Clinical Development and Summary of KEYNOTE-057 Efficacy and Safety

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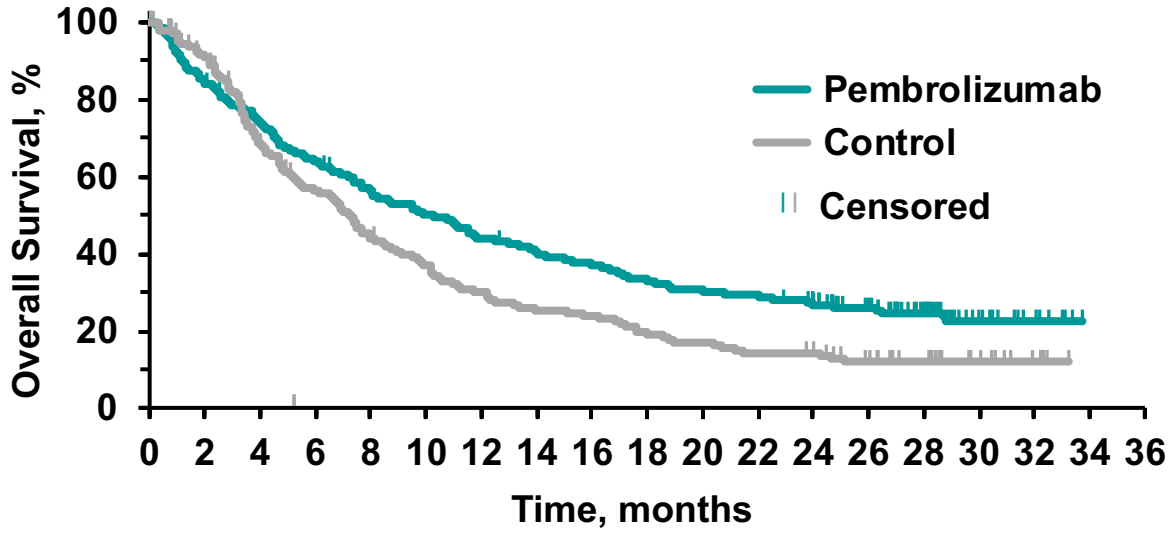
Pembrolizumab Is Approved in Advanced Urothelial Cancer

CE-2

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

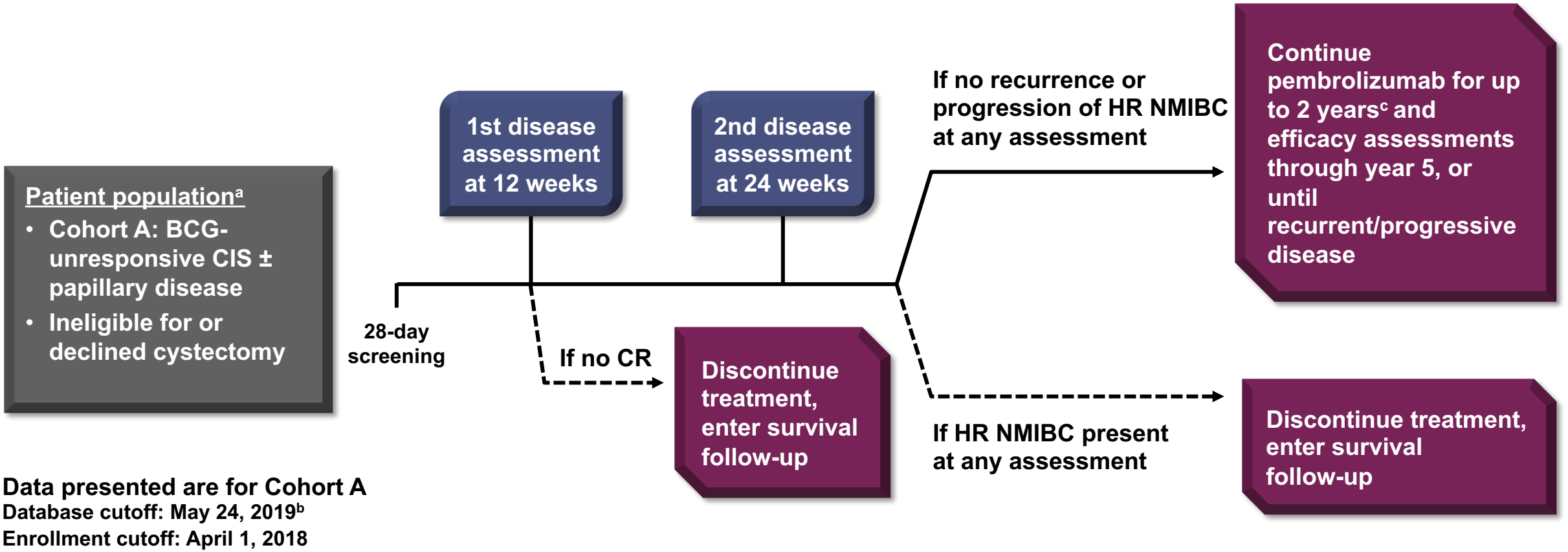
- Recognized as area with significant unmet medical need for development of nonsurgical therapies
  - Patients have few available alternative options if ineligible for or elect not to undergo radical cystectomy
- NMIBC is amenable to immunotherapies
- Pembrolizumab has shown significant activity in locally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

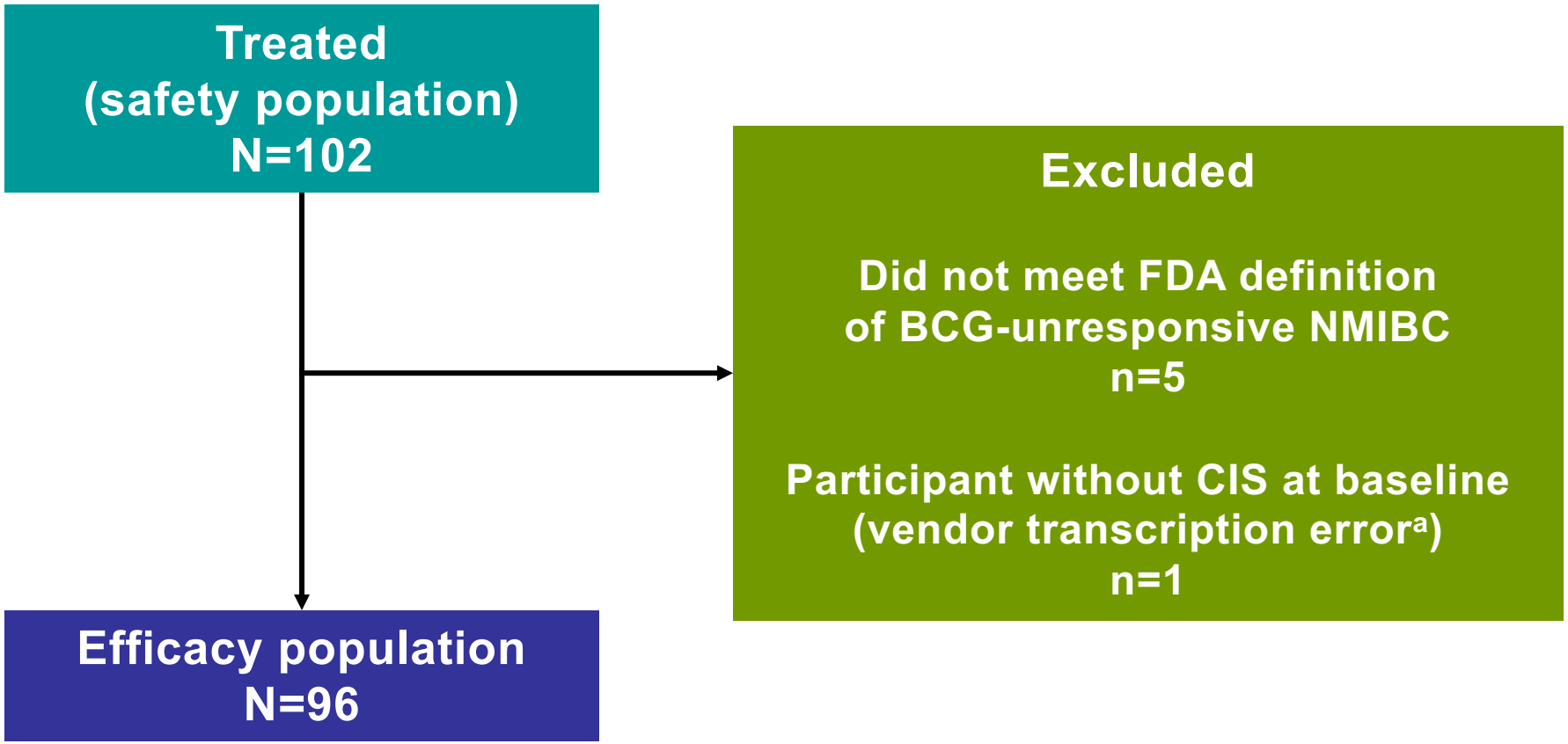
- **Primary** – Complete response (CR) rate
  - Proportion of patients free of high-risk NMIBC or progressive urothelial cancer (UC)
  - Evaluated using exact binomial method comparing lower bound of the 95% confidence interval (CI) with historical control rate of 20%
    - Historical control rate based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

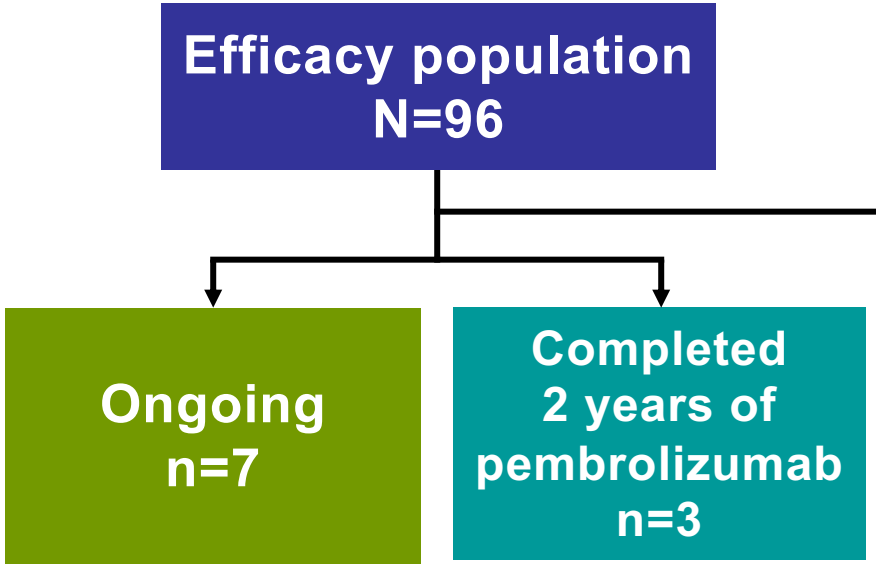
Key Baseline Characteristics Are Representative of Patients With High-Risk NMIBC

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

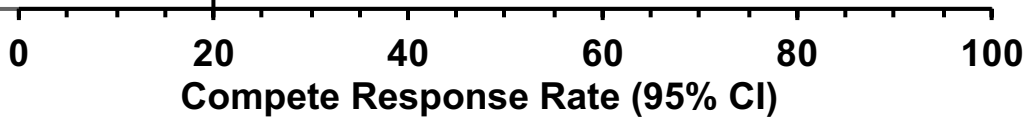
	N=96	
Best Response	**n (%)**	**95% CI**
CR	39 (40.6)	30.7, 51.1
Non-CR	56 (58.3)	47.8, 68.3
Persistent	40 (41.7)	31.7, 52.2
Recurrent	6 (6.3)	2.3, 13.1
NMIBC stage progression to T1	9 (9.4)	4.4, 17.1
Progression to T2	0	NA, NA
Extravesical disease[a]	1 (1.0)	0.0, 5.7
Non-evaluable (NE)	1 (1.0)	0.0,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

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

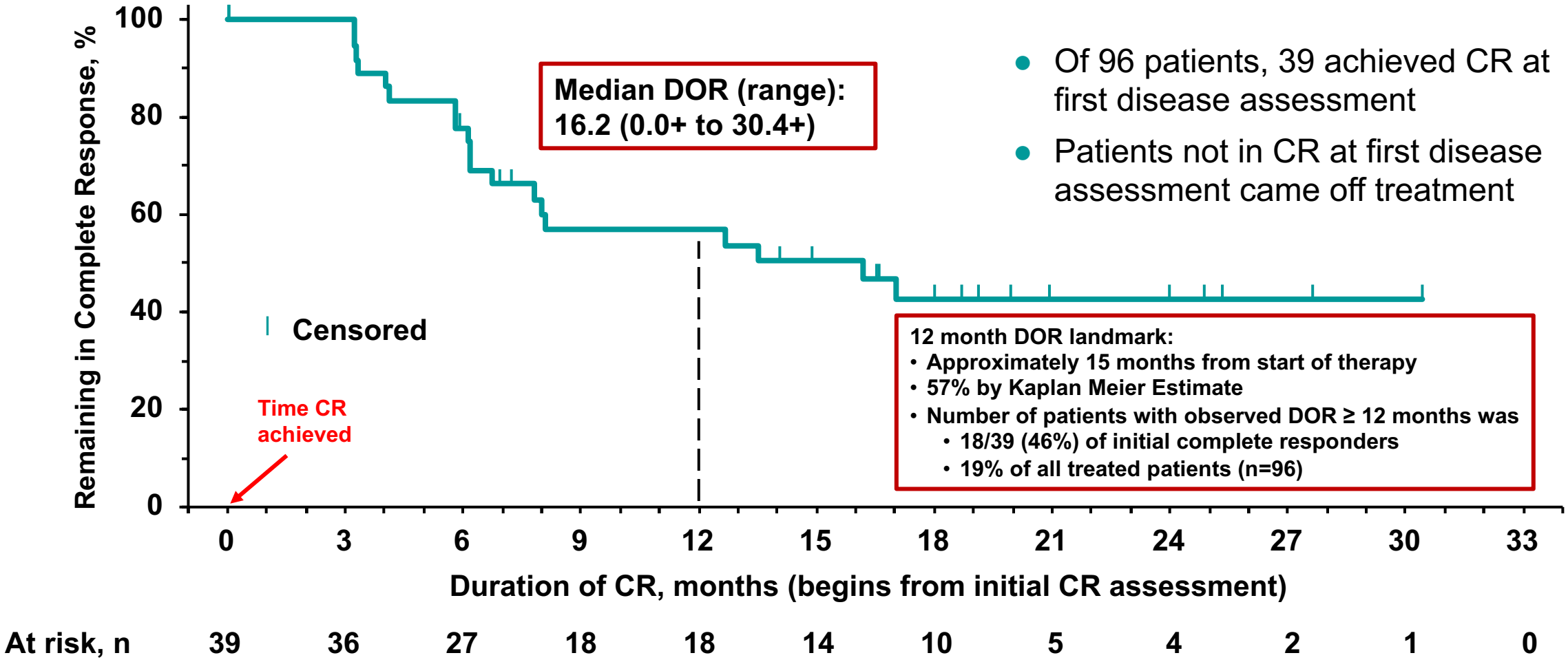
[a] Extravesical disease is defined as the presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. The one patient included in this category developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent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

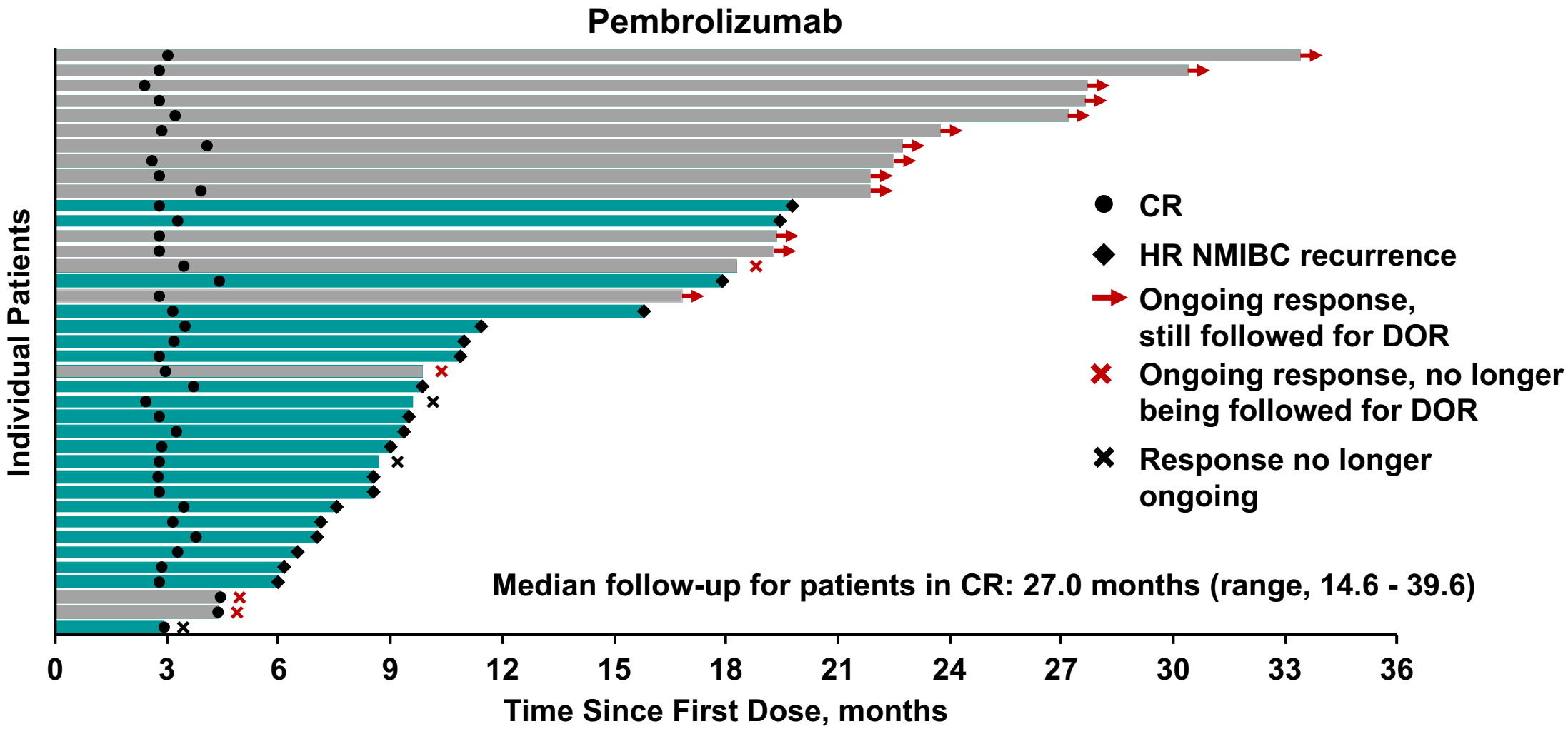


Duration of Complete Response Is Clinically Meaningful



- 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

Adverse Events	Patients, n (%)	
	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.