# EVOLVING MANAGEMENT OF NONMETASTATIC UROTHELIAL BLADDER CANCER (UBC)

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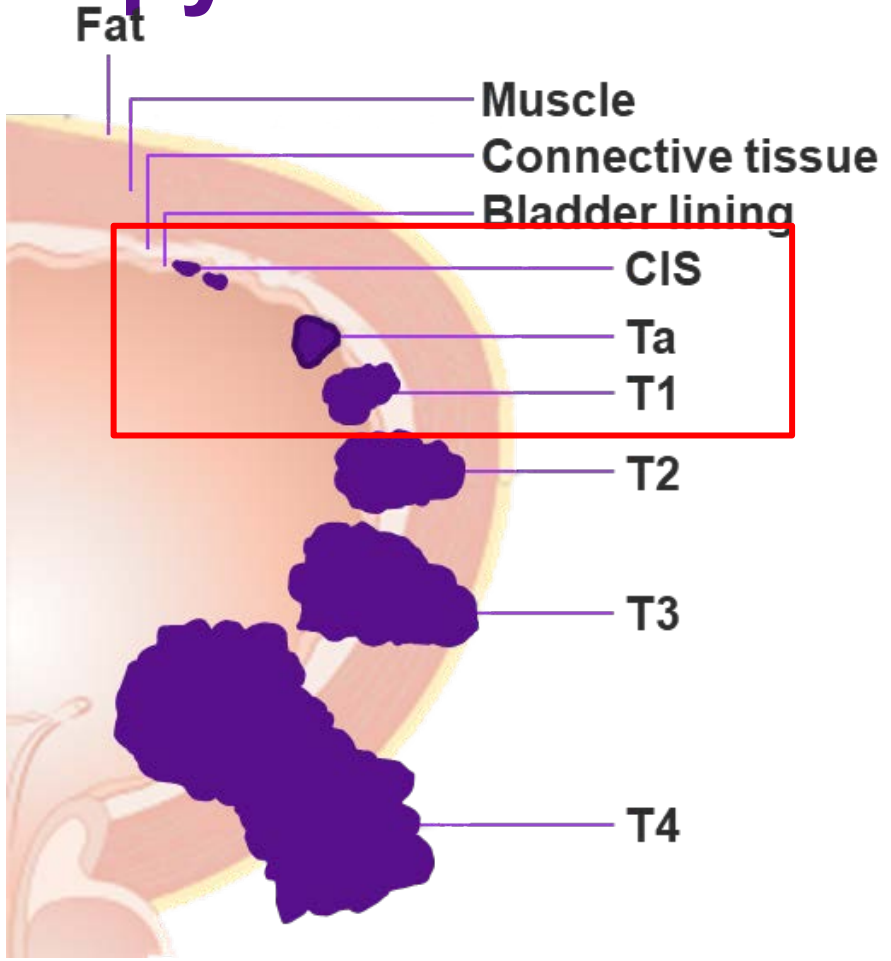
# High-Risk NMIBC: A Disease of Systemic Potential, in Need of Systemic Therapy

- High-risk (HR) NMIBC = High Grade (Carcinoma in situ (CIS), HG Ta/T1)[2]
- TURBT and intravesical Bacillus Calmette-Guérin (BCG) is SOC[2]
  - High rate of complete response (70%) to initial intravesical BCG, most will not maintain response[3-5]
    - 30% of patients experience recurrence within 1 year
    - 40% of patients at high risk progress to muscle-invasive disease
    - 20%-30% of patients progress to metastatic disease
- BCG unresponsive disease – standard of care is cystectomy
  - A morbid procedure, but justified.



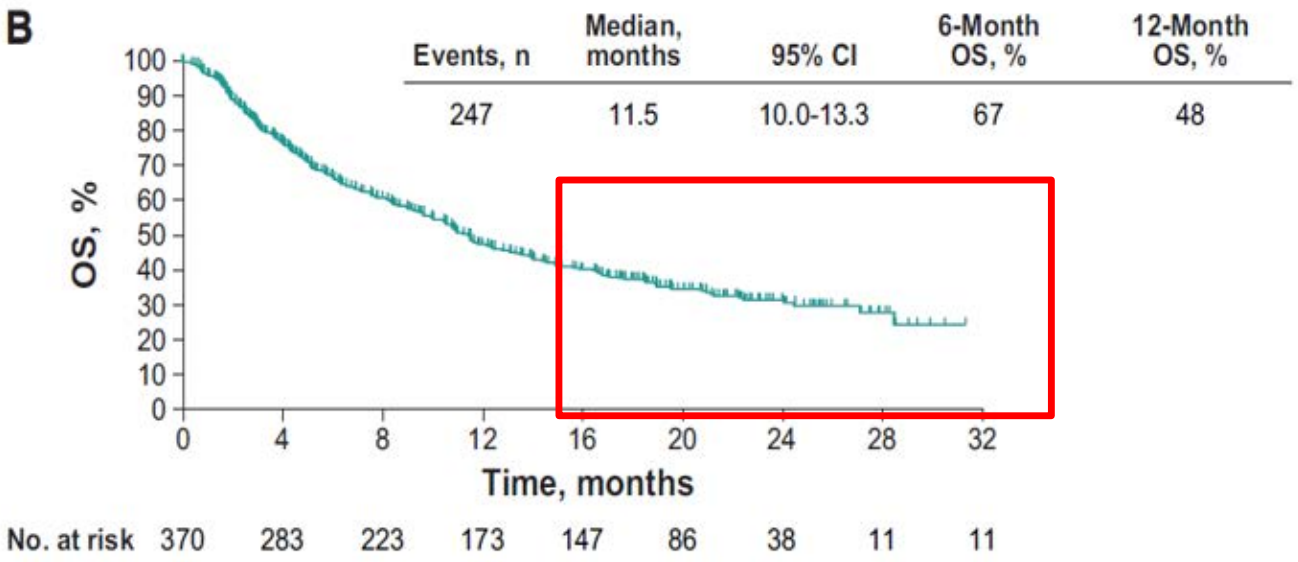

1. Cumberbatch MGK et al. *Eur Urol.* 2018;74:784-795. 2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): bladder cancer (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed January 7, 2019. 3. Hemdan T et al. *J Urol.* 2014;191:1244. 4. Herr HW et al. *Urol Oncol.* 2015;33:108.e1-4. 5. Anastasiadis A et al. *Ther Adv Urol.* 2012;4:13-32. 5. US Department of Health and Human Services. BCG-unresponsive nonmuscle invasive bladder cancer: developing drugs and biologics for treatment—Guidance for industry. February 2018. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm529600.pdf. Accessed February 5, 2019. 3. Babjuk M et al. *Eur Urol.* 2017;71:447-461.

Courtesy of Arjun Balar, MD

# First-line Immunotherapy in Cis-ineligible mUC

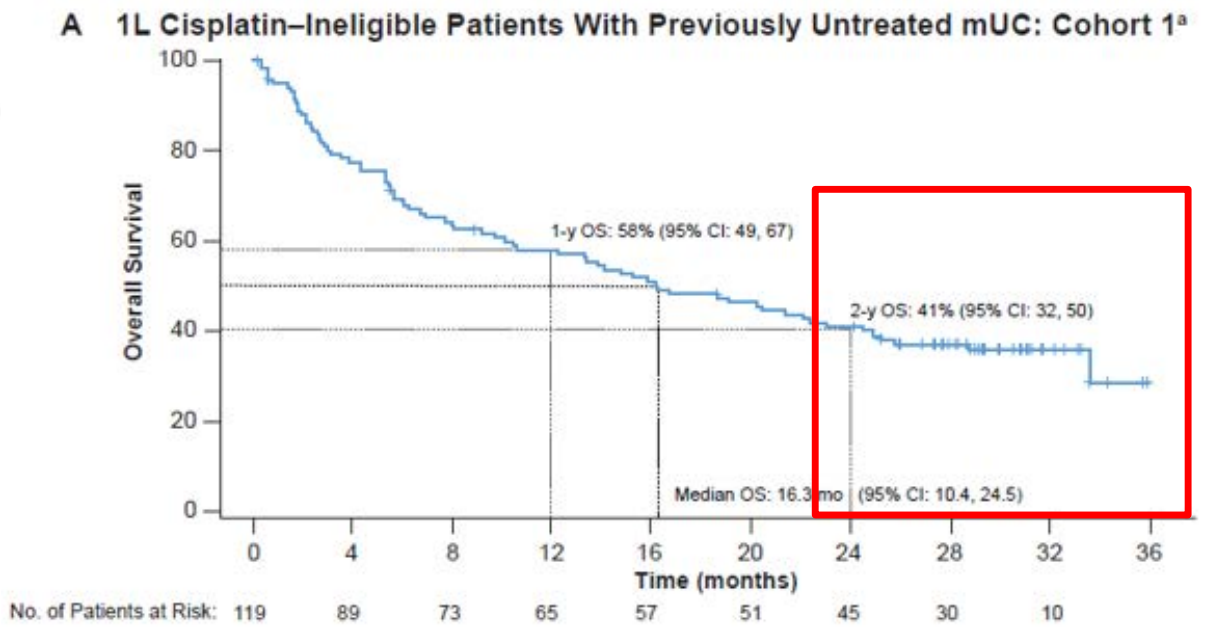
- ORR 23-29% in first-line
  - Durable PRs and in particular CRs

## KEYNOTE-052 Trial




Balar et al Lancet Oncol 2017; Vuky et al ASCO 2018

## IMvigor210 Trial




Balar et al J Clin Oncol 36, 2018 (suppl; abstr 4523)

Courtesy of Arjun Balar, MD

# KEYNOTE-057 Phase 2 Trial of Pembrolizumab for Patients With High-Risk Non–Muscle-Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin: Updated Interim Results

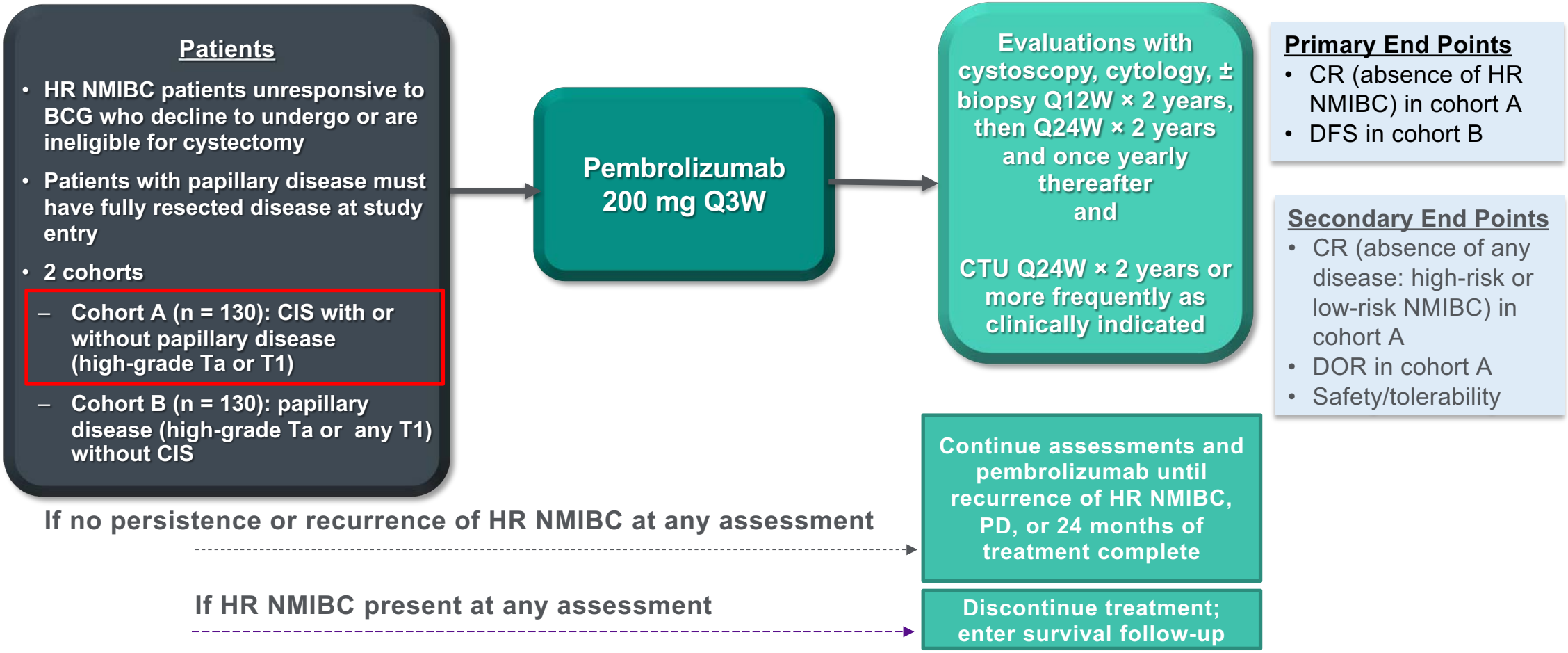
A. V. Balar[1]; G. S. Kulkarni[2]; E. Uchio[3]; J. L. Boormans[4]; L. Mourey[5]; L. Krieger[6]; E. A. Singer[7]; D. Bajorin[8]; A. Kamat[9]; P. Grivas[10]; H. K. Seo[11]; H. Nishiyama[12]; B. Konety[13]; K. Nam[14]; E. Kapadia[14]; T. Frenkl[14]; R. de Wit[4]

[1]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [2]UHN Princess Margaret Cancer Center, University of Toronto, Toronto, ON, Canada; [3]UC Irvine Health, Orange, CA, USA; [4]Erasmus University Medical Center, Rotterdam, Netherlands; [5]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [6]Royal North Shore Hospital, Northern Cancer Institute, St Leonards, NSW, Australia; [7]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]University of Washington, Seattle, WA, USA; [11]National Cancer Center, Goyang, Republic of Korea; [12]University of Tsukuba, Tsukuba, Ibaraki, Japan; [13]University of Minnesota, Minneapolis, MN, USA; [14]Merck & Co., Inc., Kenilworth, NJ, USA

*Extended Follow Up Poster 451*
*ASCOGU21*

Courtesy of Arjun Balar, MD

# KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)




Courtesy of Arjun Balar, MD

# KEYNOTE-057 Baseline Characteristics

| Characteristic, n (%) | N = 102 |
|---|---|
| Age, median (range), years | 73.0 (44-92) |
| ≥65 | 72 (70.6) |
| <65 | 30 (29.4) |
| Male | 85 (83.3) |
| Female | 17 (16.7) |
| Race | |
| White | 69 (67.6) |
| Asian | 27 (26.5) |
| Missing | 6 (5.9) |
| ECOG PS | |
| 0 (normal activity) | 75 (73.5) |
| 1 (symptomatic but ambulatory) | 27 (26.5) |

| Characteristic, n (%) | N = 102 |
|---|---|
| No. of prior BCG instillations, median (range) | 12.0 (6.0-45.0) |
| Tumor histology: urothelial (transitional cell) carcinoma | 102 (100.0) |
| Tumor pattern at study entry (pretreatment bladder cancer stage) | |
| CIS with T1 | 12 (11.8) |
| CIS with high-grade Ta | 25 (24.5) |
| CIS alone | 65 (63.7) |
| PD-L1 status | |
| CPS ≥10 | 39 (38.2) |
| CPS <10 | 58 (56.9) |
| Not evaluable | 5 (4.9) |

Values are n (%) unless specified otherwise.
Database cutoff: September 14, 2018.

Courtesy of Arjun Balar, MD

# KEYNOTE-057 Primary Efficacy Endpoint: CR Rate at 3 months

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

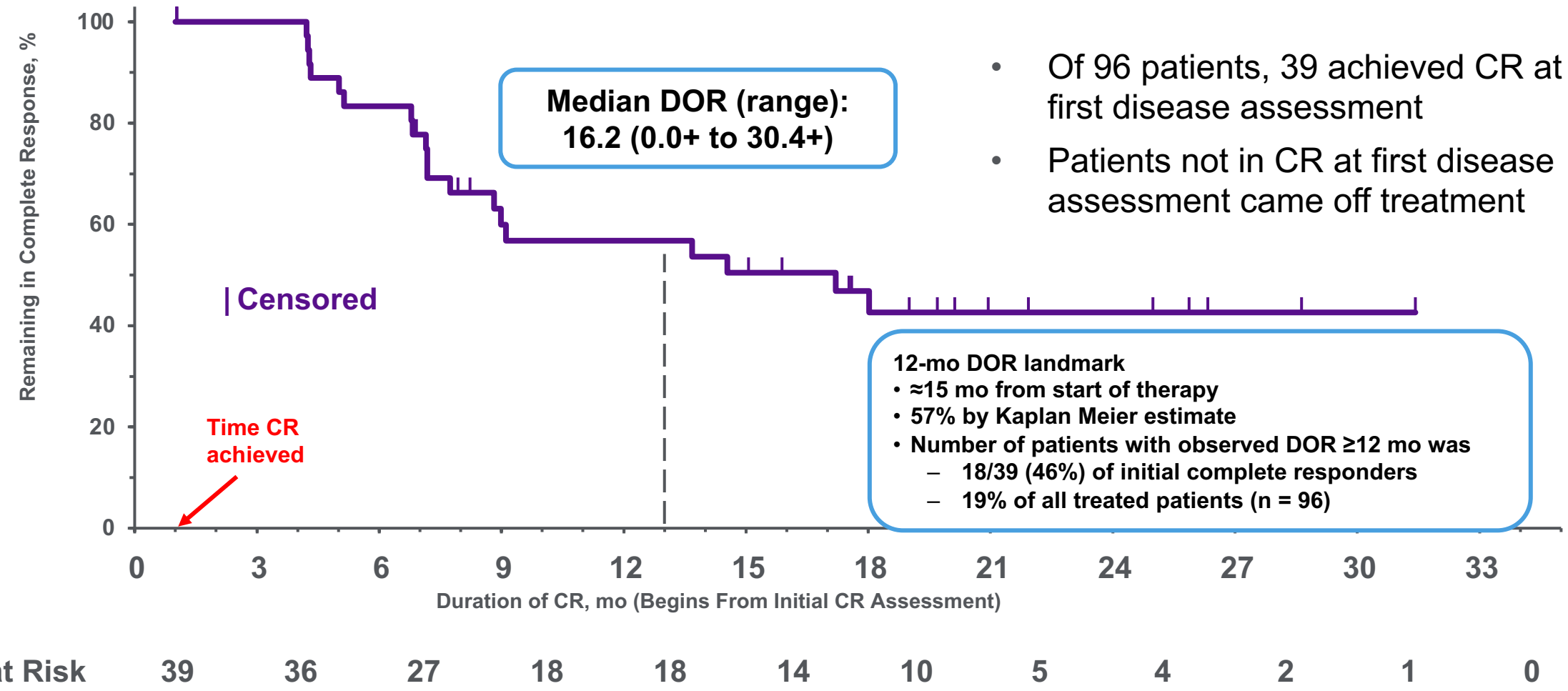
| Best Response | N = 96 | |
|---|---|---|
| | n (%) | 95% CI |
| CR | 39 (40.6) | 30.7-51.1 |
| Non-CR | 56 (58.3) | 47.8-68.3 |
| Persistent | 40 (41.7) | 31.7-52.2 |
| Recurrent | 6 (6.3) | 2.3-13.1 |
| NMIBC stage progression to T1 | 9 (9.4) | 4.4-17.1 |
| Progression to T2 | 0 | NA-NA |
| Extravesical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

[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.

1. Balar A et al. ASCO GU 2019. Abstract 350. 2. Balar A. Food and Drug Administration Oncologic Drugs Advisory Committee (FDA ODAC) submission 2019.

Courtesy of Arjun Balar, MD

# KEYNOTE-057: Duration of Complete Response



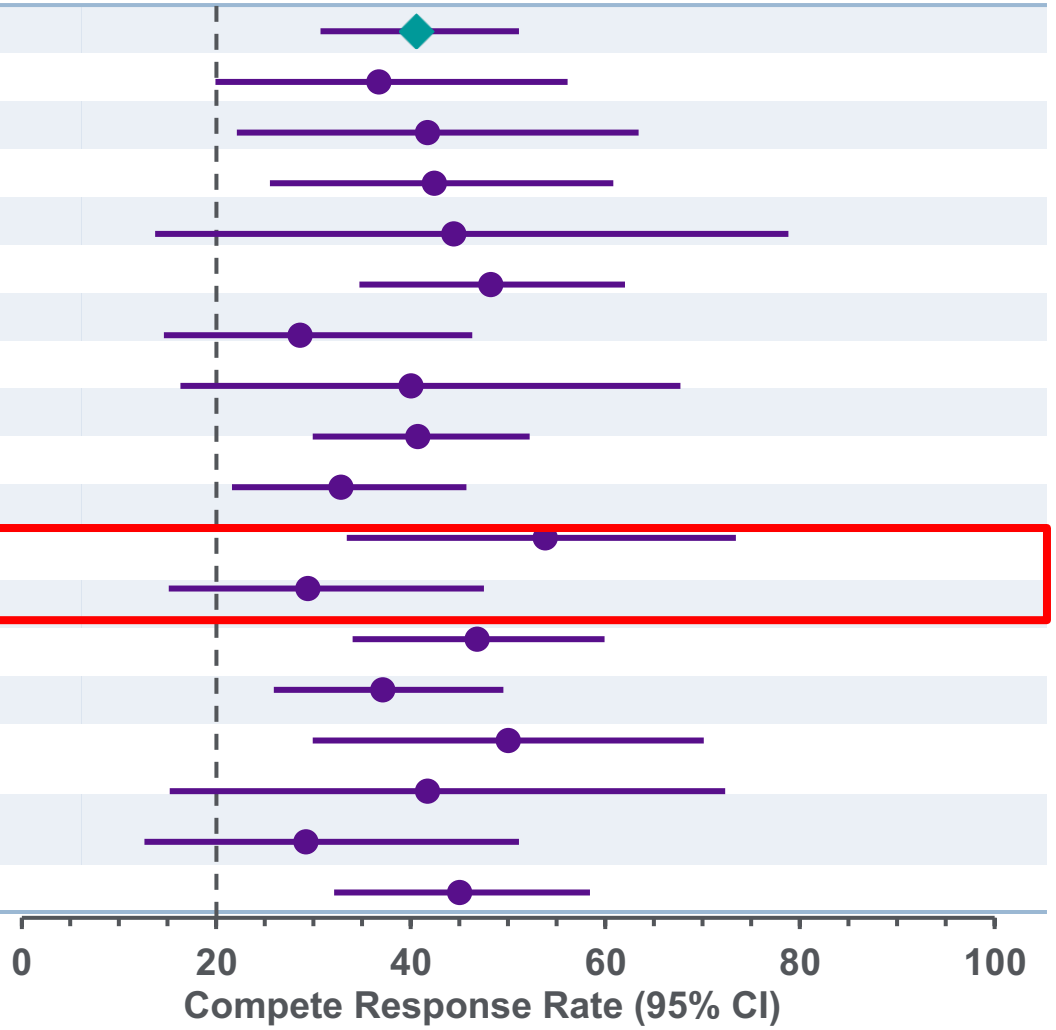

- Of 96 patients, 39 achieved CR at first disease assessment
- Patients not in CR at first disease assessment came off treatment

1. Balar A et al. ASCO GU 2019. Abstract 350. 2. Balar A. FDA ODAC submission 2019.

Courtesy of Arjun Balar, MD

# KEYNOTE-057: Complete Responses in Key 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 |




Courtesy of Arjun Balar, MD

# Systemic Immunotherapy: Toxicity Concerns

Treatment-Related Toxicity

- Majority will tolerate treatment well
- Severe and irreversible irAEs are uncommon

Financial Toxicity

Table 4. Immune-Mediated AEs[a] of Any Grade and Corresponding Grade 3/4 Events

| n (%) | N = 102 | |
|---|---|---|
| | All Grades | Grade 3/4 |
| **Any** | 21 (20.6) | 3 (2.9) |
| Hypothyroidism | 8 (7.8) | 0 (0) |
| Hyperthyroidism | 5 (4.9) | 0 (0) |
| Pneumonitis | 3 (2.9) | 0 (0) |
| Hypophysitis | 1 (1.0) | 0 (0) |
| Colitis | 1 (1.0) | 0 (0) |
| Adrenal insufficiency | 1 (1.0) | 1 (1.0) |
| Nephritis | 1 (1.0) | 0 (0) |
| Severe skin reaction | 1 (1.0) | 1 (1.0) |
| Type 1 diabetes mellitus | 1 (1.0) | 1 (1.0) |
| Uveitis | 1 (1.0) | 0 (0) |
| Hepatitis | 1 (1.0) | 0 (0) |

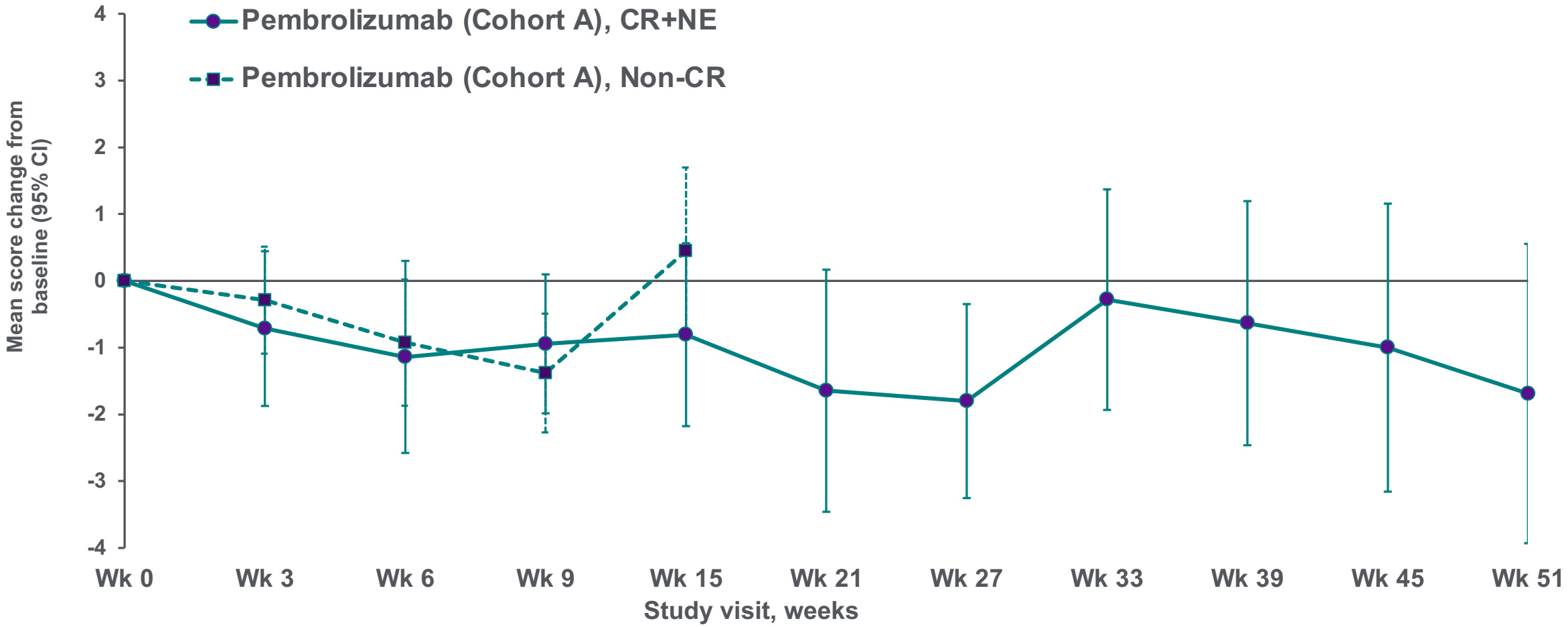
rence, progression, and ineffective treatments. It costs approxi-
mately $300 000 to treat a BCG-unresponsive patient with NMIBC
with a full course of pembrolizumab and $200 000 based on the
average duration of response.[7] Comparatively, BCG costs about

J Gill and V. Prasad. **Pembrolizumab for Non-Muscle-Invasive Bladder Cancer-A Costly Therapy in Search of Evidence;** JAMA Oncol . 2020 Dec 30. doi: 10.1001/jamaoncol.2020.6142

It only costs more if it works!

Courtesy of Arjun Balar, MD

# KEYNOTE-057: Quality of Life — CLSS




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CR+NE | 39 | 35 | 36 | 35 | 36 | 31 | 30 | 32 | 30 | 24 | 16 |
| Non-CR | 54 | 52 | 53 | 50 | 47 | | | | | | |

De Wit ESMO 2019

Courtesy of Arjun Balar, MD

# Phase III Trial: Efficacy

| | Nadofaragene (n=103) | Pembrolizumab (N=97) |
|---|---|---|
| CR @ 3 months | 53% | 41% |
| CR @ 6 months | 41% | 31% |
| CR @ 9 months | 35% | 22% |
| CR @ 12 months | 24%* | - |
| CR @ 15 months | - | 20% |
| Progression MIBC | 5% | 3% |

* mandatory biopsy

Boorjian et al, ASCO-GU 2020

Balar et al, ASCO-GU 2019

ODAC Briefing Document

Courtesy of Arjun Balar, MD

# Delaying Cystectomy and Risk for Disease Progression

## N= 38 patients

| | Patient, n n = 38[a] | Maximum T Stage | N Stage[b] | Achieved Initial CR, n | Interval Between Last Dose of Pembrolizumab and Radical Cystectomy, days |
|---|---|---|---|---|---|
| NMIBC | 6 | pT0 | N0 = 5<br>Nx = 1 | 4 | 134.5 (60-149)[d] |
| | 5 | pTa | N0 = 5 | 0 | 103 (70-819)[d] |
| | 18 | pTis | N0 = 16<br>Nx = 2 | 6 | 76.5 (42-861)[d] |
| | 6 | pT1 | N0 = 6 | 0 | 133 (51-566)[d] |
| MIBC | 2 | pT2 | N0 = 1<br>N1 = 1[c] | 0 | 60<br>86 |
| | 1 | pT3 | N1 | 0 | 457 |

***3/38 = 8%***

Balar et al ASCO 2020

Courtesy of Arjun Balar, MD

# Phase 3 Trials of PD-1/PD-L1 Inhibitors in NMIBC

**Primary endpoint:** CR

**KEYNOTE-676 (NCT03711032)[1]; N = ≈550**

- High-risk NMIBC persistent or recurrent after BCG induction and following cytoscopy/ transurethral resection
- ECOG PS ≤2

R → Pembrolizumab + BCG

R → BCG

**Primary endpoint:** DFS

**POTOMAC (NCT03528694)[2]; N = ≈975**

- High-risk NMIBC previously resected and naïve to BCG and cancer immunotherapy

R → Durvalumab + BCG (induction and maintenance)

R → Durvalumab + BCG (induction only)

R → BCG

**Primary endpoint:** RFS

**ALBAN (NCT03799835)[3]; N = 614**

- High-risk NMIBC previously resected and naïve to BCG
- Tumor tissue available for PD-L1 assay

R → BCG × 1 y

R → BCG + atezolizumab every 3 wk × 1 y

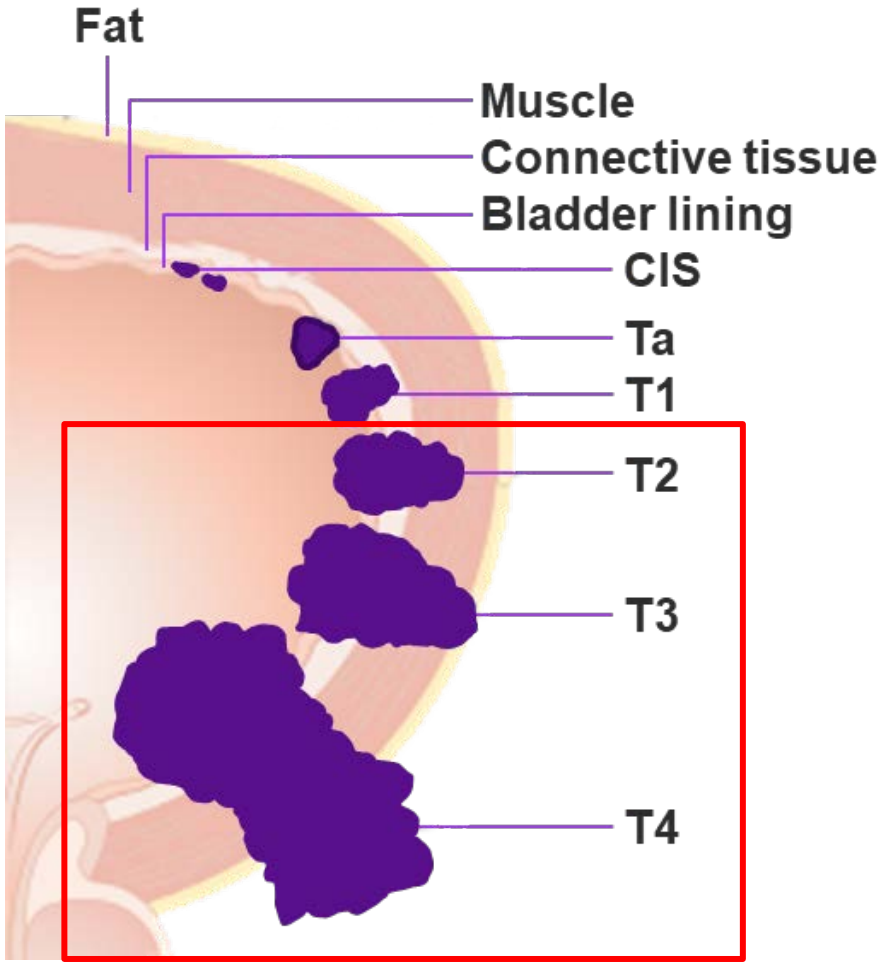
1. https://clinicaltrials.gov/ct2/show/NCT03711032. Accessed February 7, 2020. 2. https://clinicaltrials.gov/ct2/show/NCT03528694. Accessed February 7, 2020.
3. https://clinicaltrials.gov/ct2/show/NCT03799835. Accessed February 7, 2020.

Courtesy of Arjun Balar, MD

# Muscle Invasive Bladder Cancer: A Medical Oncologist's Perspective

- Inherently a Systemic Disease (~50% develop metastases)
  - Purpose of local therapy is local control/tumor eradication *before* the dissemination of micrometastases.
  - Peri-operative therapy addresses potential micrometastases
  - Success of neoadjuvant (SOC) therapy measured in-vivo
    - cT0 ≠ pT0 (i.e. best assessed with cystectomy)

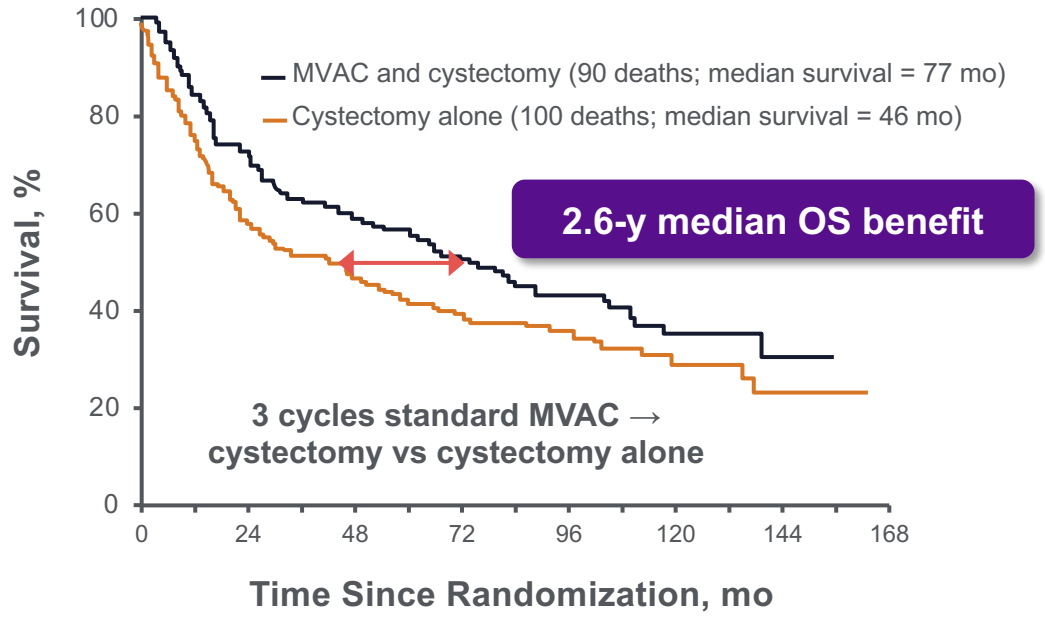
- Ideal Local therapy
  - Definitively addresses local disease reliably
    - Can radiation be truly "definitive"?
  - Preserves quality of life
    - Cystectomy is morbid (60% complication rate)




Courtesy of Arjun Balar, MD

# Neoadjuvant Therapy for MIBC

## Neoadjuvant Cisplatin-Based Chemotherapy Is SOC for MIBC[1]




## Neoadjuvant Checkpoint Inhibition in Bladder Cancer: Early Results of Phase 2 Trials[2]

| | PURE-01 trial of pembrolizumab (n = 43)[2] | ABACUS trial of atezolizumab (n = 68)[3] |
|---|---|---|
| Eligibility | T2-T3b<br>N1 allowed (5%)<br>T4b not allowed | T2-T3b<br>N+ not allowed<br>T4b allowed (7%) |
| Patients ineligible for cisplatin, % | 0 | 100 |
| Patients who received neoadjuvant CT, % | 12 | 0 |
| Duration of therapy | 3 cycles (9 wk) | 2 cycles (6 wk) |
| Safe | Yes | Yes |
| Pathologic complete response rate (pT0), % | 40 | 29 |
| Biomarker data presented | Yes | Yes |

**pT0 rates with CT**

**Gem/Cis 15%-26%**

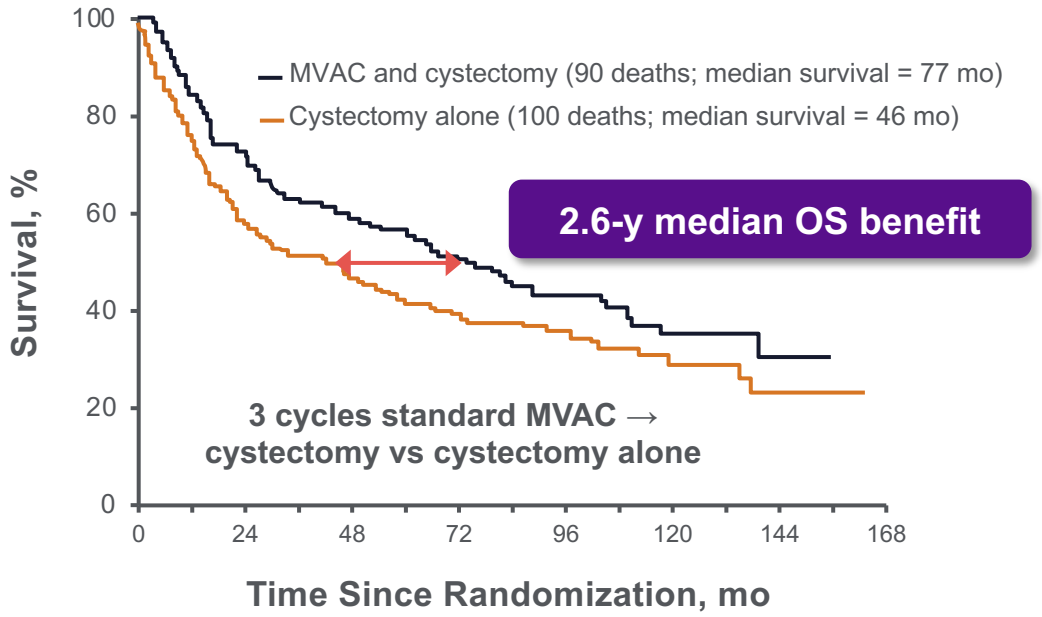
**DDMVAC 26%-43%**

1. Grossman HB et al. *N Engl J Med*. 2003;349:859-866. 2. Necchi A et al. ASCO 2018. Abstract 4507. 3. Powles T et al. ASCO 2018. Abstract 4506.

Courtesy of Arjun Balar, MD

# Neoadjuvant Therapy for MIBC

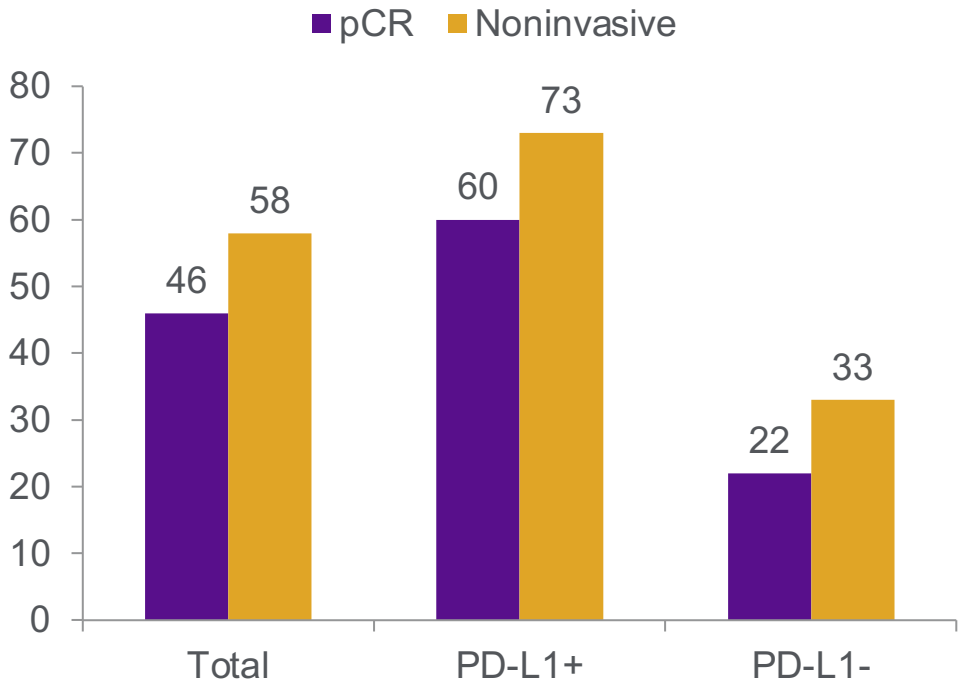
## Neoadjuvant Cisplatin-Based Chemotherapy Is SOC for MIBC[1]




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MVAC and cystectomy | 153 | 112 | 92 | 75 | 46 | 23 | 6 |
| Cystectomy alone | 154 | 88 | 67 | 50 | 37 | 18 | 7 |

**NABUCCO: pre-operative ipilimumab + nivolumab in stage III UC patients who were either cisplatin ineligible or refused chemotherapy (N = 24)[2,3]**




**Encouraging data, but randomized data demonstrating a DFS and ultimately OS benefit are needed**

1. Grossman HB et al. *N Engl J Med*. 2003;349:859-866. 2. Van der Heijden et al. ESMO 2019. Abstract 904. 3. Van Dijk NV et al. ASCO 2020. Abstract 5020.

Courtesy of Arjun Balar, MD

# Neoadjuvant checkpoint inhibition in patients with MIBC

- **October 2020 update**

| | PURE-01 | ABACUS | NABUCCO | HOG GU14-188 | | BLASST | DUTRENEO | MDACC |
|---|---|---|---|---|---|---|---|---|
| **Treatment** | **Pembrolizumab** (PURE-01) | **Atezolizumab** (ABACUS) | **Ipilimumab > Ipi/Nivolumab > Nivo** (NABUCCO) | **Pembrolizumab-GEM/CIS** (HOG GU14-188) | **Pembrolizumab-GEM** (HOG GU14-188) | **Nivolumab-GC** (BLASST) | **Durva/Treme** (DUTRENEO) | Durva/Treme (MDACC) |
| Reference | [1] | [2] | [3] | [4] | [5] | [6] | [7] | [9] |
| Sample size | 114 | 88 | 24 | 43 | 37 | 41 | 23 | 28 |
| cT2-stage | 54% (CT+mpMRI) | 73% | 0 | 47% | 43.2 | 90% | 78.2% | 43% |
| cN+ stage | 0 (but 6% PET+) | 0 | 42% | 0 | 0 | 3% | 8.7% | 0 |
| pT0N0 rate | **37%** | **31%** | **46%** | **44.4%** | **45.2%** | **34%** | **34.8%** | **37.5%** |
| pT≤1N0 rate | 55% | | 58% | 61.1% | 51.6% | 66% | 56.5% | 58% |
| 1-y RFS | 91% (85-98) [EFS: 87%] [8] | 79% (95%CI: 67-87) | 92% | 2-y: 66% | 67% | n.a. | n.a. | 82.8% |
| Biomarkers | PD-L1+ (TMB) Immune-gene signatures | Pre-existing T-cell activation+ (CD8/GZMB, tGE8-high) | PD-L1+; DDR-GA; TLS signature | none | none | Immune-gene signatures | Pre-selected with 18-gene IFN-γ signature | TLS signature |

***References:***
1. Necchi A, et al. *Eur Urol*. 2020;77:439-446; 2. Powles, T, et al. *Nat Med*. 2019;25:1706-1714; 3. van Dijk N, et al. *Nat Med*. 2020. (Epub ahead of print); 4. Holmes CJ, et al. ASCO 2020; 5. Kaimakliotis HZ, et al. ASCO 2020; 6. Gupta S, et al. GU-ASCO 2020; 7. Grande E, et al. ASCO 2020; 8. Bandini M, et al. *Ann Oncol*. 2020 (Epub ahead of print); 9. Gao J, et al. *Nat Med*. 2020. (Epub ahead of print)

Andrea Necchi ESMO 2020

Courtesy of Arjun Balar, MD

# Neoadjuvant Immunotherapy in UC: Ongoing Phase 3 Trials

**NIAGARA (NCT03732677)[1]**

- Resectable muscle-invasive transitional cell bladder cancer that will be surgically treated with radical cystectomy
- No prior systemic chemoTx or immunotherapy
- ECOG PS ≤1

**Primary endpoints:** pCR, EFS

R

- Durvalumab + chemoTx → adjuvant durvalumab
- ChemoTx

N = ~1,050

**ENERGIZE (NCT03661320)[2]**

- Muscle-invasive bladder cancer eligible for radical cystectomy
- ECOG PS ≤1

**Primary endpoints:** pCR, EFS

R

- ChemoTx + nivolumab → adjuvant nivolumab
- ChemoTx + nivolumab + linrodostat (BMS-986205, an IDO inhibitor) → adjuvant nivolumab + linrodostat
- ChemoTx

N = ~1,200

1. https://clinicaltrials.gov/ct2/show/NCT03732677. Accessed April 25, 2019. 2. https://clinicaltrials.gov/ct2/show/NCT03661320. Accessed April 26, 2019.

Courtesy of Arjun Balar, MD

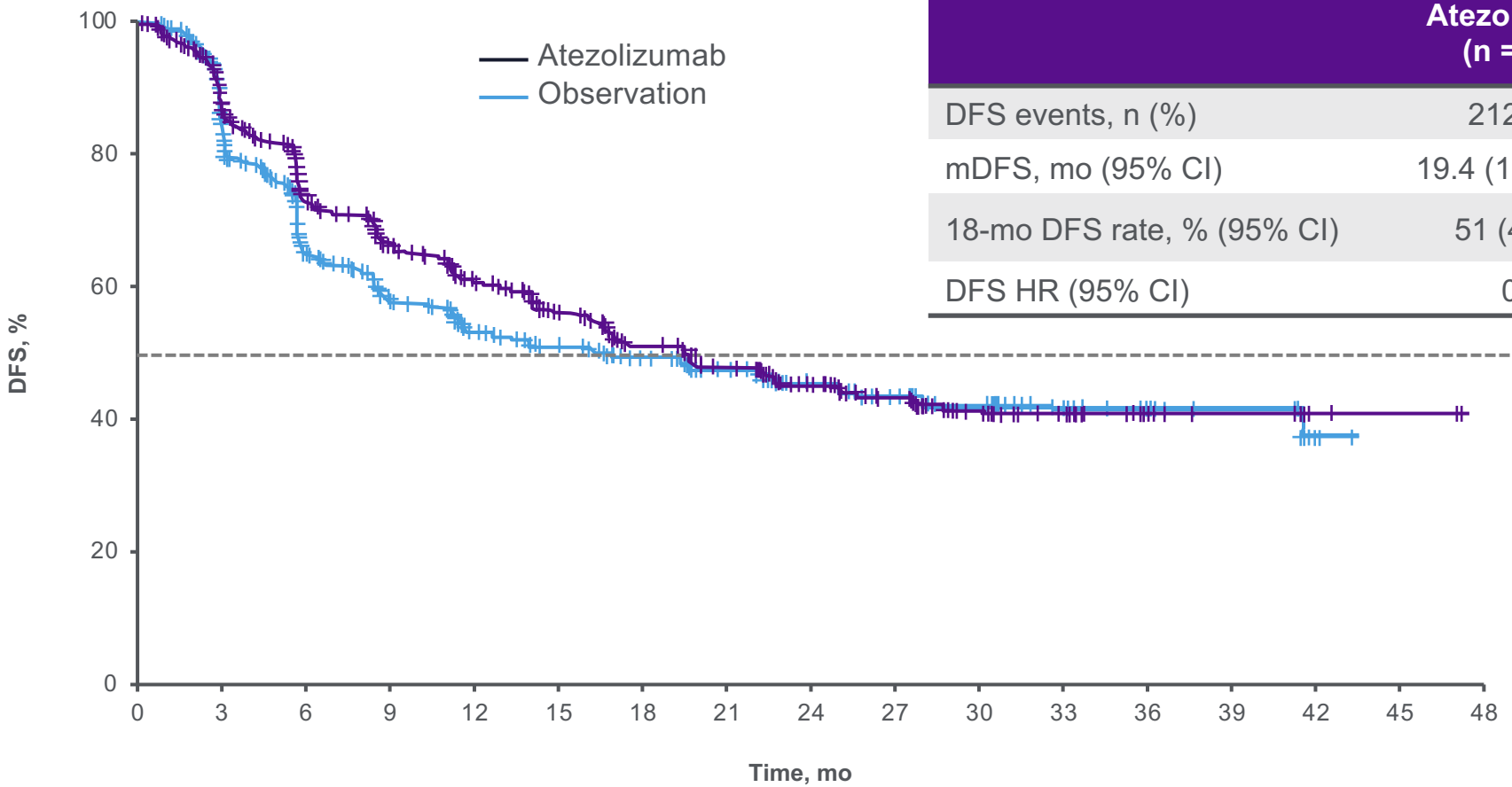
# Several Neoadjuvant Immunotherapy Trials Are Ongoing

| Phase 3 Trial<br>*Primary endpoints* | Population | Treatment Arms |
|---|---|---|
| **NIAGARA** [1]<br>***pCR, EFS*** | Resectable muscle-invasive transitional cell bladder cancer that will be surgically treated with radical cystectomy | Durvalumab + chemotherapy → adjuvant durvalumab vs chemotherapy |
| **ENERGIZE**[2]<br>***pCR, EFS*** | MIBC eligible for radical cystectomy | Nivolumab + chemotherapy or nivolumab/linrodostat + chemotherapy → immuno-oncology therapy after radical cystectomy vs chemotherapy |
| **KEYNOTE-905**[3]<br>***pCR, EFS*** | MIBC patients eligible for radical cystectomy; cisplatin-ineligible | Pembrolizumab → Radical cystectomy + pelvic lymph node dissection → pembrolizumab |
| **KEYNOTE-866**[4]<br>***pCR, EFS*** | Cisplatin-eligible MIBC | Perioperative pembrolizumab + neoadjuvant chemotherapy versus perioperative placebo +neoadjuvant chemotherapy |
| **Nivolumab/bempegaldesleukin (NKTR-214)**[5]<br>***pCR, EFS*** | MIBC; cisplatin-ineligible | Neoadjuvant and adjuvant nivolumab + bempegaldesleukin vs nivolumab alone vs SOC |

1. https://clinicaltrials.gov/ct2/show/NCT03732677. 2. https://clinicaltrials.gov/ct2/show/NCT03661320. 3. https://clinicaltrials.gov/ct2/show/NCT03924895.
4. https://clinicaltrials.gov/ct2/show/NCT03924856. 5. https://clinicaltrials.gov/ct2/show/NCT04209114.

Courtesy of Arjun Balar, MD

# IMvigor010 Sounds a Cautionary Note
## *DFS With Adjuvant Atezolizumab*[1]




| | Atezolizumab (n = 406) | Observation (n = 403) |
|---|---|---|
| DFS events, n (%) | 212 (52) | 208 (52) |
| mDFS, mo (95% CI) | 19.4 (15.9-24.8) | 16.6 (11.2-24.8) |
| 18-mo DFS rate, % (95% CI) | 51 (46-56) | 49 (44-54) |
| DFS HR (95% CI) | 0.89 (0.74-1.08); *P* = .2446 | |

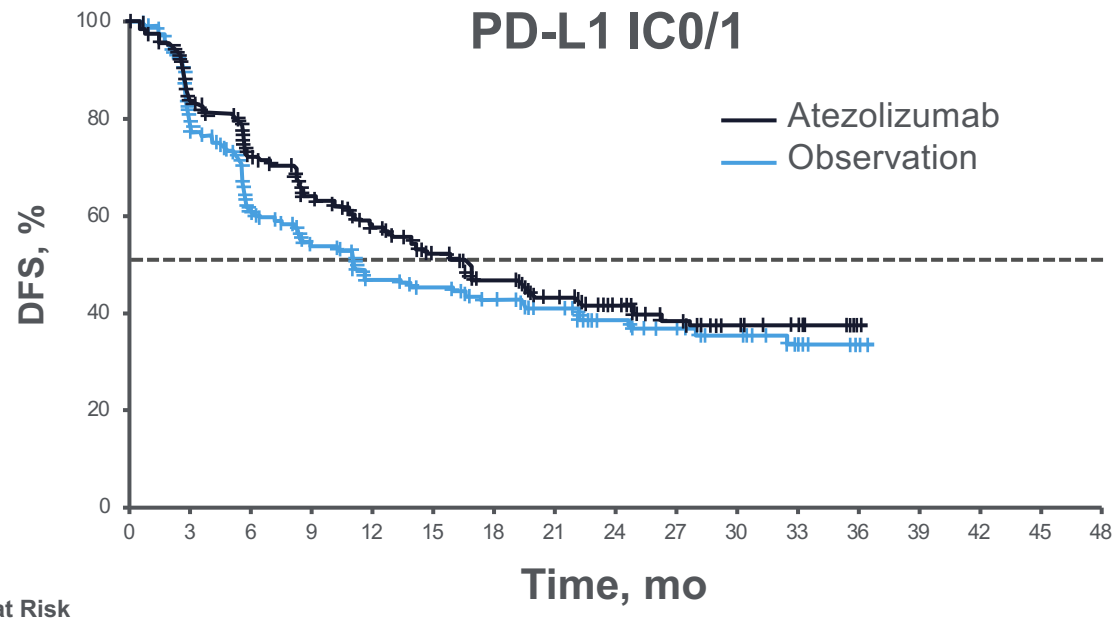
**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 406 | 332 | 281 | 248 | 223 | 201 | 169 | 142 | 115 | 92 | 67 | 52 | 15 | 10 | 3 | 2 |
| Observation | 403 | 305 | 240 | 211 | 188 | 177 | 156 | 131 | 109 | 87 | 67 | 42 | 17 | 12 | 2 | – |

1. Hussain M et al. ASCO 2020. Abstract 5000.

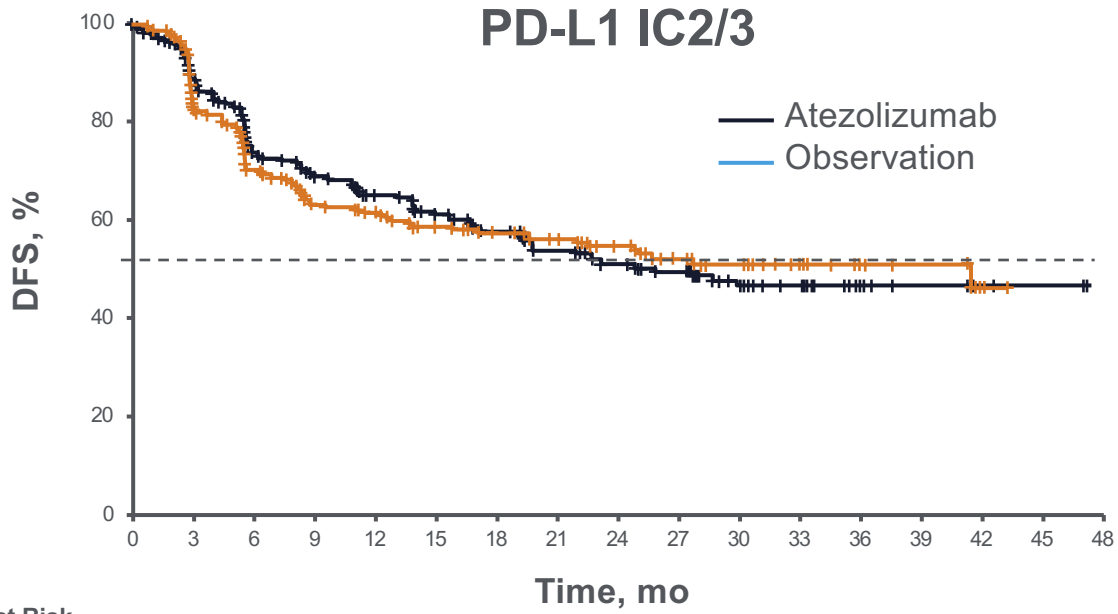
Courtesy of Arjun Balar, MD

# IMvigor010: DFS by PD-L1 Status[1]




**No. at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 210 | 167 | 145 | 122 | 109 | 96 | 77 | 64 | 48 | 33 | 22 | 14 | 1 |
| Observation | 207 | 149 | 114 | 100 | 83 | 80 | 69 | 56 | 42 | 34 | 26 | 14 | 2 |




**No. at Risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 196 | 165 | 136 | 126 | 114 | 105 | 92 | 78 | 67 | 59 | 45 | 38 | 14 | 10 | 3 |
| Observation | 196 | 156 | 126 | 111 | 105 | 97 | 87 | 75 | 67 | 53 | 41 | 30 | 15 | 12 | 2 |

| | Atezolizumab (n = 210) | Observation (n = 207) |
|---|---|---|
| DFS events, n (%) | 118 (56) | 120 (58) |
| HR (95% CI) | 0.81 (0.63-1.05) | |

| | Atezolizumab (n = 196) | Observation (n = 196) |
|---|---|---|
| DFS events, n (%) | 94 (48) | 88 (45) |
| HR (95% CI) | 1.01 (0.75-1.35) | |

1. Hussain M et al. ASCO 2020. Abstract 5000.

Courtesy of Arjun Balar, MD

# What About Other Trials of Adjuvant PD-1/PD-L1 Inhibitors in High-Risk Muscle-Invasive UC?

Nivolumab Significantly Improves Disease Free-Survival vs. Placebo as Adjuvant Therapy for Patients with High-Risk, Muscle-Invasive Urothelial Carcinoma in Phase 3 CheckMate -274 Trial

09/24/2020

CATEGORY: Corporate/Financial News

In an interim analysis, CheckMate -274 met primary endpoints of disease-free survival in both all randomized patients and in patients whose tumor cells express PD-L1 ≥1%

DFS

**AMBASSADOR[2]**

- MIBC or UTUC; history of cystectomy or nephrectomy within 16 wk; pT2-4aNx– or pTxN-positive postneoadjuvant chemoTx

*OR*

- pT3-4Nx– or pN-positive postsurgery with no chemoTx

- **PD-L1 status**
- **Neoadjuvant chemoTx (yes/no)**
- **Pathologic stage (pT2/3/4aN0 vs pT4bNx or N1-3)**

**N = 739**

**R**

**Pembrolizumab** 200 mg every 3 wk × 1 y

**Observation**

**Primary endpoints:** OS and DFS

1. https://clinicaltrials.gov/ct2/show/NCT02632409. 2. https://clinicaltrials.gov/ct2/show/NCT03244384.

Courtesy of Arjun Balar, MD

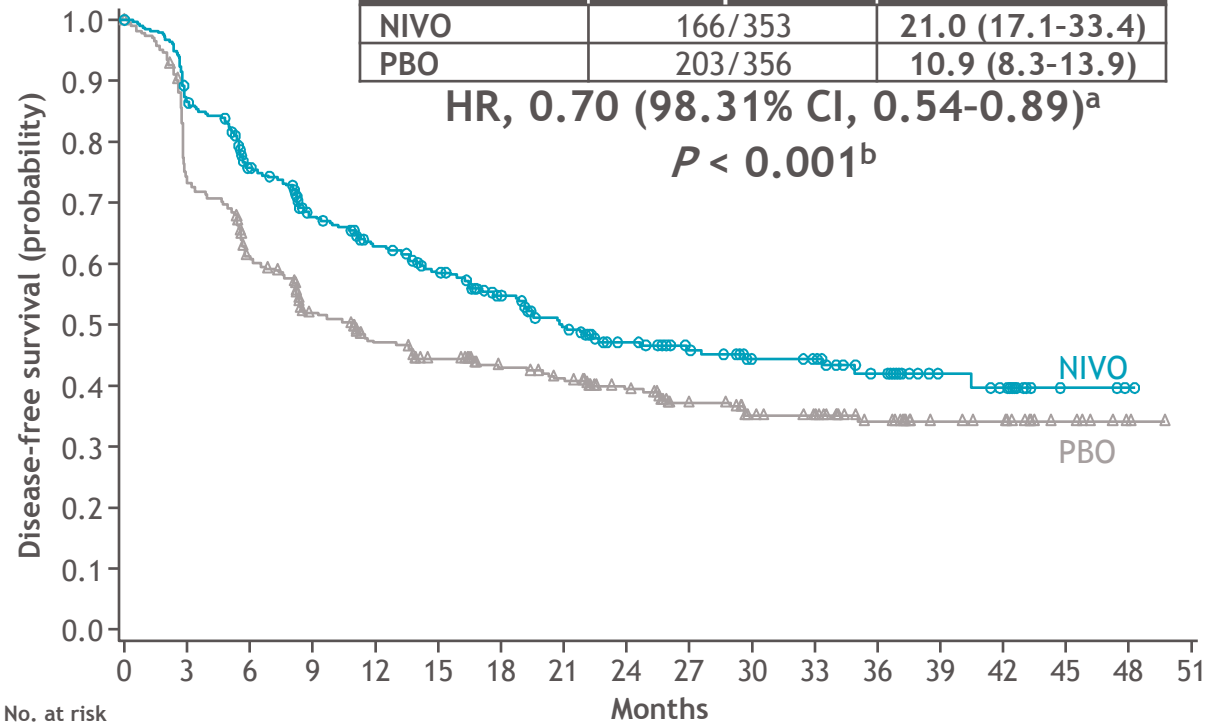
# Disease-free survival

## ITT

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 166/353 | 21.0 (17.1-33.4) |
| PBO | 203/356 | 10.9 (8.3-13.9) |

HR, 0.70 (98.31% CI, 0.54-0.89)[a]

*P* < 0.001[b]




No. at risk

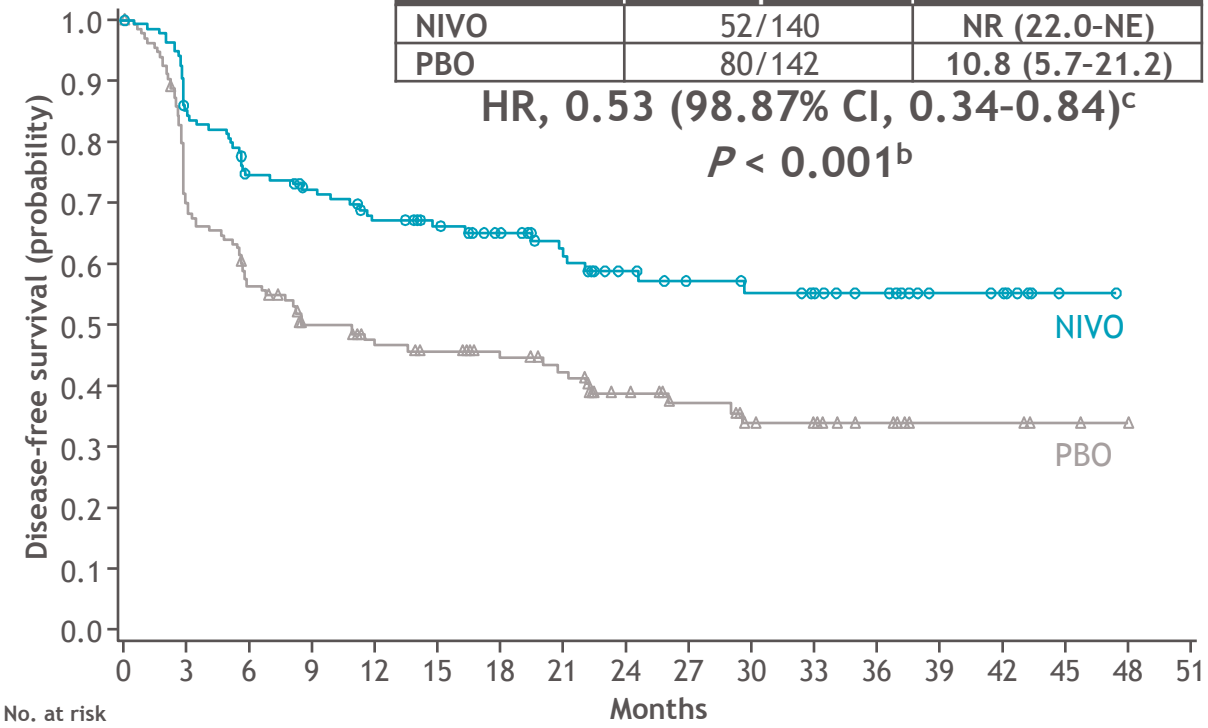
| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 353 | 297 | 245 | 204 | 175 | 151 | 125 | 103 | 83 | 67 | 53 | 49 | 34 | 18 | 15 | 3 | 1 | 0 |
| PBO | 356 | 251 | 201 | 156 | 132 | 119 | 103 | 95 | 80 | 62 | 48 | 44 | 31 | 20 | 18 | 7 | 2 | 0 |

## PD-L1 ≥ 1%

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 52/140 | NR (22.0-NE) |
| PBO | 80/142 | 10.8 (5.7-21.2) |

HR, 0.53 (98.87% CI, 0.34-0.84)[c]

*P* < 0.001[b]




No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 140 | 113 | 97 | 87 | 74 | 66 | 57 | 49 | 37 | 30 | 27 | 24 | 20 | 9 | 8 | 1 | 0 | 0 |
| PBO | 142 | 92 | 74 | 59 | 52 | 48 | 41 | 37 | 28 | 22 | 17 | 15 | 9 | 5 | 5 | 2 | 1 | 0 |

Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

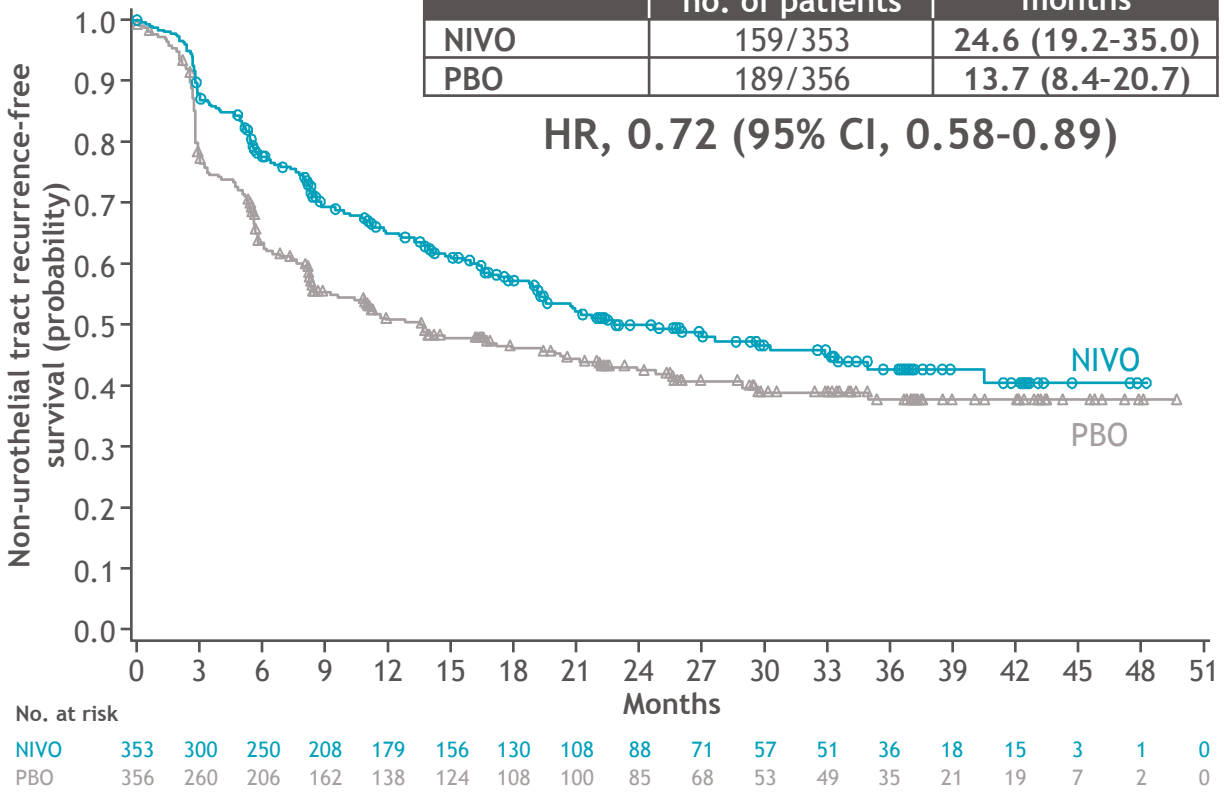
Courtesy of Arjun Balar, MD

# Non-urothelial tract recurrence-free survival

## ITT

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 159/353 | 24.6 (19.2-35.0) |
| PBO | 189/356 | 13.7 (8.4-20.7) |

HR, 0.72 (95% CI, 0.58-0.89)



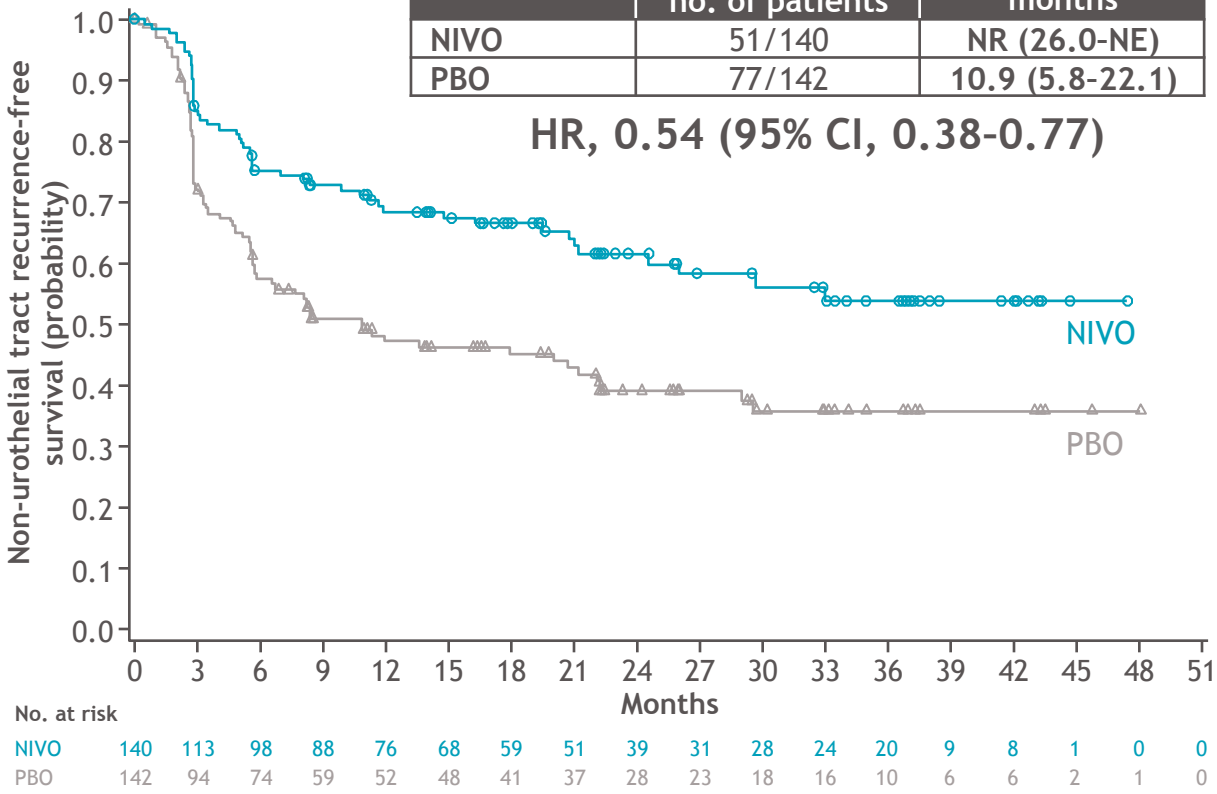

No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 353 | 300 | 250 | 208 | 179 | 156 | 130 | 108 | 88 | 71 | 57 | 51 | 36 | 18 | 15 | 3 | 1 | 0 |
| PBO | 356 | 260 | 206 | 162 | 138 | 124 | 108 | 100 | 85 | 68 | 53 | 49 | 35 | 21 | 19 | 7 | 2 | 0 |

## PD-L1 ≥ 1%

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 51/140 | NR (26.0-NE) |
| PBO | 77/142 | 10.9 (5.8-22.1) |

HR, 0.54 (95% CI, 0.38-0.77)




No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 140 | 113 | 98 | 88 | 76 | 68 | 59 | 51 | 39 | 31 | 28 | 24 | 20 | 9 | 8 | 1 | 0 | 0 |
| PBO | 142 | 94 | 74 | 59 | 52 | 48 | 41 | 37 | 28 | 23 | 18 | 16 | 10 | 6 | 6 | 2 | 1 | 0 |

Minimum follow-up, 5.9 months.
NUTRFS was defined as the time between the date of randomization and the date of first local non-urothelial tract or distant recurrence or death.

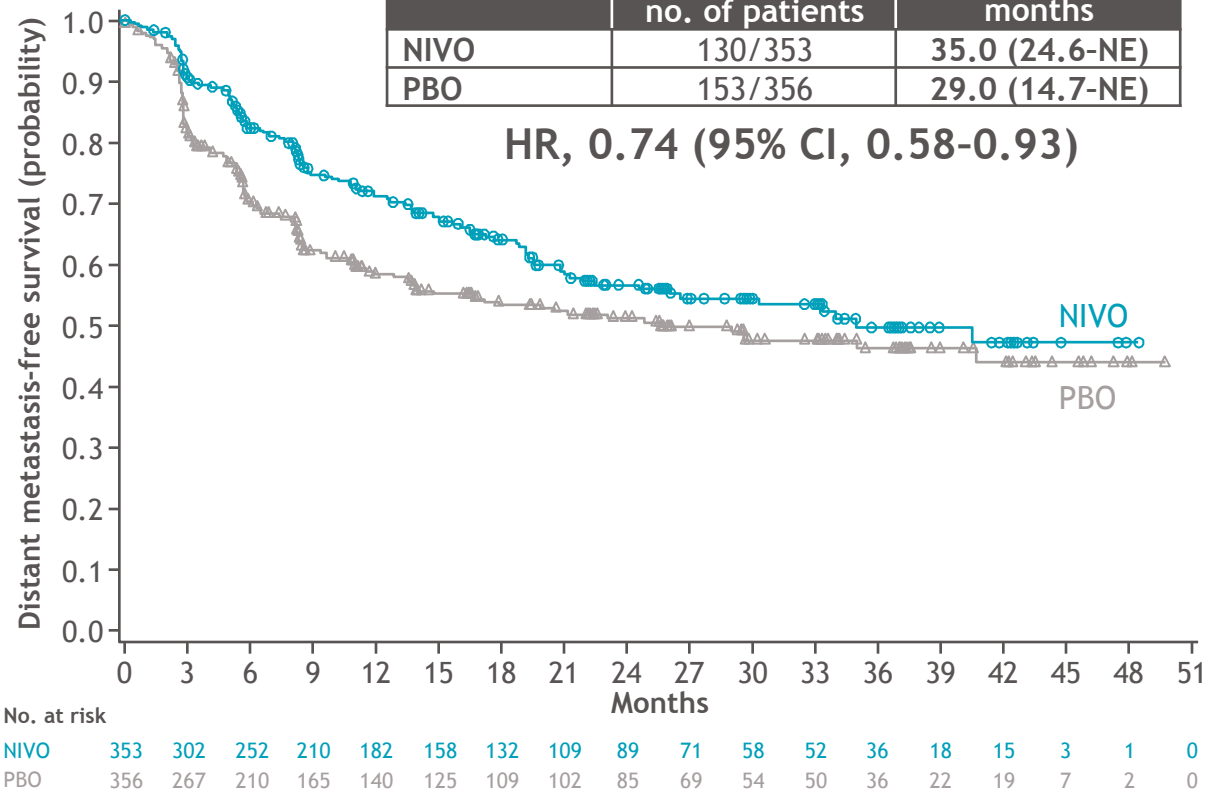
Courtesy of Arjun Balar, MD

# Distant metastasis-free survival

## ITT

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 130/353 | 35.0 (24.6-NE) |
| PBO | 153/356 | 29.0 (14.7-NE) |

HR, 0.74 (95% CI, 0.58-0.93)



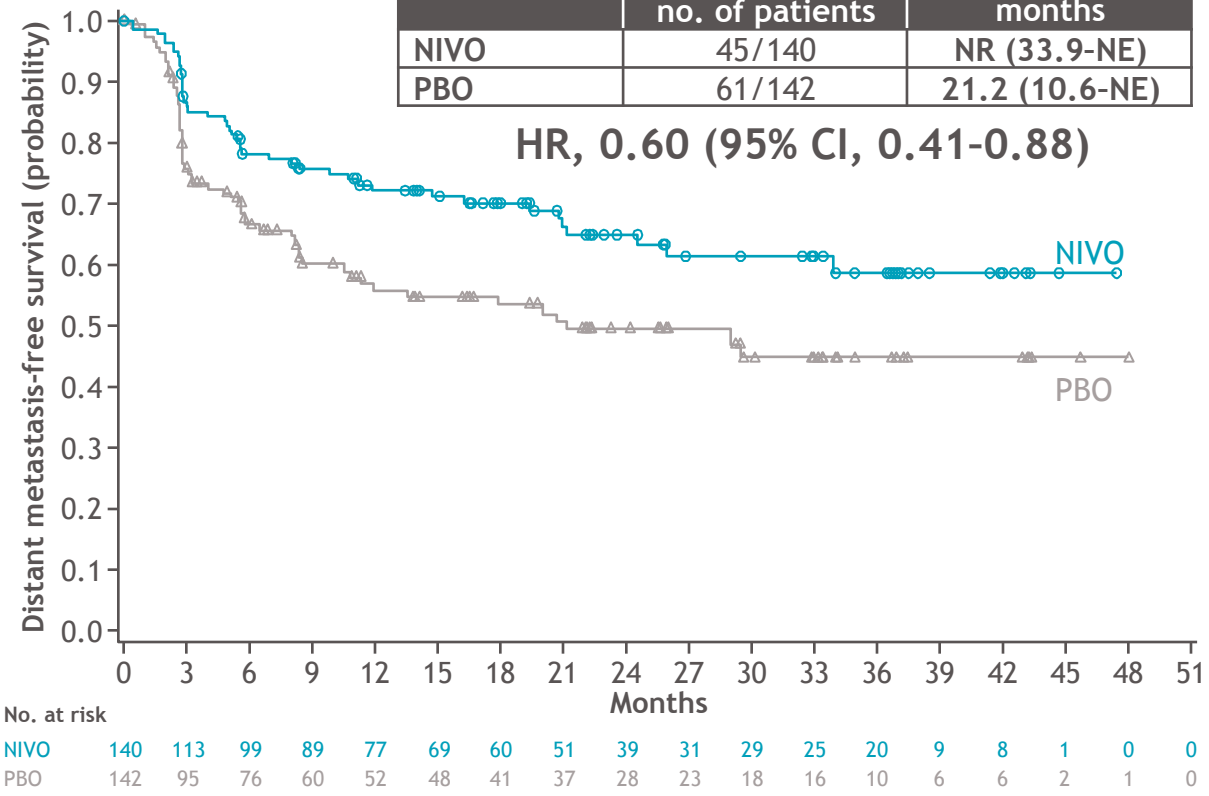

No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 353 | 302 | 252 | 210 | 182 | 158 | 132 | 109 | 89 | 71 | 58 | 52 | 36 | 18 | 15 | 3 | 1 | 0 |
| PBO | 356 | 267 | 210 | 165 | 140 | 125 | 109 | 102 | 85 | 69 | 54 | 50 | 36 | 22 | 19 | 7 | 2 | 0 |

## PD-L1 ≥ 1%

| | No. of events/ no. of patients | Median (95% CI), months |
|---|---|---|
| NIVO | 45/140 | NR (33.9-NE) |
| PBO | 61/142 | 21.2 (10.6-NE) |

HR, 0.60 (95% CI, 0.41-0.88)




No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO | 140 | 113 | 99 | 89 | 77 | 69 | 60 | 51 | 39 | 31 | 29 | 25 | 20 | 9 | 8 | 1 | 0 | 0 |
| PBO | 142 | 95 | 76 | 60 | 52 | 48 | 41 | 37 | 28 | 23 | 18 | 16 | 10 | 6 | 6 | 2 | 1 | 0 |

Minimum follow-up, 5.9 months.
DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death.

Courtesy of Arjun Balar, MD

# Case 1: HR NMIBC

- 75 year old man, former 40 pack-year tobacco smoker
  - HTN
  - COPD
- HR NMIBC (CIS) diagnosed in 2015 -> Intravesical BCG induction x 2, maintenance x 2 courses (last 12/2016)
- Recurrent CIS in March 2017
- BCG Unresponsive CIS
- Enrolled to KEYNOTE-057

Courtesy of Arjun Balar, MD

# Case 1: Continued

- Pembrolizumab started 5/2017
  - 4 cycles without incident
  - Cystoscopy/cytology @ month 3: normal appearance, normal biopsy and cytology

- Pneumonitis in 4/2018 -> treated with prednisone
- Pembrolizumab stopped

- Last cystoscopy/cytology 2/2021: normal

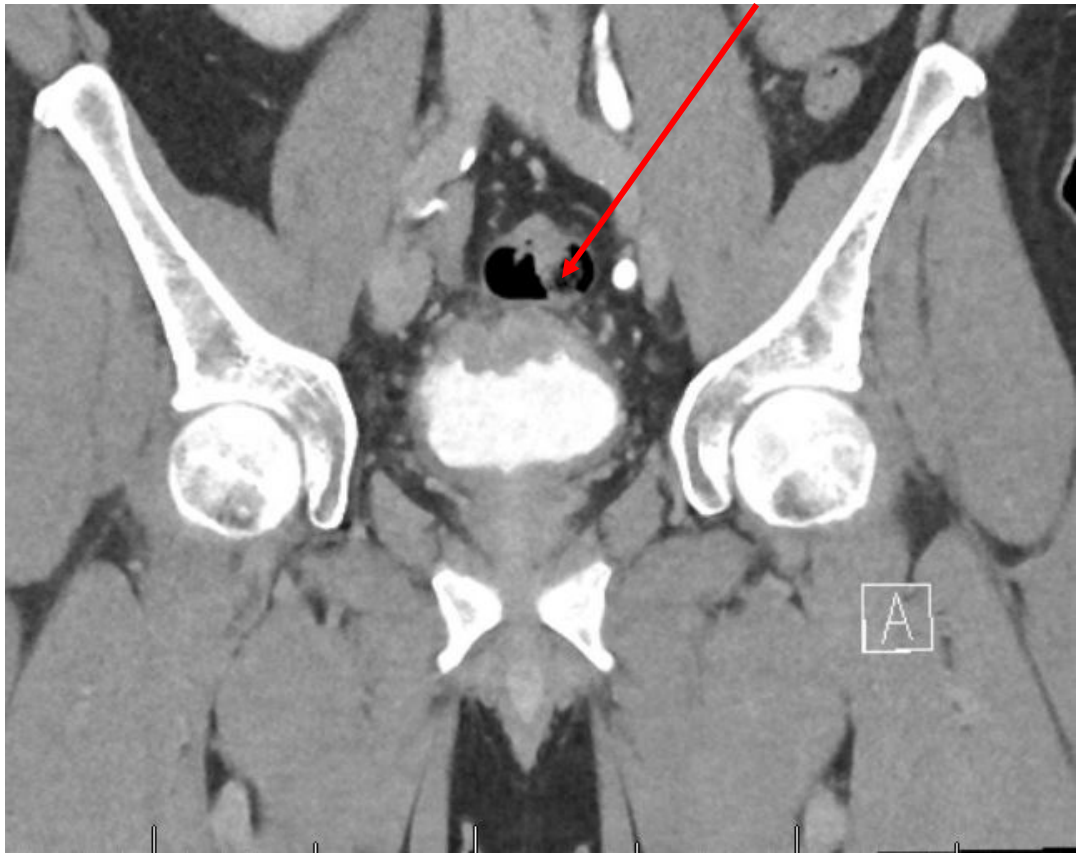
Courtesy of Arjun Balar, MD

# Case 2: Adjuvant Immunotherapy in MIBC

- 73 year old semi-retired photographer, previous heavy smoker
  - HTN
  - Urethral strictures
- Diagnosed with muscle-invasive bladder cancer 4/2019 at the bladder dome

Gemcitabine/Cisplatin x 3 cycles (5/2019 – 6/2019)

Radical Cystectomy 8/2019 (ypT2bN1 HG UC)




Courtesy of Arjun Balar, MD

# Case 2: Continued

- High-risk MIBC s/p neoadjuvant chemotherapy and radical cystectomy
  - Risk of relapse >60-70%

- Consented to AMBASSADOR
  - Randomized phase 3 trial of adjuvant pembrolizumab vs observation
  - Randomized to pembrolizumab
  - Tolerated treatment well, remains disease-free as of 12/2020

Courtesy of Arjun Balar, MD

# Conclusions

- PD-1 pathway inhibitors have revolutionized bladder cancer management and how we think about the disease
- FDA approval in HR BCG-Unresponsive CIS Jan 2020
- New questions and challenges have emerged
  - Encouraging data in the neoadjuvant setting
    - Randomized trials underway
  - The benefit for adjuvant therapy alone remains controversial
    - IMvigor010 was a clearly negative trial
    - CheckMate 274 DFS benefit
  - Benefit should extend to those receiving bladder preservation therapy
    - PD-1 pathway inhibition may synergize with chemoradiation and improve the efficacy of TMT

Courtesy of Arjun Balar, MD