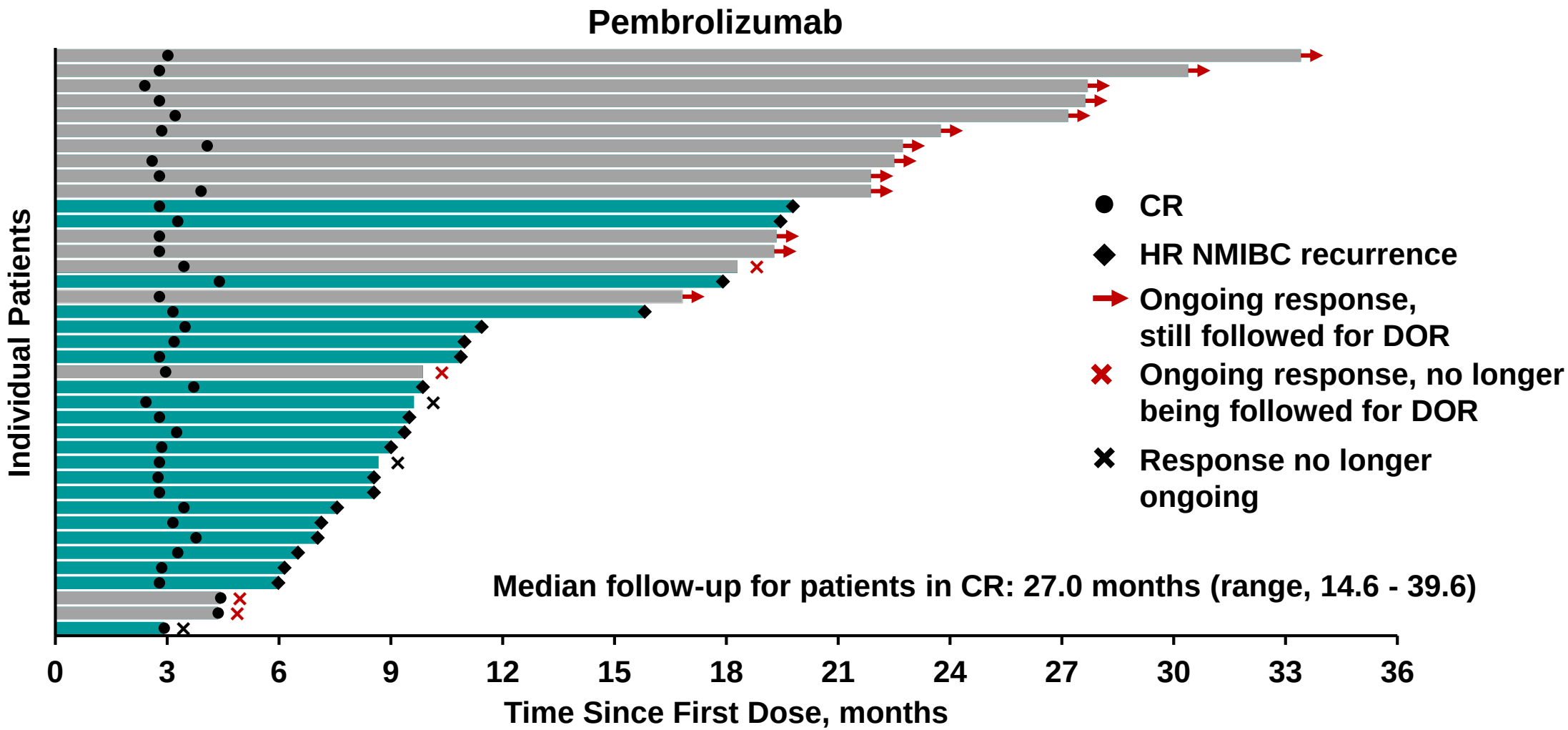


Duration of Complete Response Is Clinically Meaningful



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

Duration of Complete Response Is Clinically Meaningful



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)

	Patients, n (%) N=96
CR	17 (17.7)
Non-CR/Recurrent	79 (82.3)
Cystectomy[a]	36 (37.5)
Therapy or procedure excluding cystectomy[a,b]	34 (35.4)
Local procedure (TURBT, biopsy, fulguration, radiation, other[c])	21 (21.9)
Intravesical therapy (BCG, chemotherapy, vicinium)	27 (28.1)
Systemic therapy (pembrolizumab)	3 (3.1)
No subsequent therapy received	10 (10.4)
Unknown	4 (4.2)

[a] Subsequent therapy includes any new anticancer therapy, radiation treatment, or surgical procedure performed to treat NMIBC that persisted or recurred after pembrolizumab treatment.
[b] Five patients received both other therapy and cystectomy and are counted in both categories.
[c] 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[1-5]
  - 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

1. Casey RG, et al. *Eur Urol.* 2015;67:876-88. 2. Guzzo TJ, et al. *Urology*. 2009;74:1276-1280. 3. Lotan Y, et al. *Eur Urol.* 2019;76:200-206. 4. Parker WP, et al. *Clin Genitourin Cancer.* 2018;16:e79-97. 5. Turker P, et al. *BJU Int*. 2012;110:804-811.

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

Adverse Events	Patients, n (%)	
	Cohort A n=102	Pembrolizumab Reference Safety Dataset n=2799
Any AE	**99 (97.1)**	**2727 (97.4)**
Grade 3-5 AE	30 (29.4)	1273 (45.5)
Serious AE	26 (25.5)	1042 (37.2)
Death	2 (2.0)[a]	110 (3.9)
Discontinuation due to AE	10 (9.8)	334 (11.9)
Discontinuation due to serious AE	4 (3.9)	253 (9.0)

[a] 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

	Patients, n (%)	
Adverse Events	Cohort A n=102	Pembrolizumab Reference Safety Dataset n=2799
Diarrhea	22 (21.6)	625 (22.3)
Fatigue	21 (20.6)	1044 (37.3)
Hematuria	21 (20.6)	39 (1.4)
Pruritus	19 (18.6)	562 (20.1)
Cough	18 (17.6)	615 (22.0)
Nausea	15 (14.7)	685 (24.5)
Arthralgia	14 (13.7)	504 (18.0)
Constipation	12 (11.8)	498 (17.8)
Urinary tract infection	12 (11.8)	162 (5.8)
Nasopharyngitis	12 (11.8)	182 (6.5)

KEYNOTE-057: Immune-Mediated Adverse Events and Infusion Reactions

Immune-Mediated Adverse Events and Infusion Reactions	Patients, n (%)	
	Cohort A n=102	Pembrolizumab Reference Safety Dataset n=2799
Any	**21 (20.6)**	**597 (21.3)**
Grade 3-5	3 (2.9)	154 (5.5)
Serious	5 (4.9)	161 (5.8)
Deaths	0	4 (0.1)
Discontinuations	4 (3.9)	83 (3.0)
Discontinuation due to serious events	2 (2.0)	68 (2.4)

KEYNOTE-057: Immune-Mediated Adverse Events and Infusion Reactions

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

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

CE-27

Introduction	**Jeffrey Stuart, PhD** Merck & Co., Inc.
Unmet Need	**Gary Steinberg, MD** NYU Langone Health
Efficacy and Safety	**Ekta Kapadia, MD** Merck & Co., Inc.
Clinical Perspective	**Ashish Kamat, MD, MBBS, FACS** MD Anderson Cancer Center
Benefit-Risk	**Scot Ebbinghaus, MD** Merck & Co., Inc.

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

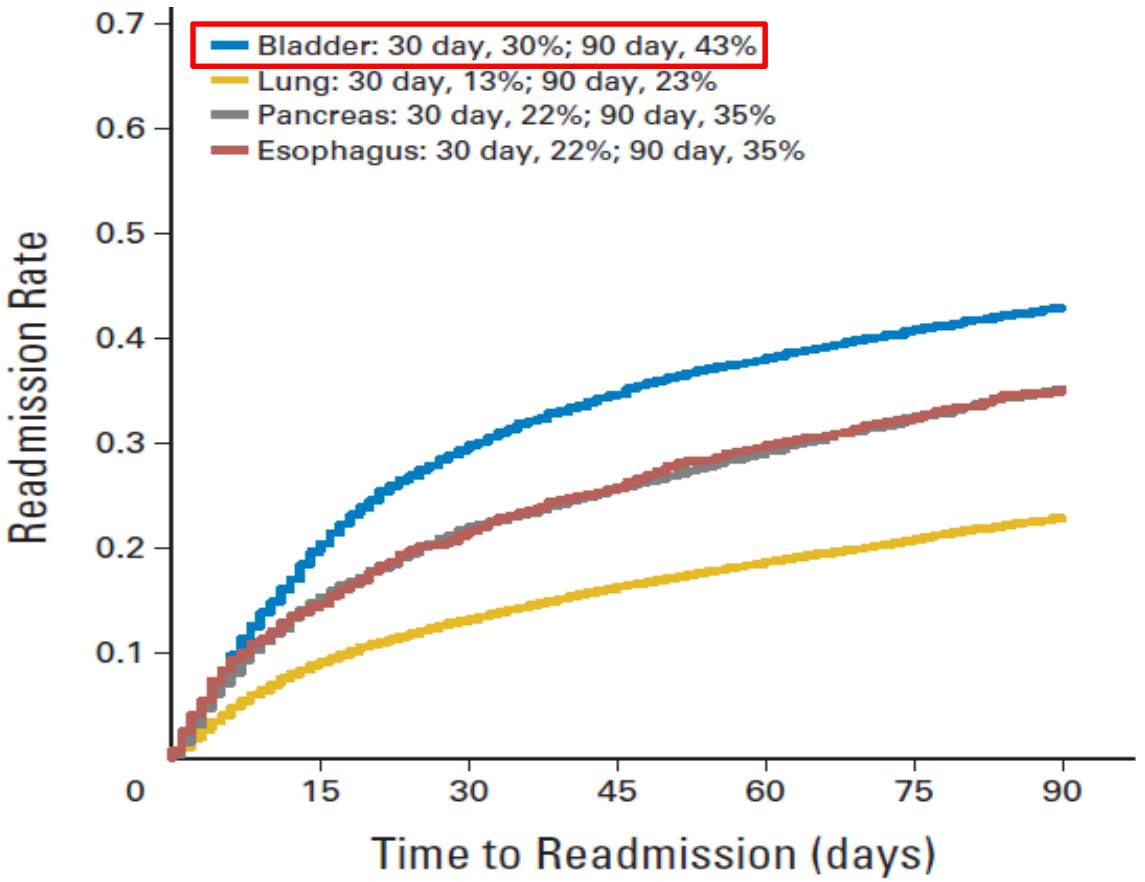
BCG-unresponsive CIS persists and progresses without effective intervention

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



15-20 days in Europe/Asia.

Stitzenberg KB, et al. *J Clin Oncol*. 2015;33(5):455-464.

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?

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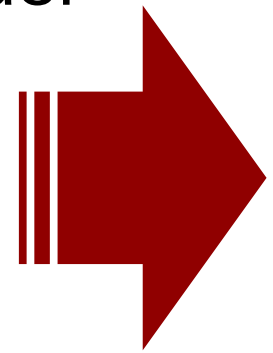


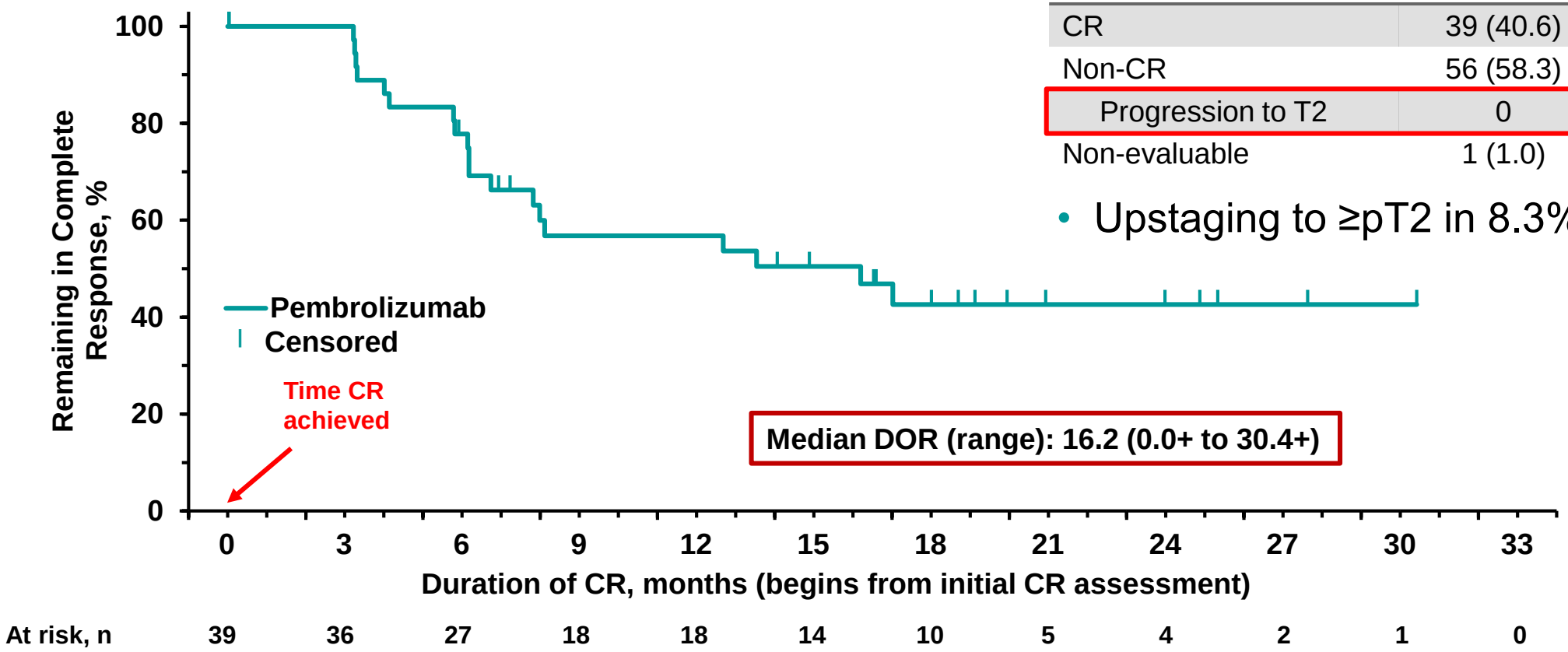
- No effective FDA-approved therapy

- Repeated procedures
- Multiple anesthetics
- Muscle invasive disease
- Risk of metastases

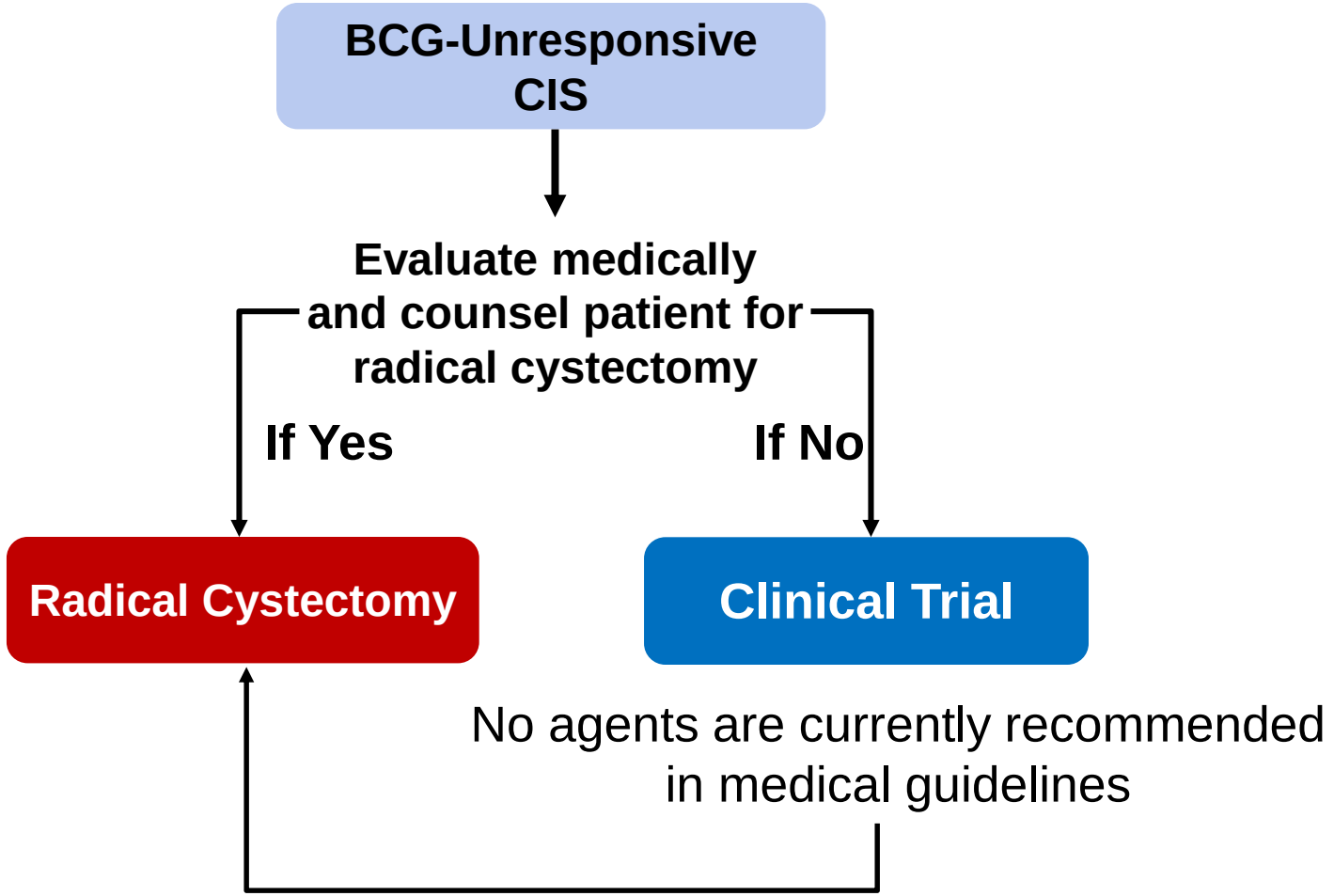
Pembrolizumab Offers an Option for Patients Who Decline or Are Ineligible for Radical Cystectomy

Best Response	N=96 n (%)	95% CI
CR	39 (40.6)	30.7, 51.1
Non-CR	56 (58.3)	47.8, 68.3
Progression to T2	0	NA, NA
Non-evaluable	1 (1.0)	0, 5.7

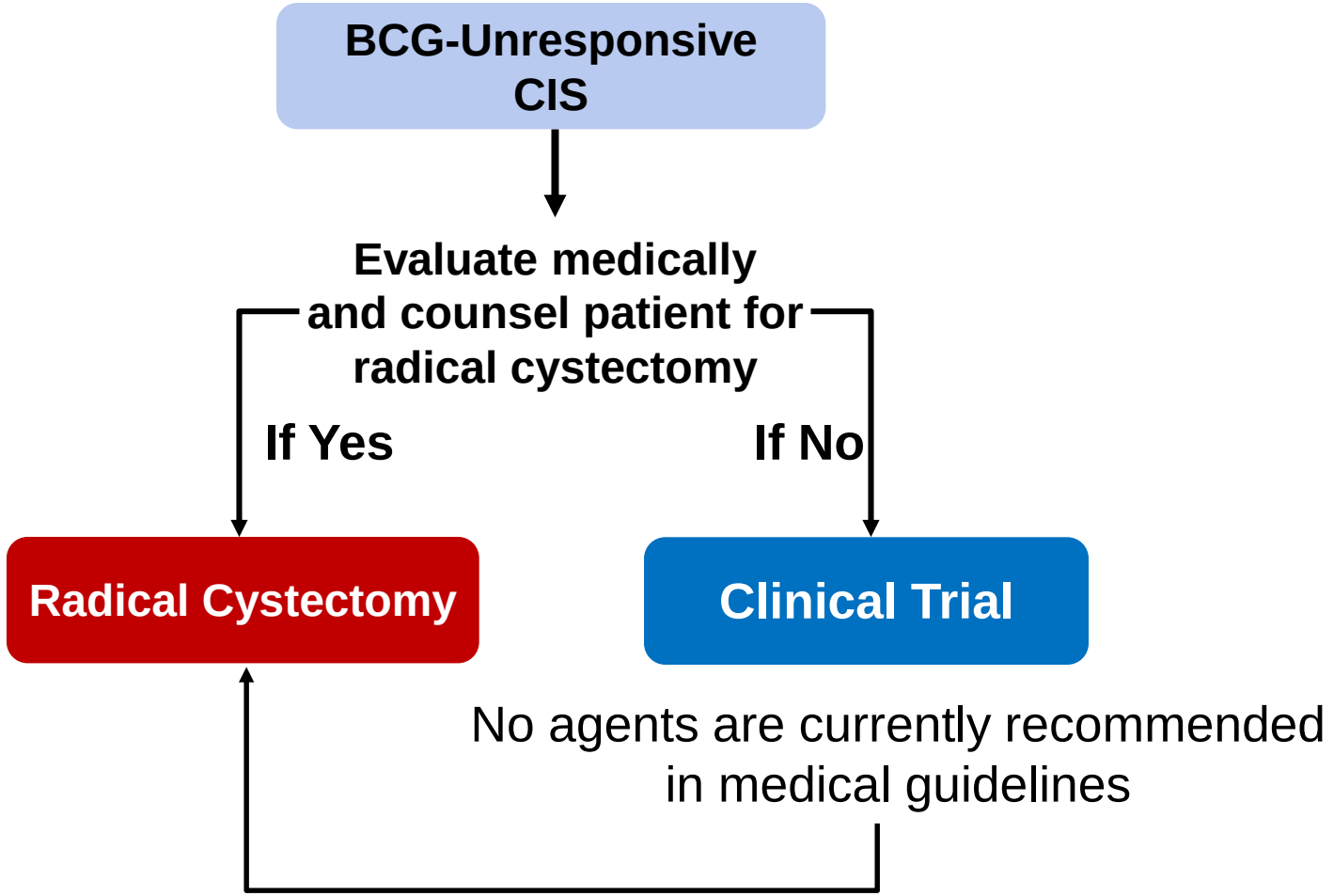
- Upstaging to ≥pT2 in 8.3% of patients



Patient Conversation



Patient Conversation



Valrubicin

Off label agents:

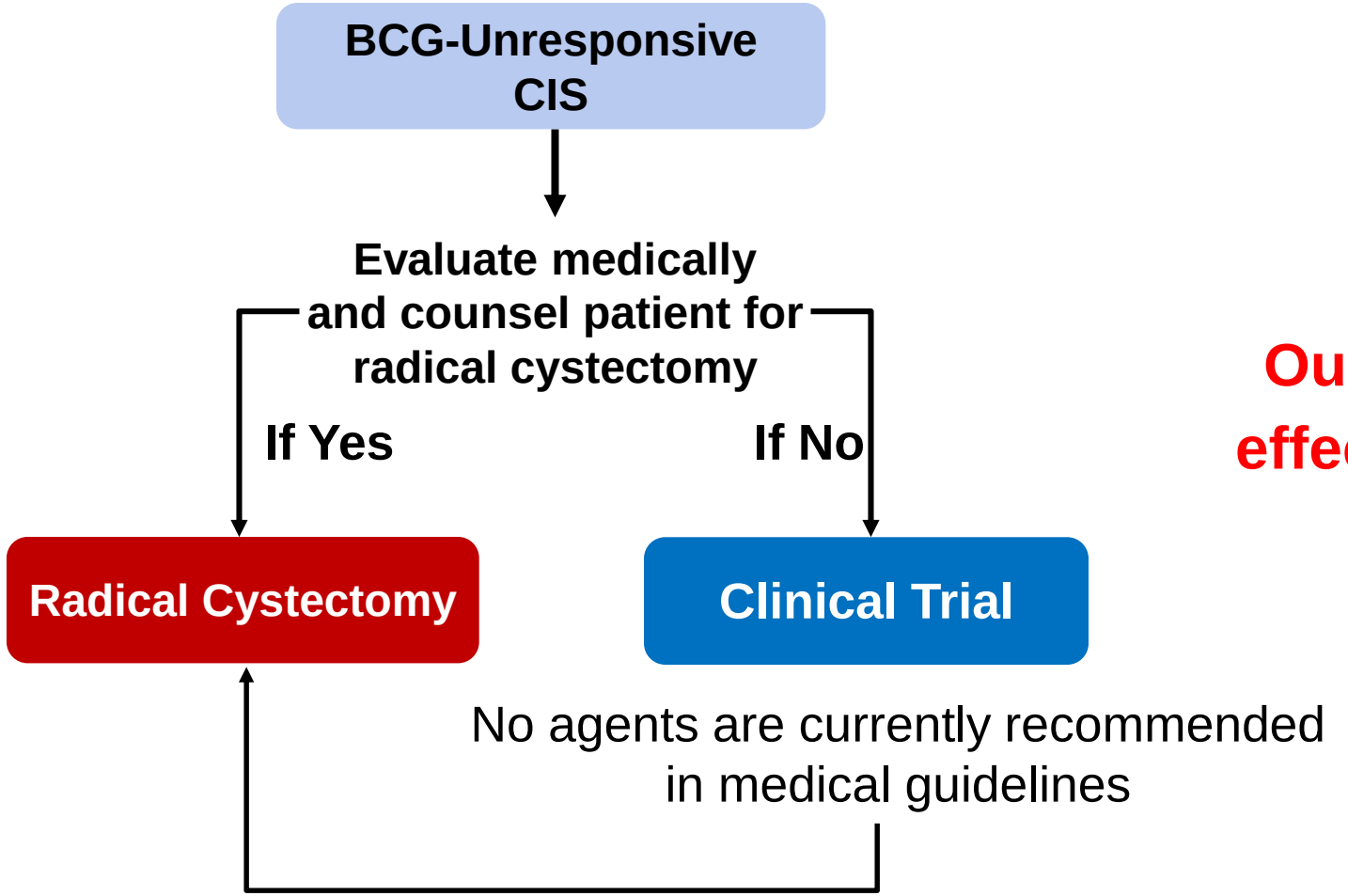
Mitomycin

Gemcitabine

Gemcitabine/Docetaxel

Hyperthermic Chemotherapy

Patient Conversation

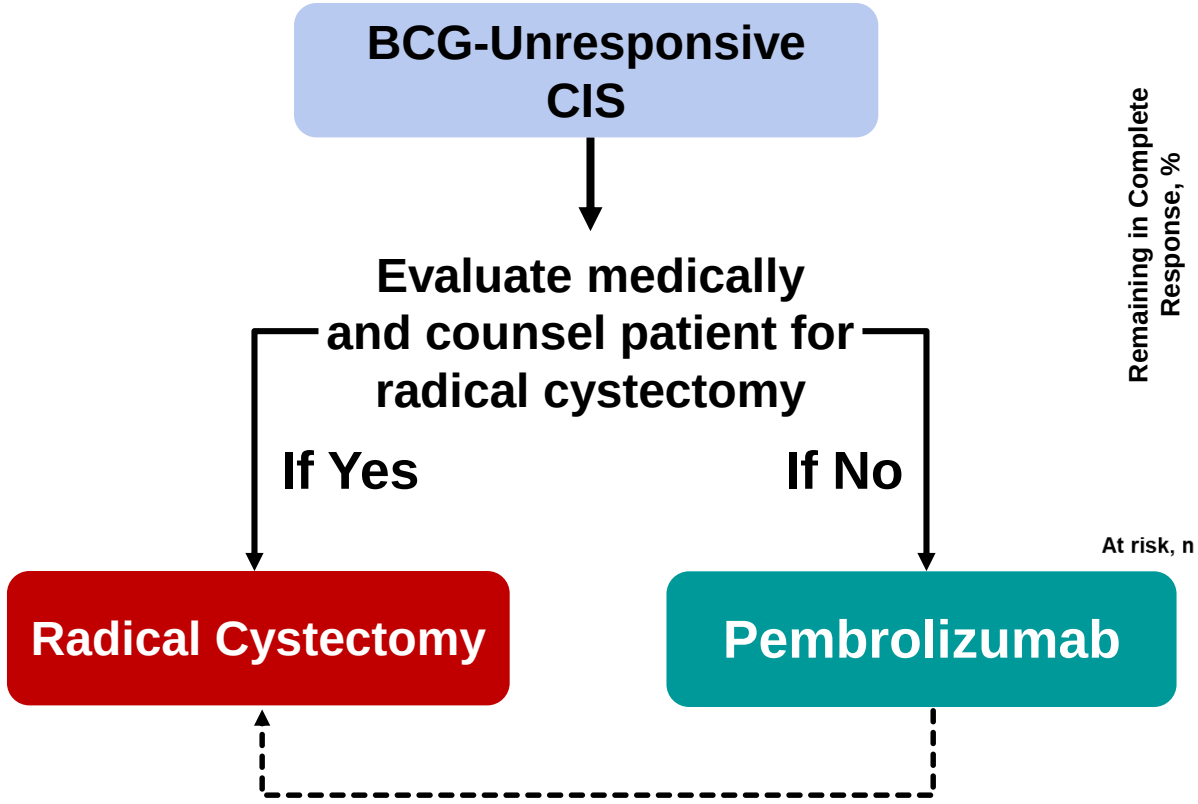


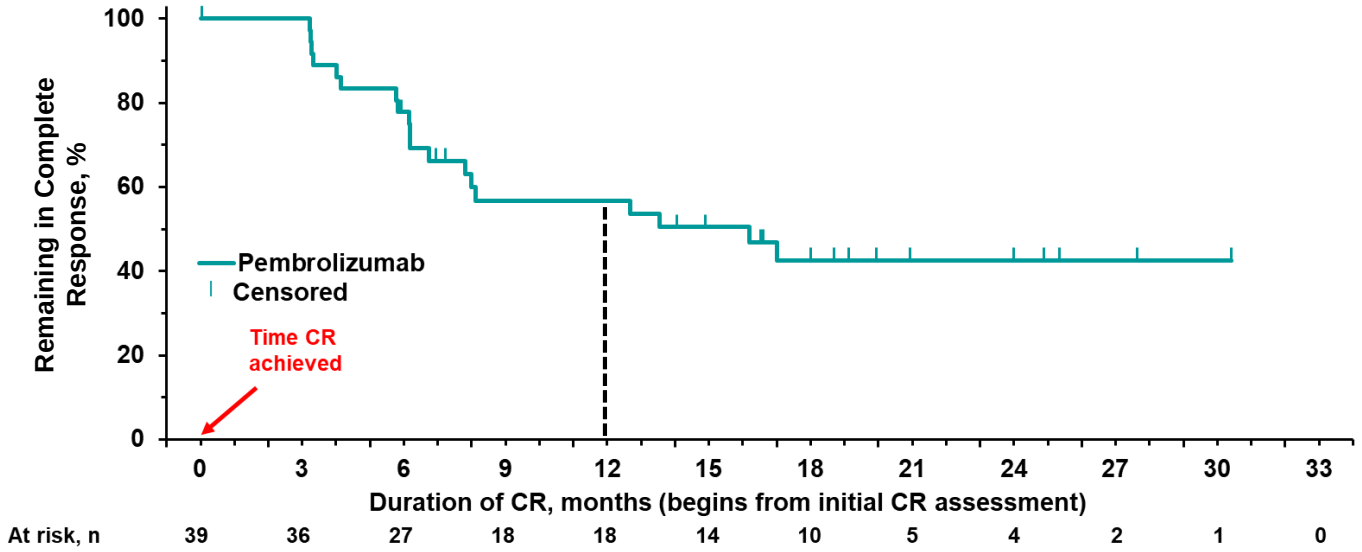
Valrubicin

Our patients are desperate for an effective alternative to cystectomy!

Hyperthermic Chemotherapy
Mitomycin
Gemcitabine

Potential to Change the Treatment Algorithm





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

19% of all treated patients achieved response lasting at least 1 year

Agenda

CP-12

Introduction	**Jeffrey Stuart, PhD** Merck & Co., Inc.
Unmet Need	**Gary Steinberg, MD** NYU Langone Health
Efficacy and Safety	**Ekta Kapadia, MD** Merck & Co., Inc.
Clinical Perspective	**Ashish Kamat, MD, MBBS, FACS** **MD Anderson Cancer Center**
Benefit-Risk	**Scot Ebbinghaus, MD** Merck & Co., Inc.

Benefit-Risk Conclusions

Scot Ebbinghaus, MD

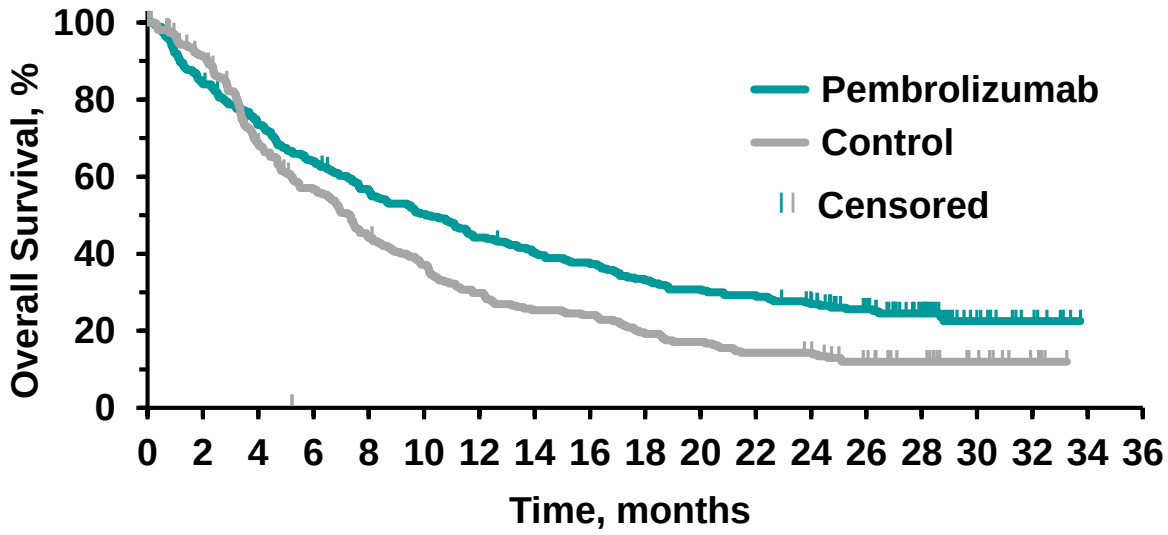
Vice President, Clinical Research, Oncology
Merck & Co., Inc.

MERCK

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

KEYNOTE-045



KEYNOTE-052

Response Evaluation	Pembrolizumab n=370
Objective response	
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+)**

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**

U.S. Food & Drug Administration Oncologic Drugs Advisory Committee December 17, 2019

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

MERCK

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

	Participants, n (N=36)	Maximum T-stage	N-Stage*	Achieved initial CR (Yes/No)	Interval between last dose of pembrolizumab and RC (days)
No tumor N=6	6	pT0	N0=5 Nx=1	Yes=3; No=2 Yes=1	Median (Range): 134.5 (60-149)
NMIBC N=27	3	pTa	N0=3	No=3	Median (Range): 77 (42-448)
	18	pTis	N0=16 Nx=2	Yes=3; No=13 Yes=1; No=1	
	6	pT1**	N0=6	Yes=1; No=5	
MIBC N=3	2	pT2	N0=1 N1=1***	No No	60 86
	1	pT3	N1	No	457

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.