# VI Jornadas Interhospitalarias de Urólogos de Extremadura.

## **Cáncer de vejiga Musculo Invasivo: Neoadyuancia.** Donde estamos y tendencias.

José María Mazo Gil- Oncólogo Hospital Llerena Zafra

Organizador del evento

Asociación de Urología de la Comunidad Extremeña

**Sábado 25 de Septiembre**

**Hotel Rio Badajoz.**

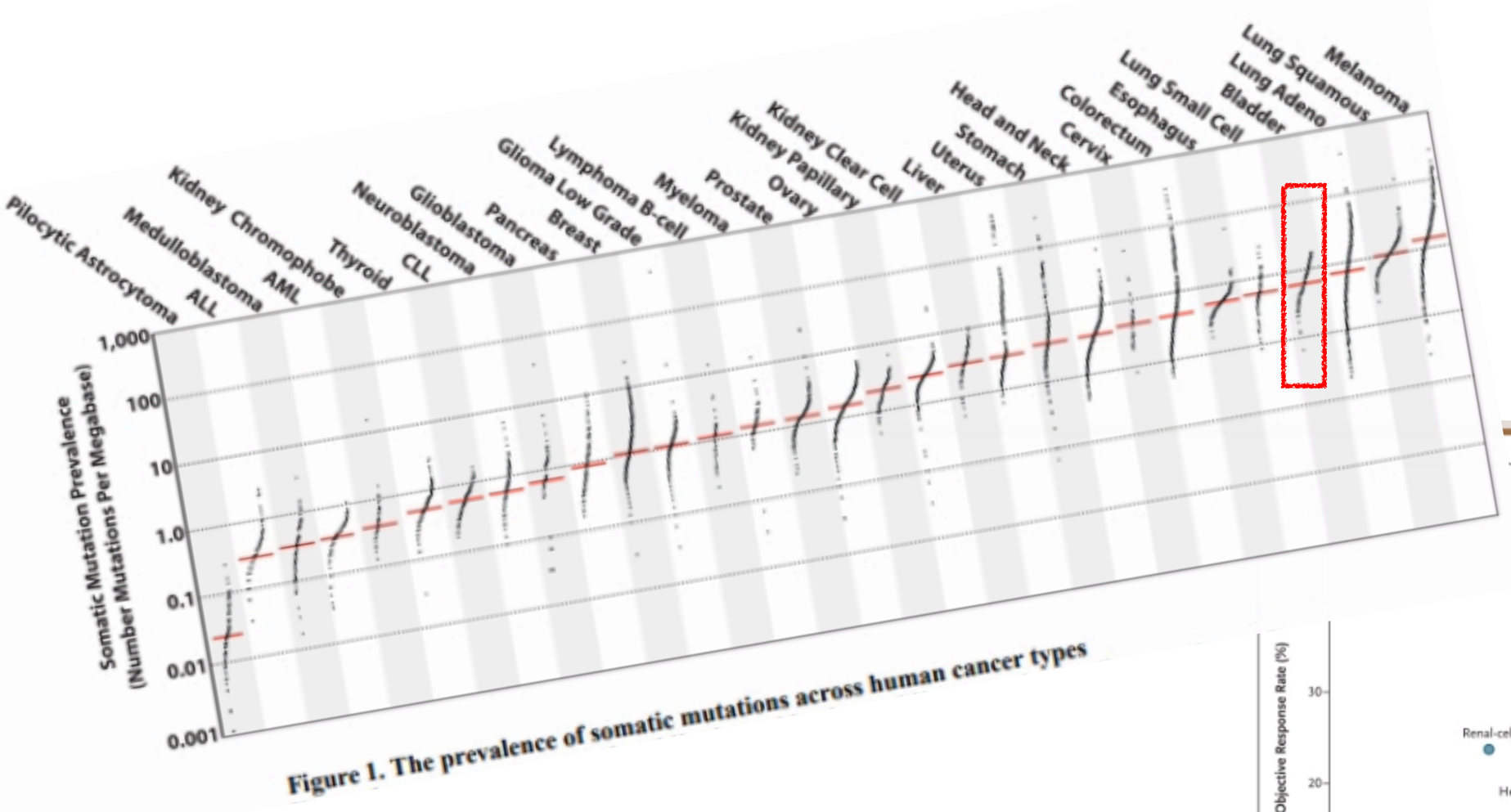



**Figure 1. The prevalence of somatic mutations across human cancer types**

Alexandrov LB, et al. Nature. 2013;500:415-421.

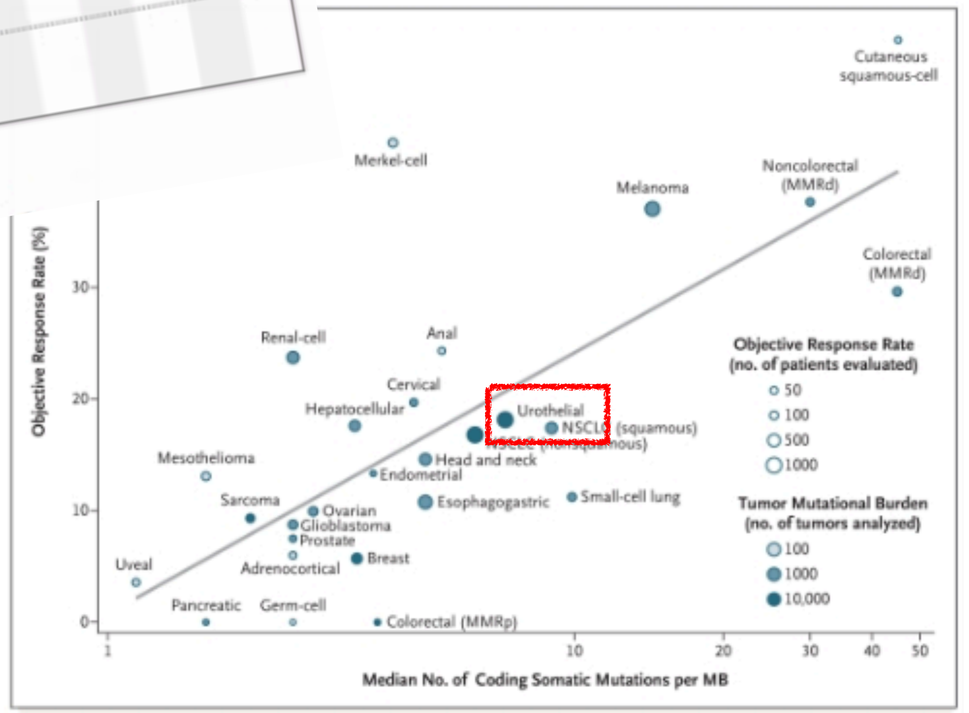
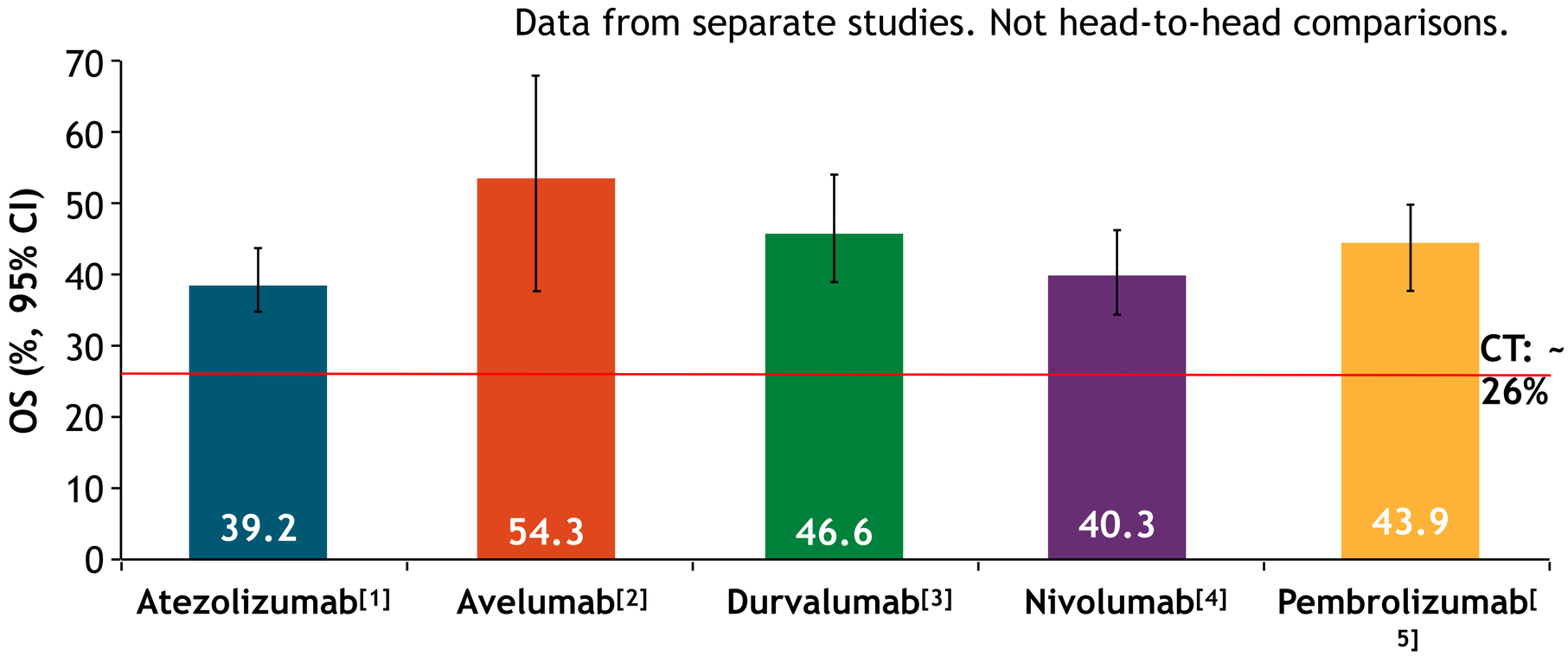



**Figure 1. Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti-PD–L1 Therapy in 27 Tumor Types.**

Yarchoan M,. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med. 2017 Dec 21;377(25):2500-2501. doi: 10.1056/NEJMc1713444.

# Post-Platinum Urothelial Carcinoma: OS at 12 Mos




1. Powles T, et al. Lancet. 2018;391:748-757. 2. Apolo AB, et al. J Clin Oncol. 2017;35:2117-2124.
3. O'Donnell P, et al. AACR 2018. Abstract CT031. 4. Sharma P, et al. AACR 2018. Abstract CT178.
5. Bellmunt J, et al. N Engl J Med. 2017;376:1015-1026.

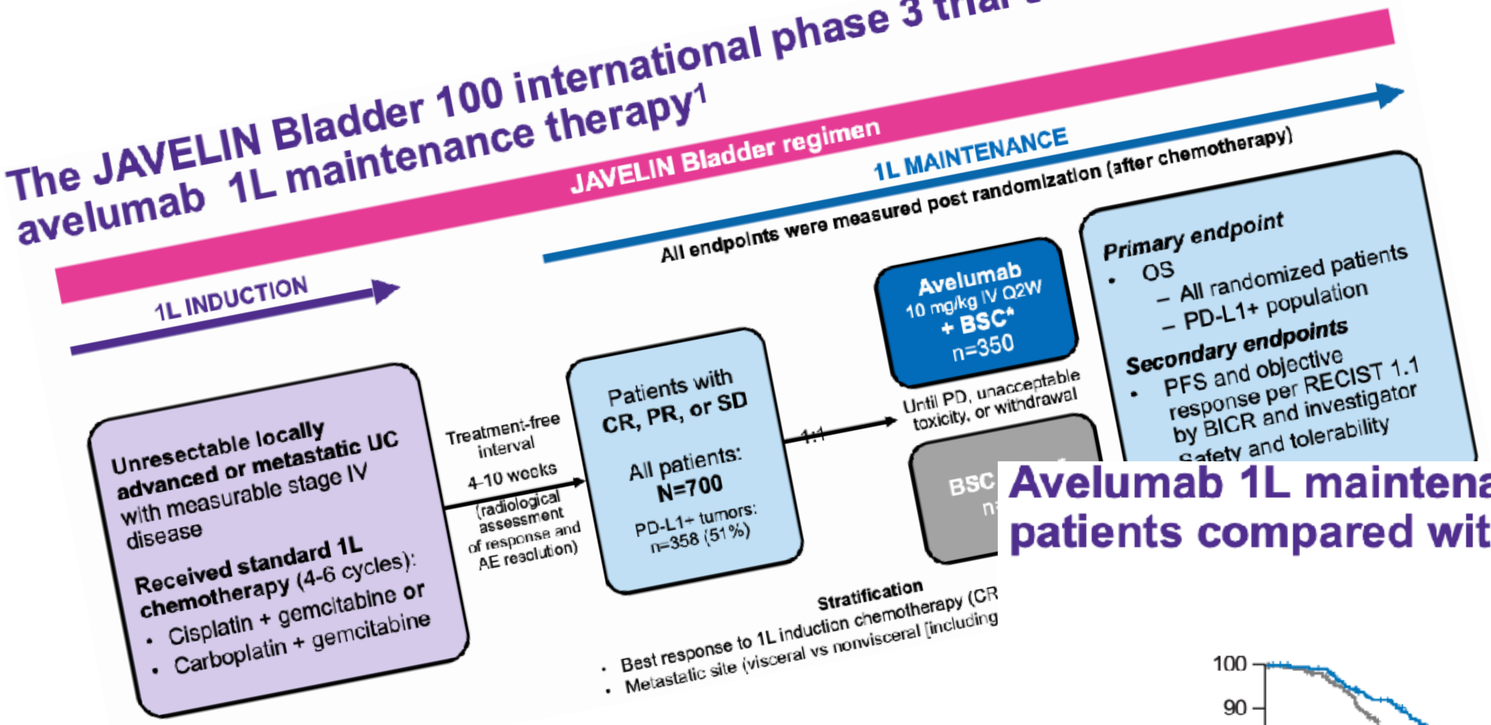
## PRINCIPLES OF SYSTEMIC THERAPY

| First-line systemic therapy for locally advanced or metastatic disease (Stage IV) | |
|---|---|
| Cisplatin eligible | Preferred regimens<br>• Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11]<br>• DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11] |
| Cisplatin ineligible | Preferred regimens<br>• Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11]<br>• Atezolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)<br>• Pembrolizumab[14] (only for patients whose tumors express PD-L1[c] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)<br><br>Other recommended regimens<br>• Gemcitabine[15]<br>• Gemcitabine and paclitaxel[16]<br><br>Useful under certain circumstances<br>• Ifosfamide, doxorubicin, and gemcitabine[17] (for patients with good kidney function and good PS) |

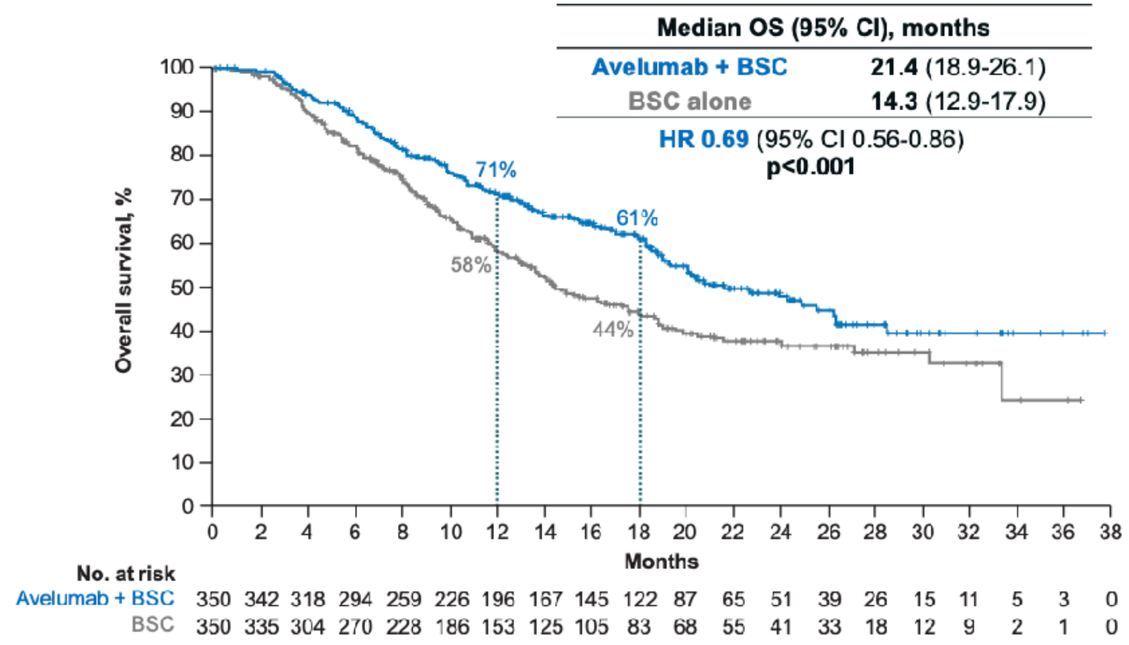
- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[18]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

[a] Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy.
[b] Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.
[c] Pembrolizumab: 22C3 antibody assay, Combined Positive Score (CPS) ≥10.

# The JAVELIN Bladder 100 international phase 3 trial evaluated avelumab 1L maintenance therapy[1]




## Avelumab 1L maintenance + BSC significantly prolonged OS in all patients compared with BSC alone, meeting the primary trial endpoint[1]

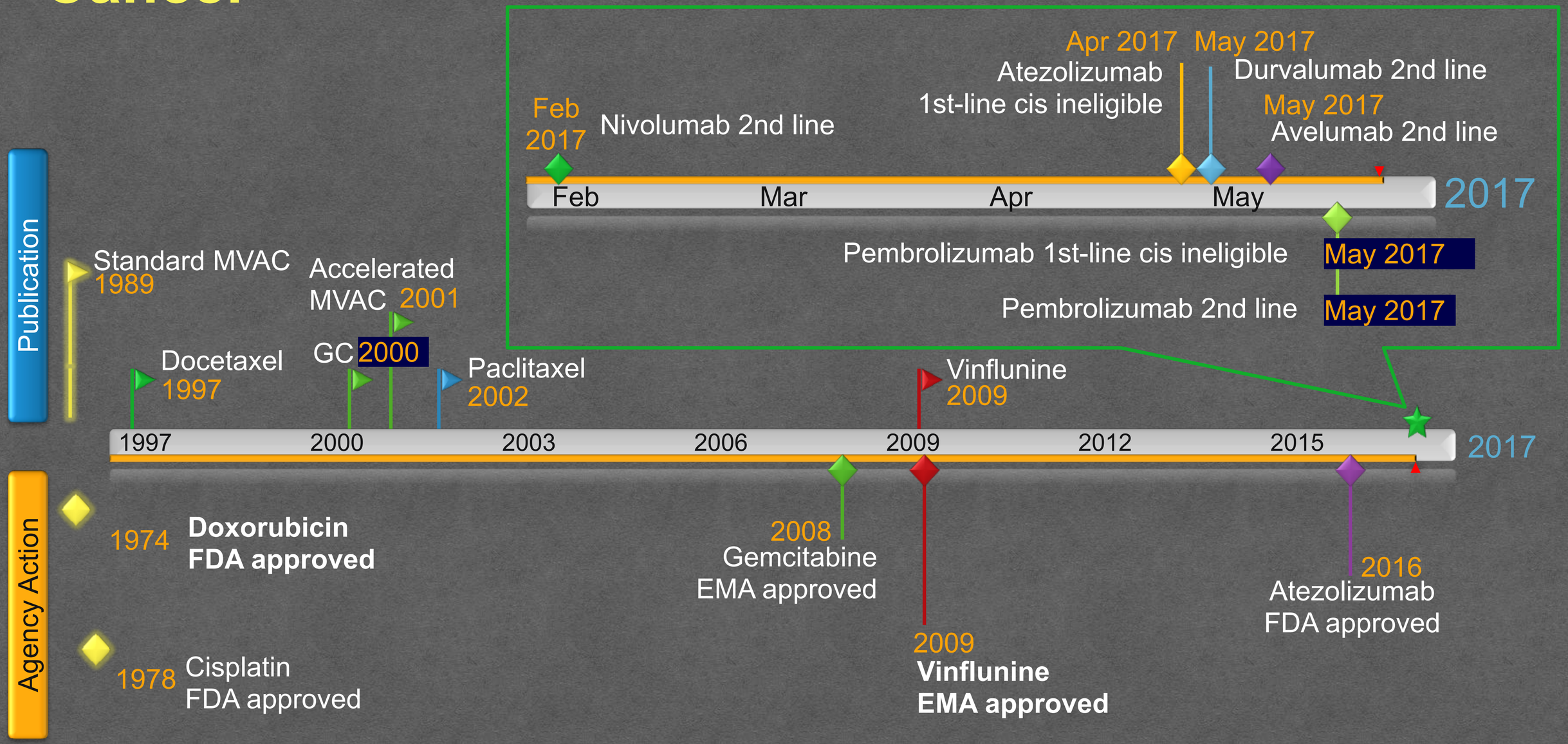



**In the overall population, the risk of death was reduced by 31% in the avelumab arm***

**71%** of patients were still alive at 12 months

OS was measured from the end of chemotherapy (post randomization)
BSC, best supportive care; OS, overall survival; UC, urothelial carcinoma
* Derived from the HR
1. Powles T, et al. N Engl J Med. 2020;383:1218-30. 2. Powles T, et al. J Clin Oncol. 2020;38(suppl):abstract LBA1 (ASCO 2020 oral presentation).

# Evolution of Systemic Therapy for Urothelial Cancer



# Bladder cancer is one of the most common cancers

## Bladder cancer incidence[1-3]

**10th most common cancer globally in 2018[1]**

| Estimated new cases | Estimated deaths |
|---|---|
| 548,393 | 199,922 |

**6th most common cancer in the Spain in 2020[3]**

| Estimated new cases | Estimated deaths |
|---|---|
| 22,300 | 4,400 |

## Bladder cancer risk factors[3,4]

| | |
|---|---|
| **AGE** | **>90% of cases** occur in individuals aged ≥55 years; median age at diagnosis is 73 years |
| **SEX** | **75% of cases** occur in men |
| **SMOKING** | **>3-fold** increased risk |
| **ETHNICITY** | **2-fold** higher incidence in whites vs African Americans and Hispanics |
| **GENETICS** | Family history of bladder cancer; genetic changes that affect toxin breakdown; tumor suppressor mutations |
| **CHEMICALS** | Exposure to specific chemicals in the workplace |
| **CHRONIC INFECTIONS** | Urinary infections; kidney and bladder stones |

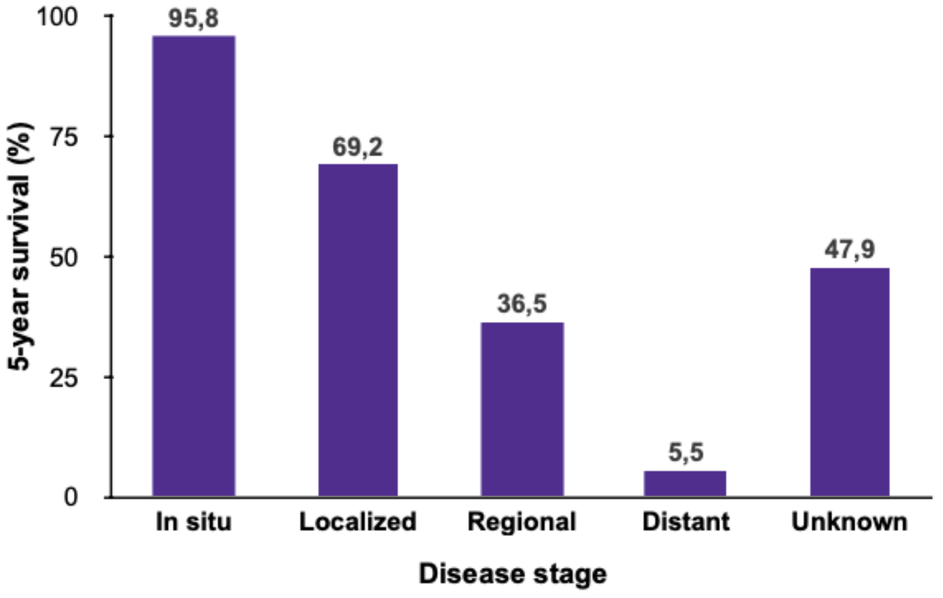
**UC is the most common type of bladder cancer, accounting for >90% of cases[3,5]**

UC, urothelial carcinoma; US, United States

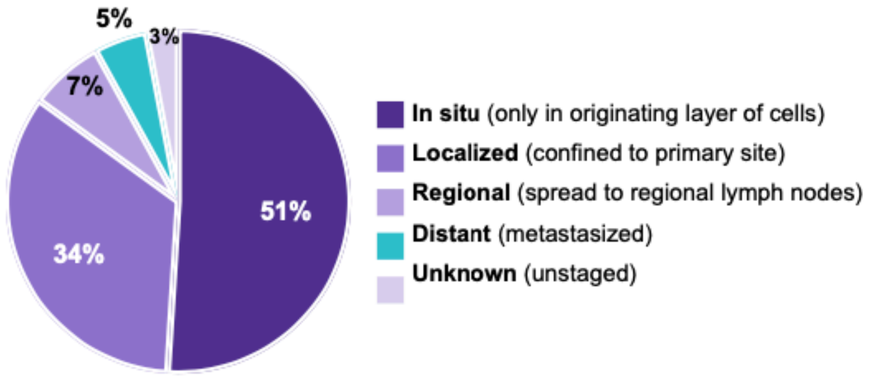
1. Bray F, et al. CA Cancer J Clin. 2018;68:394-424; 2. Siegel RL, et al. CA Cancer J Clin. 2019;69:7-34; 3.Informe SEOM. Cifras del cancer 2020; 4. Richters A, et al. World J Urol. 2020;38:1895-904; 5. NCCN Guidelines: Bladder Cancer, V6.2020. https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf.

# Patients with locally advanced or metastatic bladder cancer have very poor outcomes

**5-year survival rate for stage IV bladder cancer is <6%[1]**

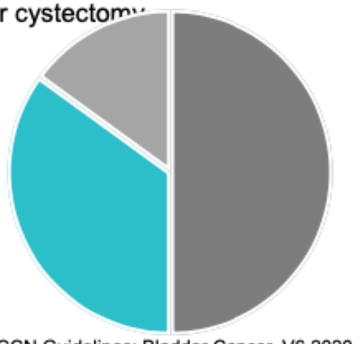



**≈5% have metastatic disease at diagnosis[1]**




**Metastatic relapse after cystectomy is common[2]**

**≈50%** of patients have relapse after cystectomy



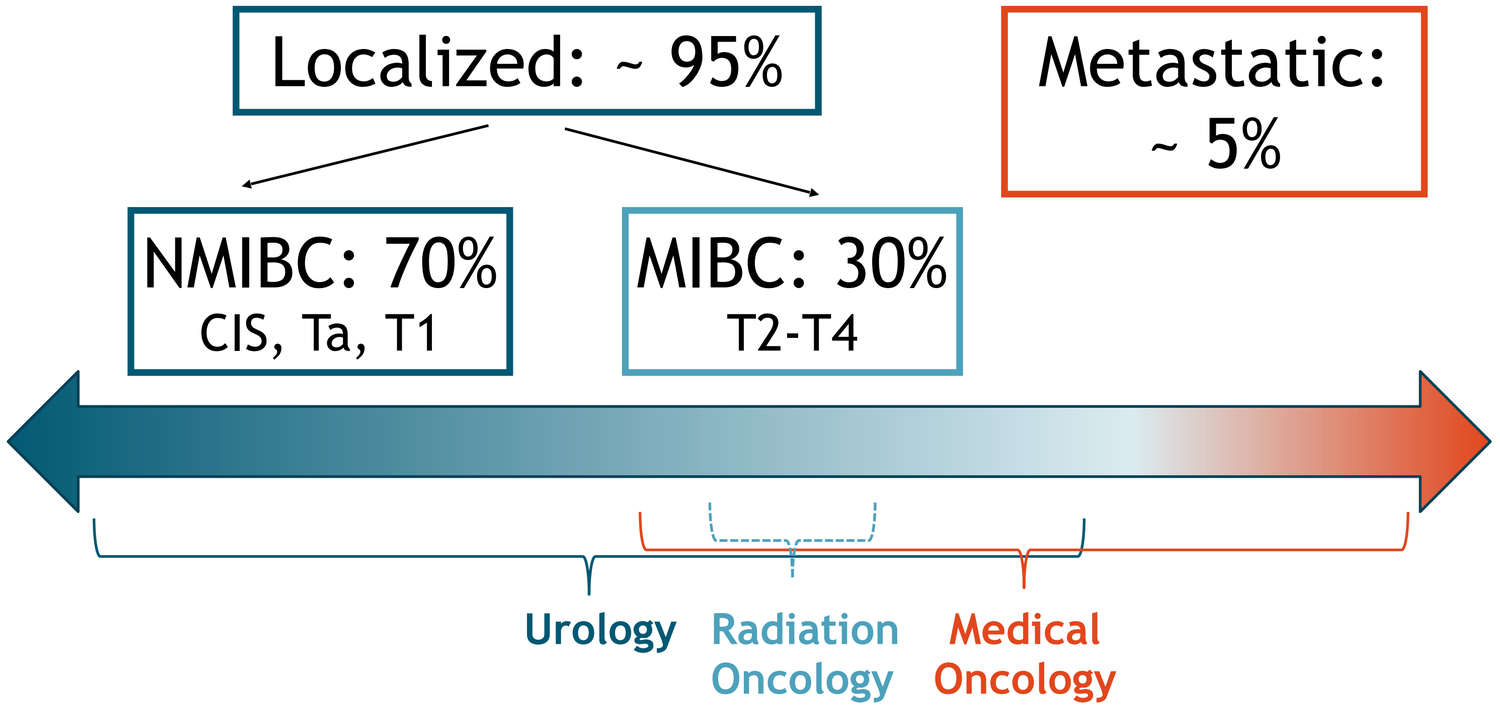
**≈70%-90%** of patients relapse with distant metastases

**Death rate from bladder cancer has remained unchanged for >15 years[1]**

1L, first-line; OS, overall survival

1. SEER research data 1975-2016. https://seer.cancer.gov/statfacts/html/urinb.html. Accessed Sep 17, 2020; 2. NCCN Guidelines: Bladder Cancer, V6.2020. https://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf.

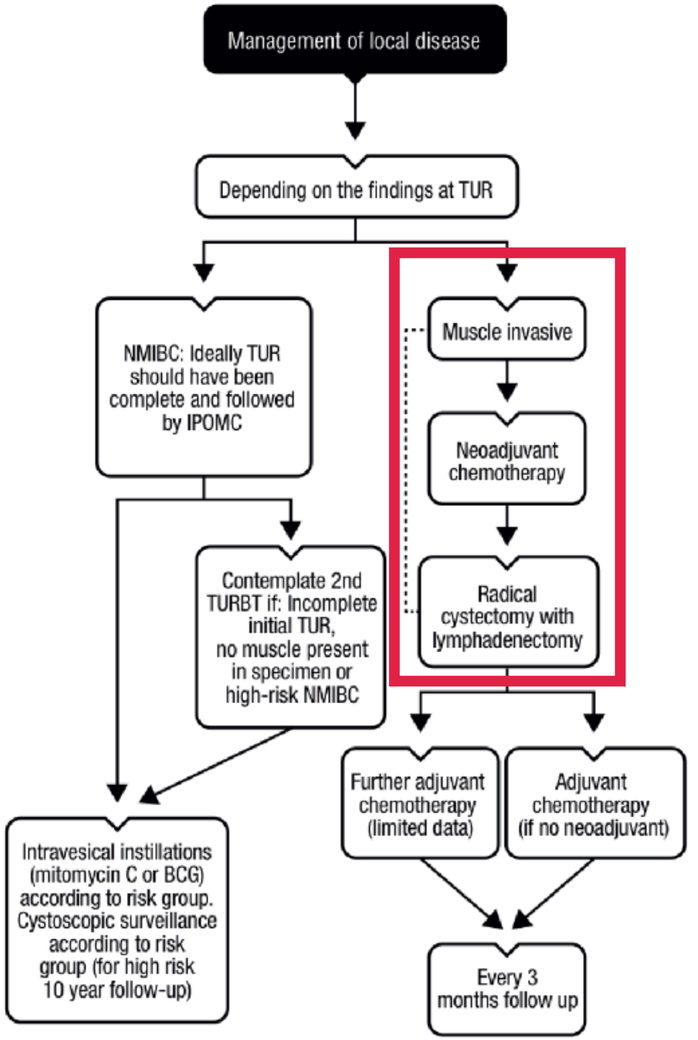
# Bladder Cancer: Spectrum of Disease



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology
Guidelines

## MANAGEMENT OF PATIENTS WITH LOCAL DISEASE

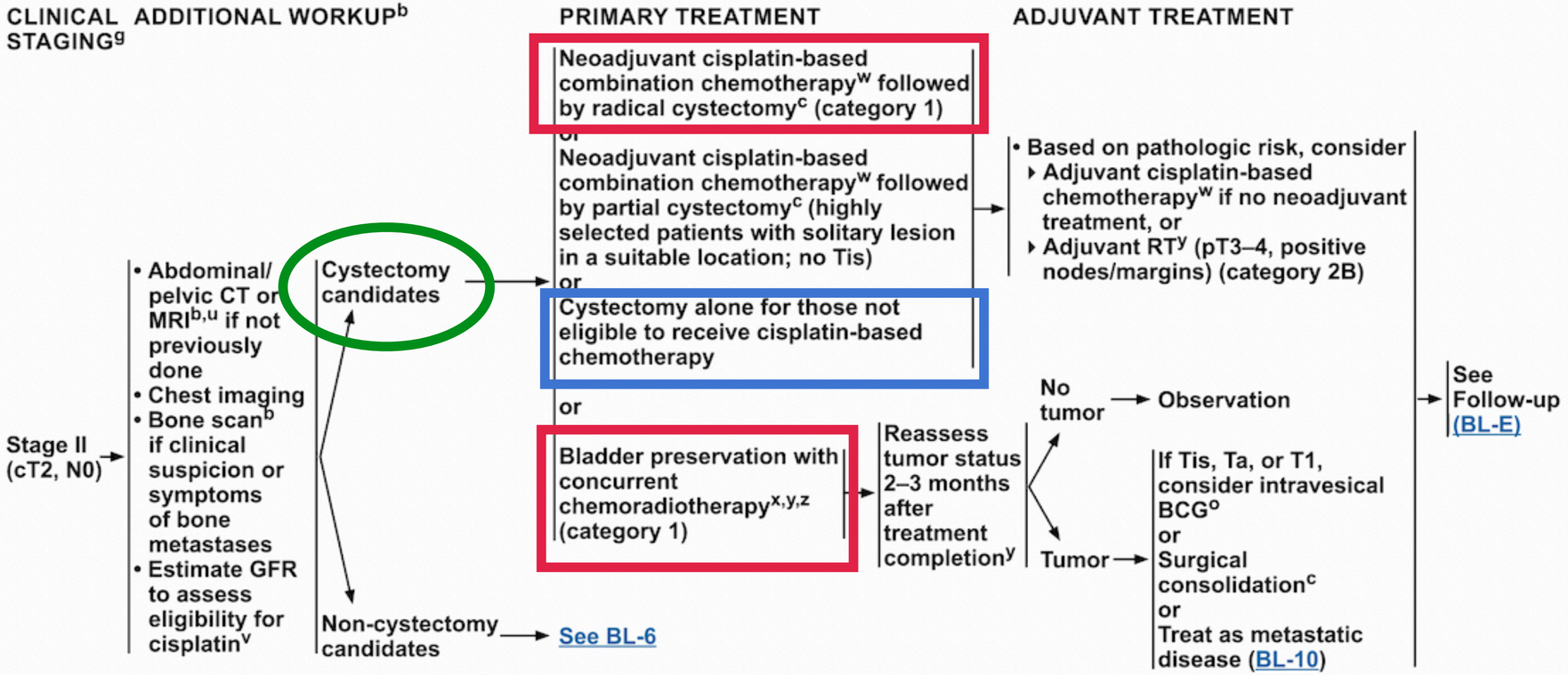



Denotes recommended therapy
Denotes optional therapy

BCG, Bacille Calmette-Guérin; IPOMC, immediate postoperative mitomycin C; NMIBC, non-muscle-invasive bladder cancer; TUR, transurethral resection; TURBT, transurethral resection of the bladder tumour

# NCCN Guidelines Version 3.2021
# Muscle Invasive Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion




[b] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[c] See Principles of Surgical Management (BL-B).
[g] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or transurethral resection), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
[o] See Principles of Intravesical Treatment (BL-F).
[u] Consider FDG-PET/CT scan (skull base to mid-thigh) (category 2B).
[v] For patients with borderline glomerular filtration rate (GFR) consider timed urine collection, which may more accurately determine eligibility for cisplatin.
[w] See Principles of Systemic Therapy (BL-G 1 of 7).
[x] See Principles of Systemic Therapy (BL-G 5 of 7).
[y] See Principles of Radiation Management of Invasive Disease (BL-H).
[z] Optimal candidates for bladder preservation with chemoradiotherapy include patients with tumors that present without moderate/severe hydronephrosis, are without concurrent extensive or multifocal Tis, and are <6 cm. Ideally, tumors should allow a visually complete or maximally debulking TURBT. See Principles of Radiation Management of Invasive Disease (BL-H).

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

See Recurrent or Persistent Disease (BL-11)

# Neoadjuvant Therapy for MIBC

Eligible for cisplatin-based therapy → Gemcitabine + Cisplatin or ddMVAC → Cystectomy

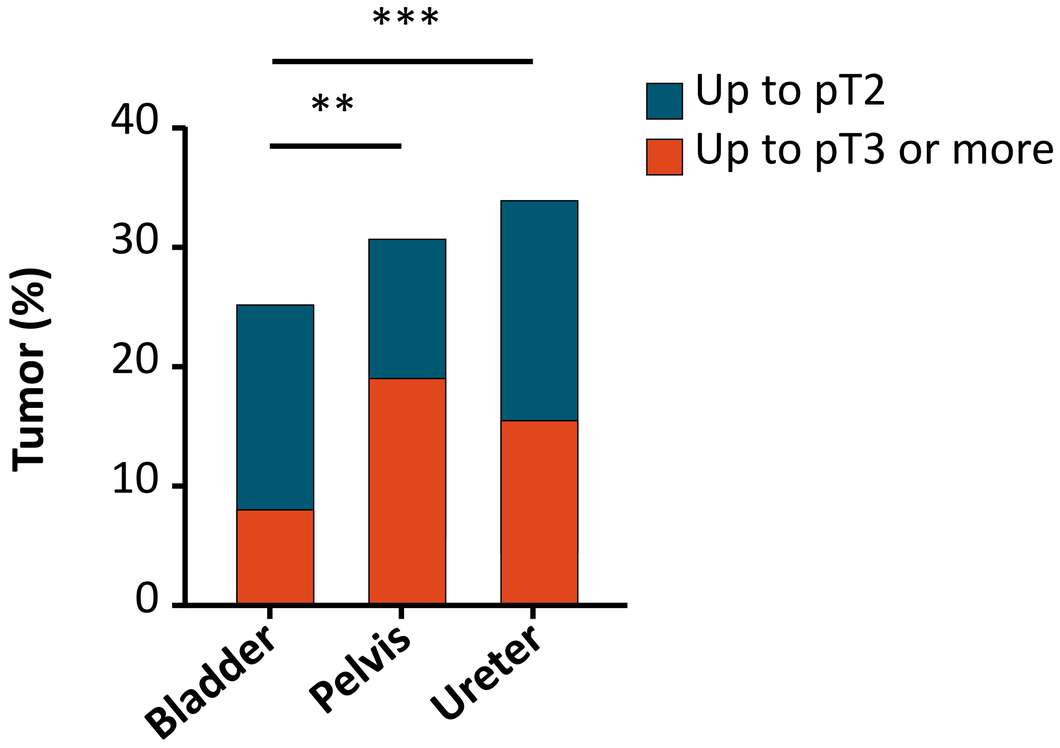
Ineligible for cisplatin-based therapy → Cystectomy

*Tabla 1: Ventajas y desventajas del empleo de quimioterapia adyuvante y neoadyuvante.*

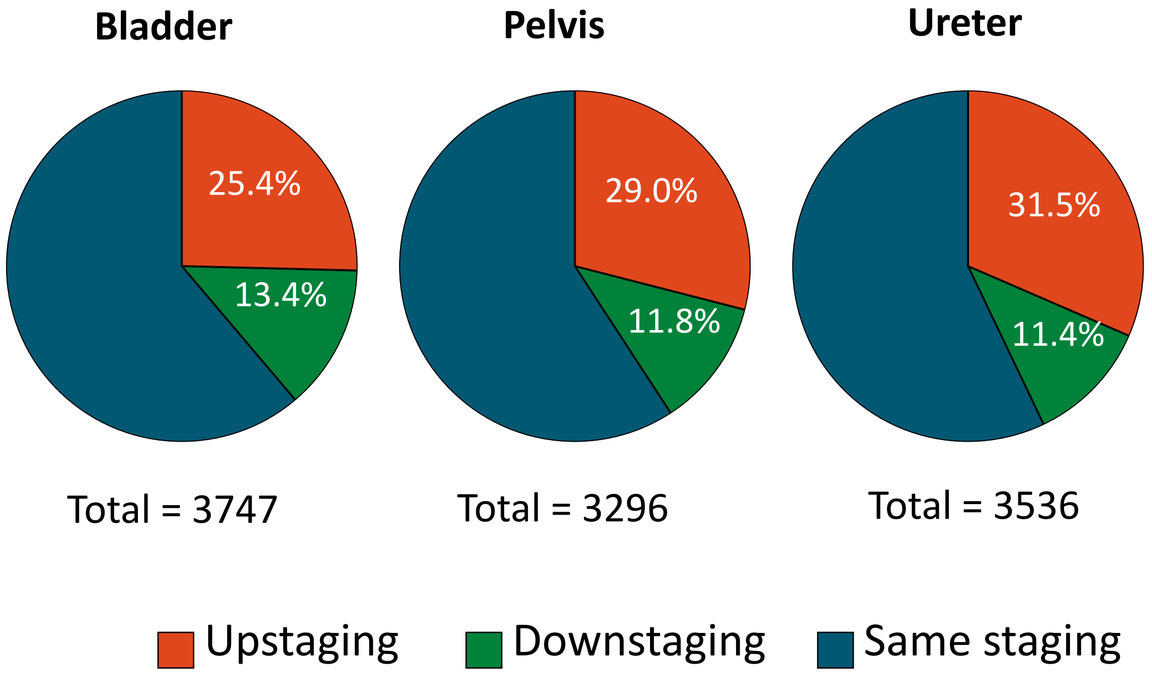
| | ADYUVANTE | NEOADYUVANTE |
|---|---|---|
| **VENTAJAS** | • Tratamiento temprano de la enfermedad micrometastática<br>• Indicación basada en el estadiaje patológico | • Tratamiento mas temprano de la enfermedad micrometastática<br>• Valoración "in vivo" de la respuesta a la quimioterapia<br>• Preservación vesical<br>• Conversión de tumores avanzados en resecables<br>• Importancia pronóstica de la respuesta a la quimioterapia |
| **DESVENTAJAS** | • Peor tolerancia a la quimioterapia<br>• Riesgo de crecimiento tumoral acelerado post-cistectomía<br>• Inexistencia de óptimos marcadores de riesgo pronóstico | • Indicación basada en el estadiaje clínico<br>• Retraso del tratamiento local<br>• Riesgo de nuevos tumores en vejigas preservadas<br>• Inexistencia de óptimos marcadores de riesgo pronóstico |

# UC is Often Upstaged

**Upstaging From Clinical Non-Muscle-Invasive (≤cT1) to Pathological Muscle-invasive Cancer (≥pT2)**




**Proportion of Overall T-Stage Discrepancies: Urothelial Cancers of the Bladder, Pelvis, and Ureter**




Shiga. Int J Urol 2021;28:814.

*Tabla 2: Estudios randomizados con quimioterapia adyuvante en el CVI.*

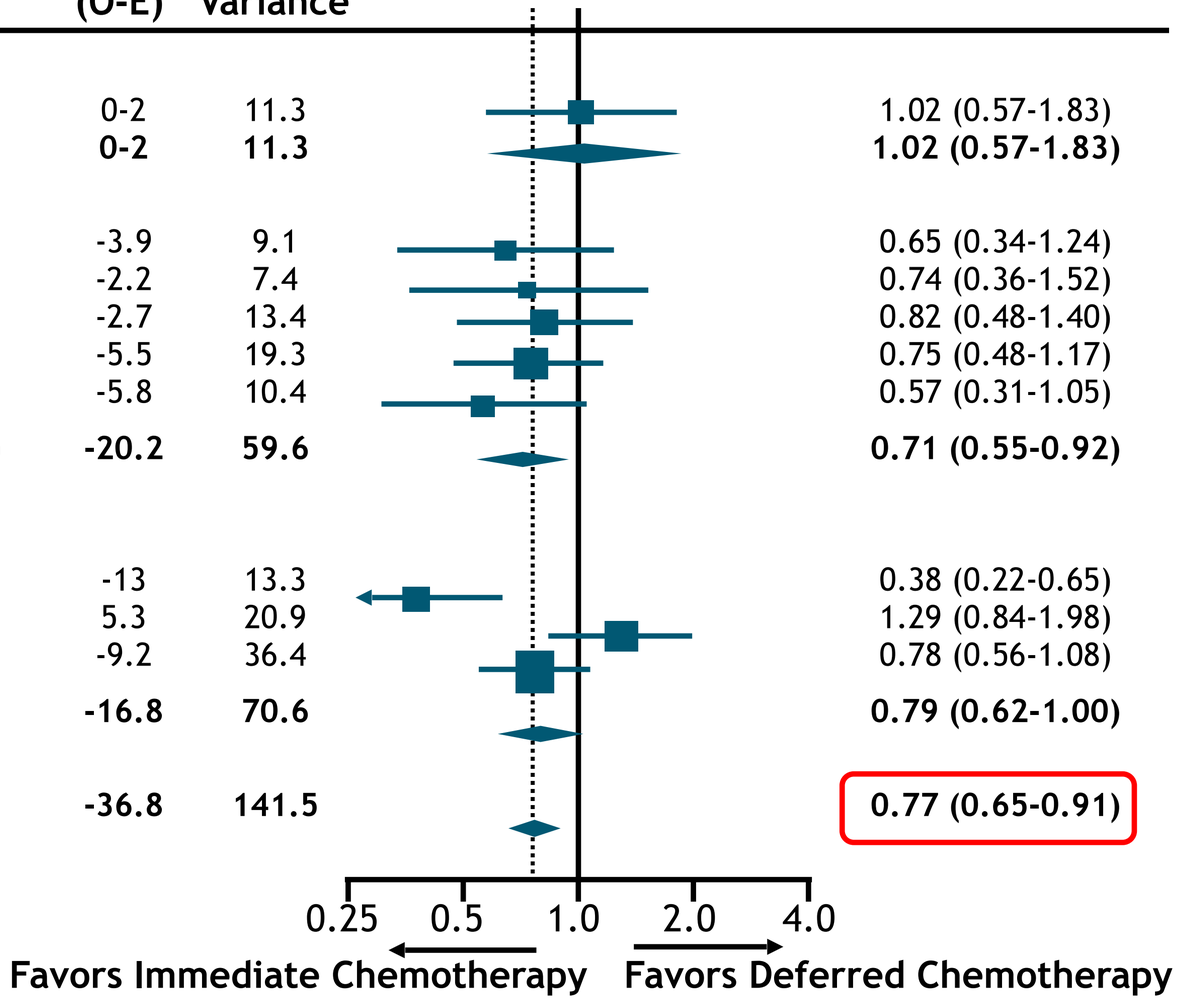
| AUTOR | ESTADIO | N° PACIENTES | TTO Local | SLE | SG |
|---|---|---|---|---|---|
| Richards [3] | cT3,Nx,Mo | 129 | RT<br>RT+5FU-ADM | | 35% (5a)<br>37% (5a) |
| Studer [4] | pTa-T2,N+,Mo | 77 | Cistectomia<br>Cistectomia+CDDP | | 54% (5a)<br>57% (5a) |
| Skinner [5] | pT3-T4,Nx,Mo | 91 | Cistectomía<br>Cistectomia+CISCA | 46% (3a)<br>70% (3a) * | 46% (5a)<br>70% (5a) |
| Stockle [6] | pT3b-T4a,N+,Mo | 49 | Cistectomía<br>Cistectomía+MVAC | 19% (3a)<br>73% (3a) * | 0% (3a)<br>63% (3a) |
| Freiha [7] | pT3b-T4a,N+,Mo | 55 | Cistectomía<br>Cistectomía+CMV | 44% (3a)<br>65% (3a) * | 40% (5a)<br>38% (5a) |

PTS: pacientes; QT: quimioterapia; TTO: tratamiento; SLE: supervivencia libre de enfermedad; SG: supervivencia global; MTX: metotrexate; CDDP: Cisplatino; RT: Radioterapia; CX: cistectomía; *: diferencia estadísticamente significativa (p< 0.05).


3. Richards B, Bastable JRG, Freedman L, et al: Adjuvant chemotherapy with doxorubicin and 5-fluorouracil in T3,NX,MO bladder cancer treated with radiotherapy. Br J Urol 55: 386-391, 1983.
4. Studer UE, Bacchi M, Biederman C, et al: Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 152: 81-84, 1994.
5. Skinner DG, Daniels JR, Russell CA, et al: The role of adjuvant chemotherapy following cystectomy for invasive bladder carcinoma: A prospective comparative trial. J Urol 145:459-467, 1991.
6. Stockle M, Meyenburg W, Wellek S, et al: Advanced bladder cancer (stages pT3b, pT4a, pN1, and pN2): Improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. J Urol 148: 302-307, 1992.
7. Freiha F, Reese J and Torti FM: A randomized trial of radical cystectomy vs radical cystectomy plus cisplatin, vinblastine and methtrexate (CMV) chemotherapy for muscle invasive bladder cancer. J Urol 155: 495-500, 1996.

# Updated Meta-analysis of Adjuvant CT

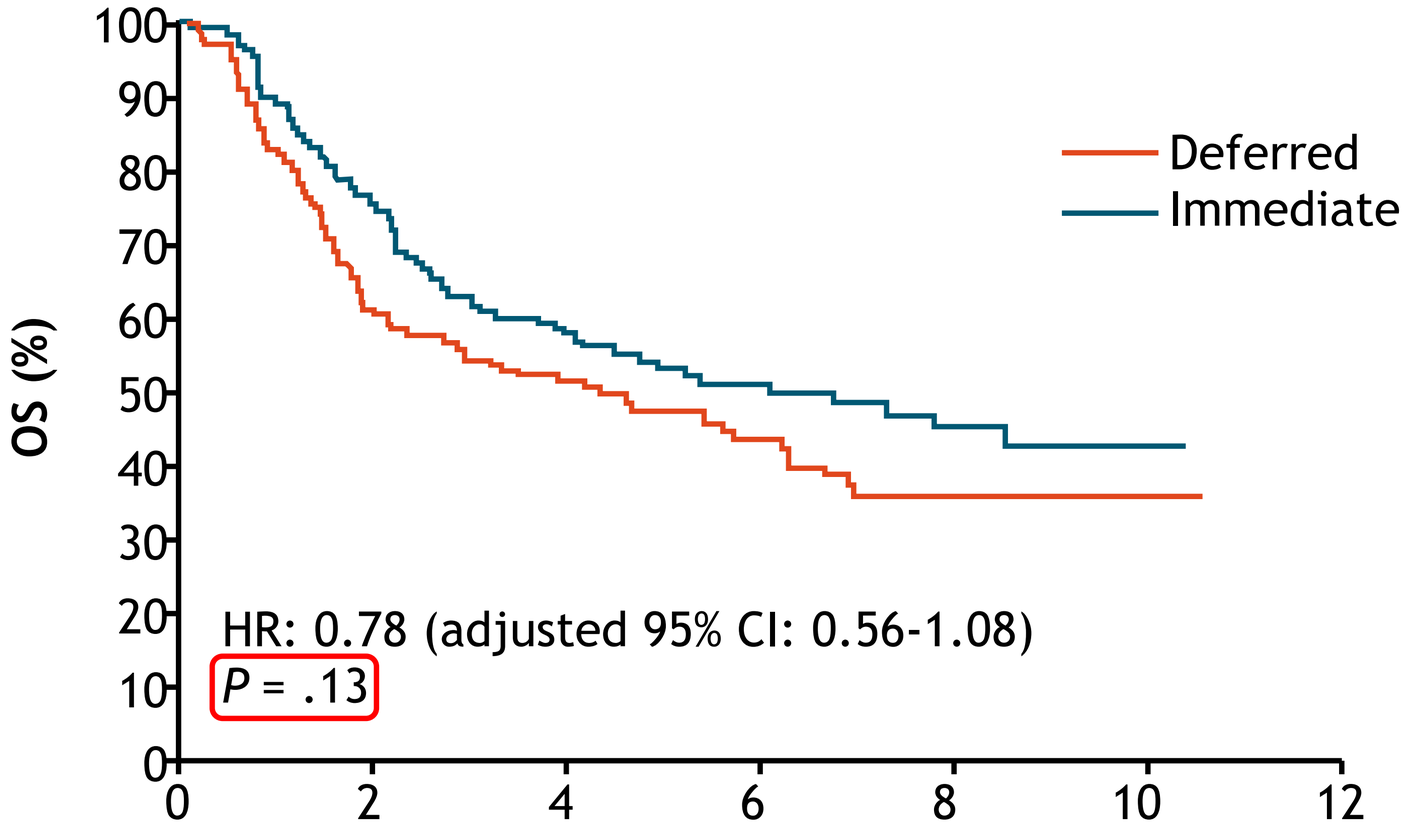
| | Events/Patients | | Statistics | | HR (95% CI) |
|---|---|---|---|---|---|
| | Adjuvant Chemotherapy | Control | (O-E) | Variance | |
| **Single-agent cisplatin** | | | | | |
| Studer et al, 1994 | 23/46 | 22/45 | 0-2 | 11.3 | 1.02 (0.57-1.83) |
| **Subtotal** | **23/46 (50%)** | **22/45 (48.9%)** | **0-2** | **11.3** | **1.02 (0.57-1.83)** |
| **Cisplatin combinations** | | | | | |
| Bono et al, 1997 | 43/14 | 47/23 | -3.9 | 9.1 | 0.65 (0.34-1.24) |
| Freiha et al, 1996 | 24/13 | 28/17 | -2.2 | 7.4 | 0.74 (0.36-1.52) |
| Otto et al, 2003 | 55/28 | 53/29 | -2.7 | 13.4 | 0.82 (0.48-1.40) |
| Skinner et al, 1991 | 50/34 | 52/40 | -5.5 | 19.3 | 0.75 (0.48-1.17) |
| Lehmann et al, 2006 | 26/20 | 23/20 | -5.8 | 10.4 | 0.57 (0.31-1.05) |
| **Subtotal** | **201/109 (184.4%)** | **203/129 (157.4%)** | **-20.2** | **59.6** | **0.71 (0.55-0.92)** |
| Heterogeneity $x^2 = 0.92$, df = 4; *P* = .92 | | | | | |
| **Gemcitabine plus cisplatin** | | | | | |
| Paz-Ares et al, 2010 | 24/68 | 45/74 | -13 | 13.3 | 0.38 (0.22-0.65) |
| Cognetti et al, 2012 | 46/102 | 38/92 | 5.3 | 20.9 | 1.29 (0.84-1.98) |
| EORTC 30994 trial | 66/141 | 82/143 | -9.2 | 36.4 | 0.78 (0.56-1.08) |
| **Subtotal** | **136/311 (43.7%)** | **165/309 (53.4%)** | **-16.8** | **70.6** | **0.79 (0.62-1.00)** |
| Heterogeneity $x^2 = 12.27$, df = 2; *P* = .002 | | | | | |
| **Total** | **360/466 (77.3%)** | **390/483 (80.7%)** | **-36.8** | **141.5** | **0.77 (0.65-0.91)** |
| Test for heterogeneity $x^2 = 14.49$, df = 8; *P* = .07 | | | | | |




Sternberg CN, et al. Lancet Oncol. 2015;16:76-86.

# EORTC 30994: Immediate vs Deferred Adjuvant CT

- No difference in OS between arms



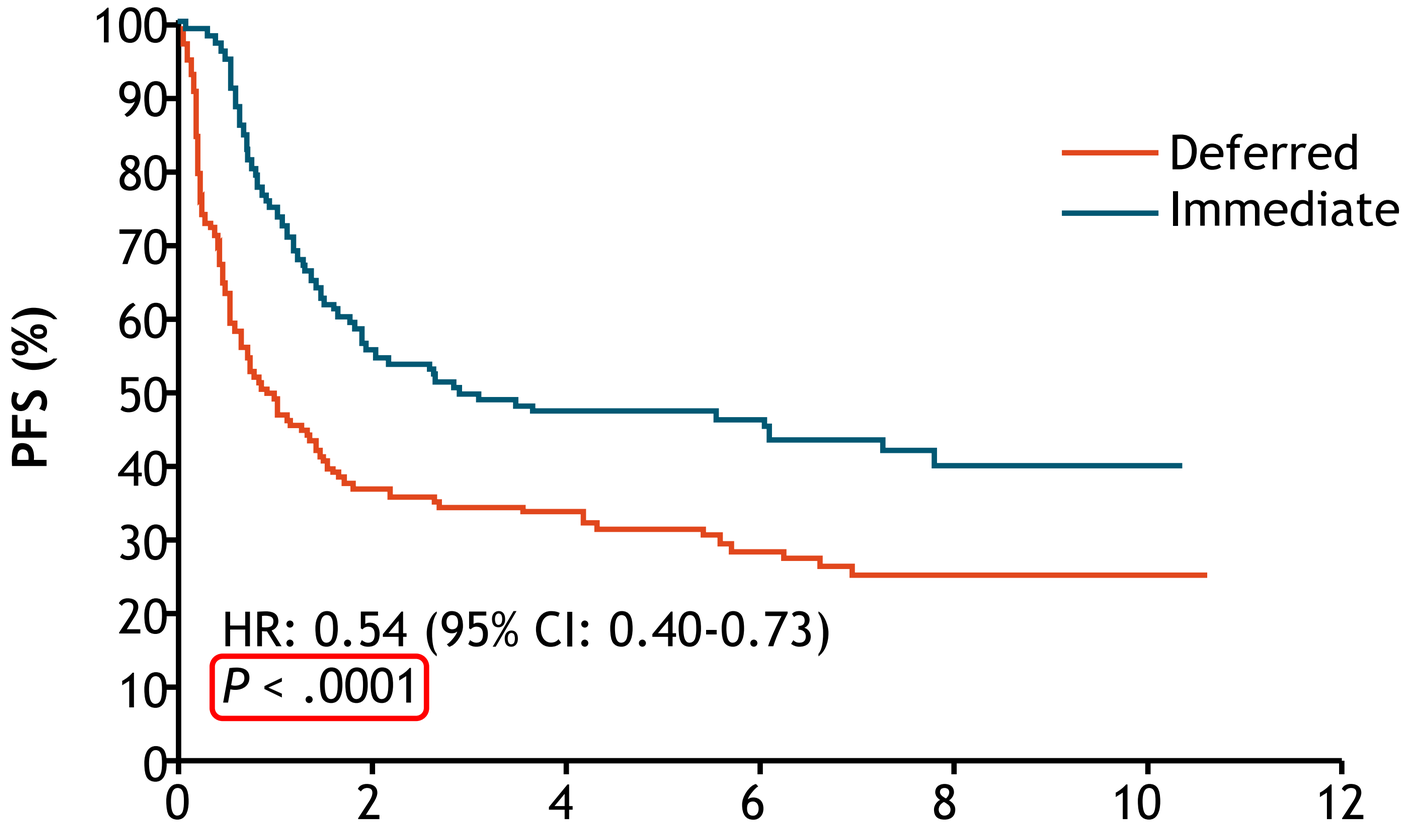

**Number at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Deferred | 143 | 83 | 67 | 42 | 21 | 4 |
| Immediate | 141 | 95 | 70 | 44 | 25 | 3 |

Sternberg CN, et al. Lancet Oncol. 2015;16:76-86.

# EORTC 30994: Immediate vs Deferred Adjuvant CT

- Improved PFS with immediate vs deferred adjuvant CT




| Patients at Risk, n | | | | | | |
|---|---|---|---|---|---|---|
| Deferred | 143 | 51 | 45 | 31 | 18 | 4 |
| Immediate | 141 | 71 | 57 | 40 | 21 | 3 |

Sternberg CN, et al. Lancet Oncol. 2015;16:76-86.

*Tabla 3: Estudios randomizados con quimioterapia neoadyuvante en el CVI.*

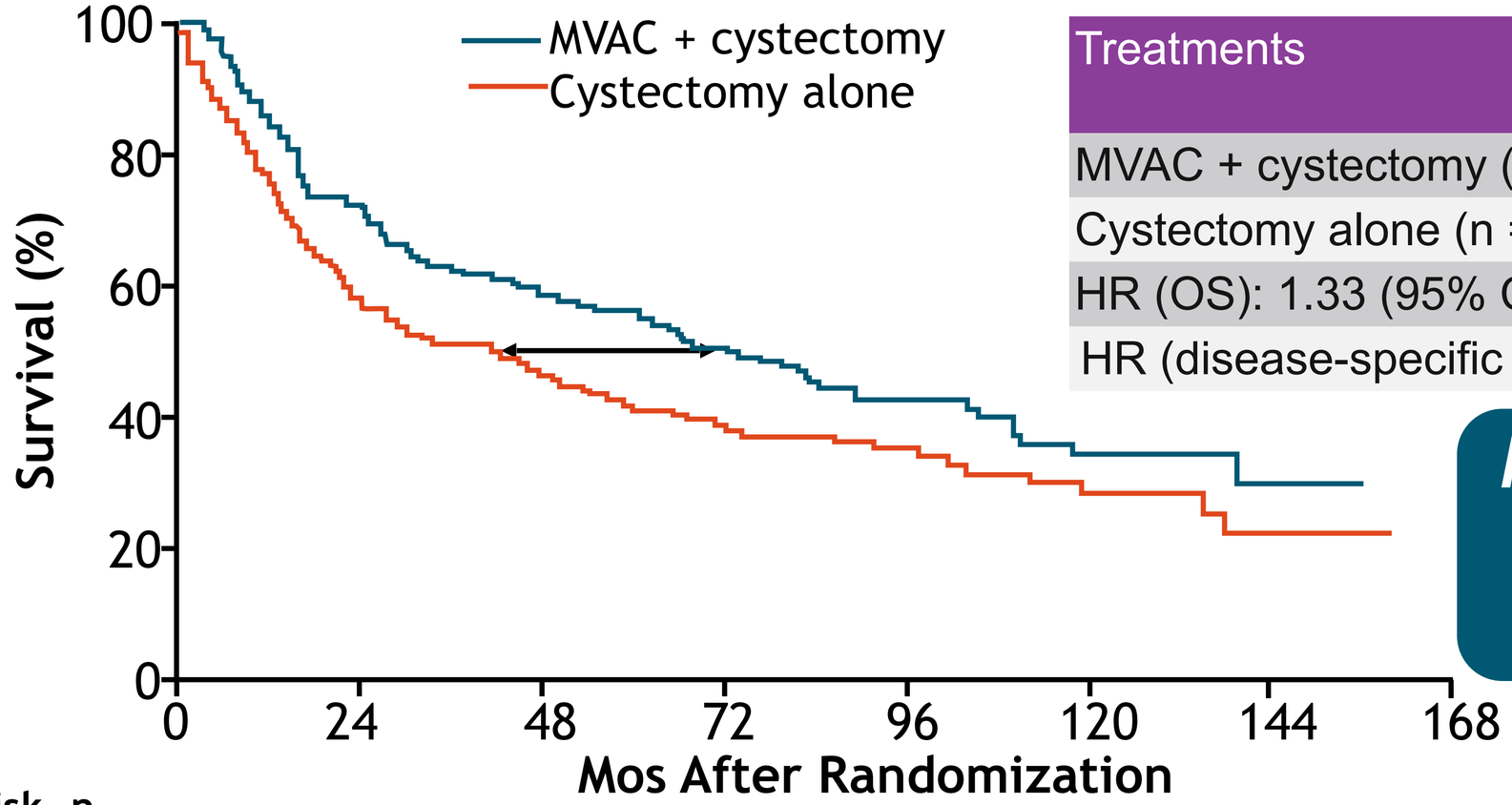
| AUTOR | ESTADIO | Nº PTS | QT | TTO LOCAL | SG |
|---|---|---|---|---|---|
| Shearer [8] | cT3NxMo | 376 | MTX<br>- | RT + CX<br>RT + CX | 39% (3a)<br>37% (3a) |
| Wallace [9] | cT2-T4NxMo | 255 | CDDP<br>- | RT<br>RT | 39% (3a)<br>40% (3a) |
| Martínez-Piñeiro [10] | cT2-T4NxMo | 122 | CDDP<br>- | CX<br>CX | 41% (5a)<br>41% (5a) |
| Rintala [11] | cT1 (grado 3)<br>ó cT2-T4NxMo | 311 | CDDP+ADM<br>- | RT + CX<br>RT + CX | 55% (5a)*<br>45% (5a) |
| Hall [12] | cT2 (grado ) 3<br>CT3-T4 $N_{0-x}$ $M_0$ | 976 | CMV<br>- | RT/CX<br>RT/CX | 55.5% (5a)<br>50% (5a) |
| Natale [13] | cT2-T4NxMo | 317 | MVAC<br>- | CX<br>CX | 6.2a (med)*<br>3.8a (med) |

PTS: pacientes; QT: quimioterapia; TTO: tratamiento; S. Global: supervivencia global; MTX: metotrexate; CDDP: Cisplatino; RT: Radioterapia; CX: cistectomía; *: diferencia estadisticamente significativa (p< 0.05).


8. Shearer RJ, Chilvers CED, Bloom HJG, et al: Adjuvant chemotherapy in T3 carcinoma of the bladder: A prospective trial: Preliminary report. Br J Urol 62: 558-564, 1988.
9. Wallace DMA, Rhavagan D, Kelly KA, et al: Neoadjuvant chemotherapy (pre-emptive) cisplatin therapy in invasive transitional carcinoma of the bladder. Br J Urol 67: 608-615, 1995.
10. Martinez-Piñeiro JA, Gonzalez-Martin M, Arocena F, et al: Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: A prospective randomized phase III study. J Urol 153: 964-973, 1995.
11. Rintala E, Hannisdal E, Fossa SD, et al: Neoadjuvant chemotherapy in bladder cancer: A randomised study. Nordic Cystectomy trial. Scand J Urol Nephrol 27: 355-362, 1993.
12. Neoadjuvant cisplatin, methotrexate, and vinblatine chamotherapy for muscle-invasive bladder cancer: a randomised controlled trial (Intergroup study). Lancet 1999; vol 354, pg 533-40.
13. Natale R, Grossman H, Blumenstein B, et al. SWOG 8710 (INT-0080): Randomized phase trial of neoadjuvant MVAC + cyatectomy versus cystectomy alone in patients with locally advanced bladder cancer. Proc Am Soc Clin Oncol 20:2ª, 2001 (abstratc 3).

# SWOG-8710: Neoadjuvant CT Is Standard of Care for Muscle-Invasive Bladder Cancer

- **Phase III Intergroup trial of 3 cycles of MVAC followed by radical cystectomy vs immediate radical cystectomy (N = 317)**




| Treatments | Median OS, Mos |
|---|---|
| MVAC + cystectomy (n = 153) | 77 |
| Cystectomy alone (n = 154) | 46 |
| HR (OS): 1.33 (95% CI: 1.00-1.76; *P* = .06) | |
| HR (disease-specific survival): 1.66 (*P* = .002) | |

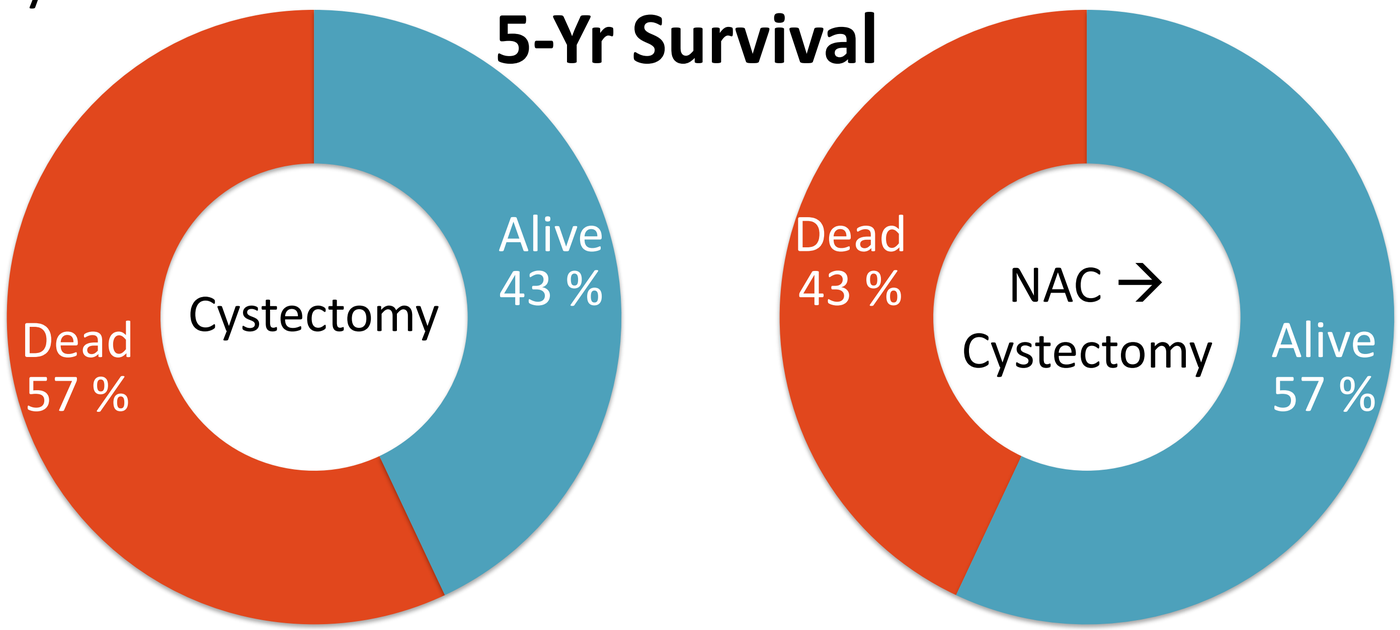
**Median OS Benefit: 2.6 yrs**

| Patients at Risk, n | | | | | | | |
|---|---|---|---|---|---|---|---|
| MVAC + cystectomy | 153 | 112 | 92 | 75 | 46 | 23 | 6 |
| Cystectomy alone | 154 | 88 | 67 | 50 | 37 | 18 | 7 |

Grossman HB, et al. N Engl J Med. 2003;349:859-866.

# The Treatment for Muscle-Invasive Bladder Cancer (MIBC) is Life-Altering

- Survival of patients with MIBC remains suboptimal despite neoadjuvant chemotherapy and cystectomy

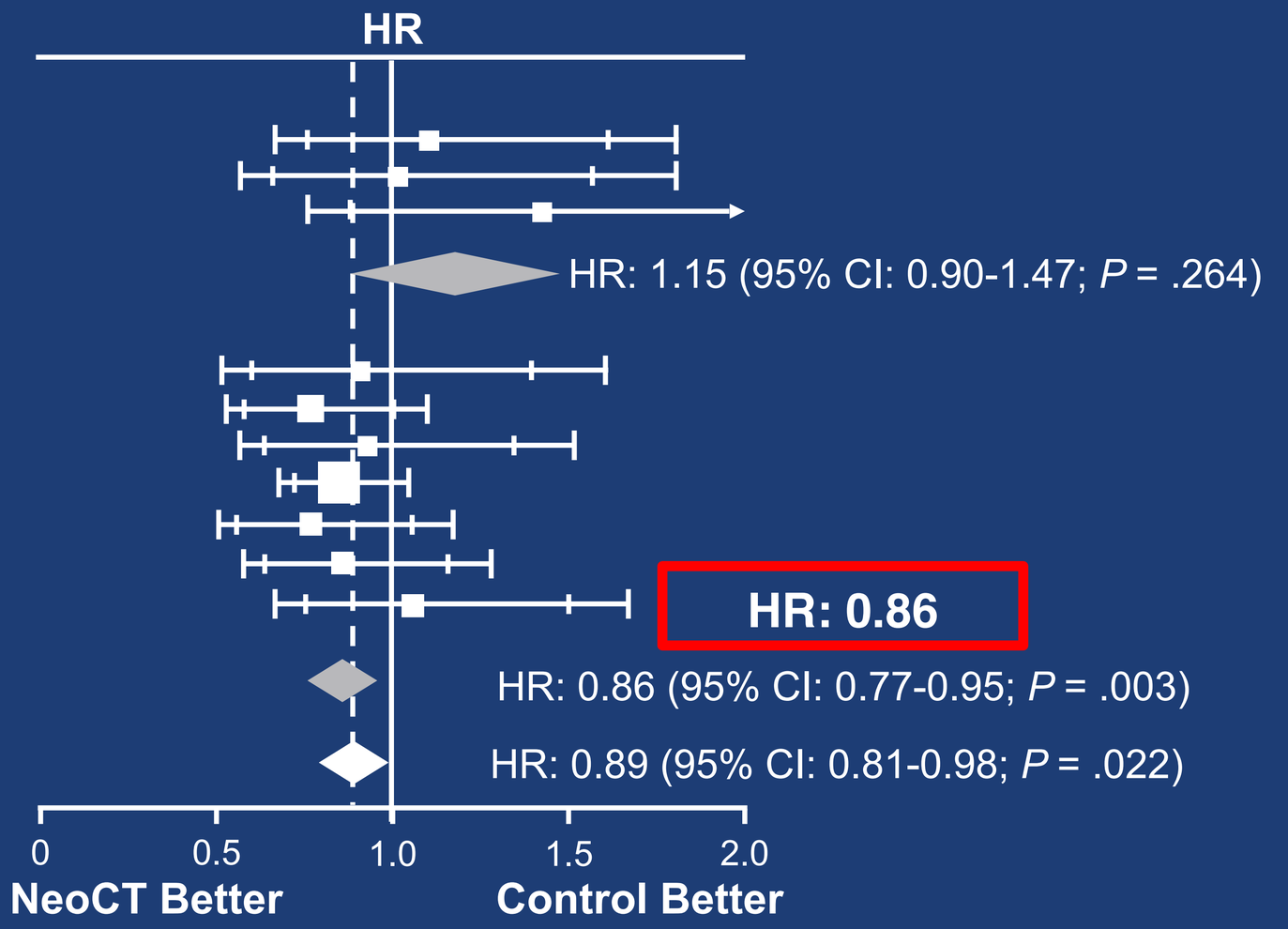



- Neoadjuvant cisplatin-based chemotherapy is underutilized: approximately 15%-17% of patients currently (2003)receive NAC → cystectomy

Grossman. NEJM. 2003;349:859.

# ABC Meta-analysis of Neoadjuvant Cisplatin-Based Chemotherapy vs Local Treatment Alone

| | No. Events/No. Entered | | | |
|---|---|---|---|---|
| | CT | Control | O-E | Variance |
| Single-agent platinum | | | | |
| Wallace | 59/83 | 50/76 | 2.74 | 27.18 |
| Martinez-Pineiro | 43/62 | 38/59 | 0.33 | 20.11 |
| Raghavan | 34/41 | 37/55 | 5.85 | 16.51 |
| **Subtotal** | 136/186 | 125/190 | 8.92 | 63.80 |
| Platinum-based combinations | | | | |
| Cortesi unpublished | 43/82 | 41/71 | -1.87 | 20.84 |
| Grossman | 98/158 | 108/159 | -13.61 | 51.00 |
| Bassi | 53/102 | 60/104 | -1.95 | 28.13 |
| MRC/EORTC | 273/491 | 301/485 | -23.69 | 143.61 |
| Malmstrōm | 68/151 | 84/160 | -9.97 | 37.94 |
| Sherif | 79/158 | 90/159 | -6.37 | 42.18 |
| Sengeløv | 70/78 | 60/75 | 1.79 | 31.96 |
| **Subtotal** | 686/1220 | 744/1213 | -55.67 | 355.65 |
| **Total** | 882/1406 | 869/1403 | -46.75 | 419.45 |




Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol. 2005;48:202-205.

# Potential Attributes of Neoadjuvant Therapy


Pre- and posttherapy tissue

Response in primary

# Cisplatin-Based Neoadjuvant CT

**40% to 60% have significant residual bladder cancer (≥ T2) after neoadjuvant CT**

| Characteristi | Gem/Cis[1] (n = 42) | Gem/Cis[2] (n = 154) | DD Gem/Cis[3] (n = 31) | DD Gem/Cis[4] (n = 46) | AMVAC[5] (n = 80) | AMVAC[6] (n = 40) | DD MVAC[7] (n = 39) |
|---|---|---|---|---|---|---|---|
| Study type | rospective | Retrospective | Prospective | Prospective | Retrospective | Prospective | Prospective |
| Cycles, n | 4 | 4 | 3 | 6 | 3-4 | 3 | 4 |
| Wks, n | 12 | 12 | 6 | 12 | 6-8 | 6 | 8 |
| pCR (pT0), % | 26 | 21 | 32 | 15 | 43 | 38 | 26 |
| PR (< pT2), % | 36 | 46 | 45 | 57 | ~ 61 | 53 | 49 |
| Median days from CT start to surgery | 138 | 120 | 65 | ~ 114+ | 75 | 68 | ~ 98 |
| Grade 3/4 AEs, % | NR | NR | 35 | 37 | 27 | 18 | 10 |
| Progression free at 2 yrs, % | 64 | ~ 68 | ~ 68 | ~ 76 | 65 | 78 | ~ 47 |
| Alive at 2 yrs,* % | 73 | ~ 75 | ~ 77 | ~ 87 | 77 | 83 | ≤ 80 |

pT0 Rates With CT:

Gem/Cis, 15% to 32%

DD MVAC, 26% to 43%

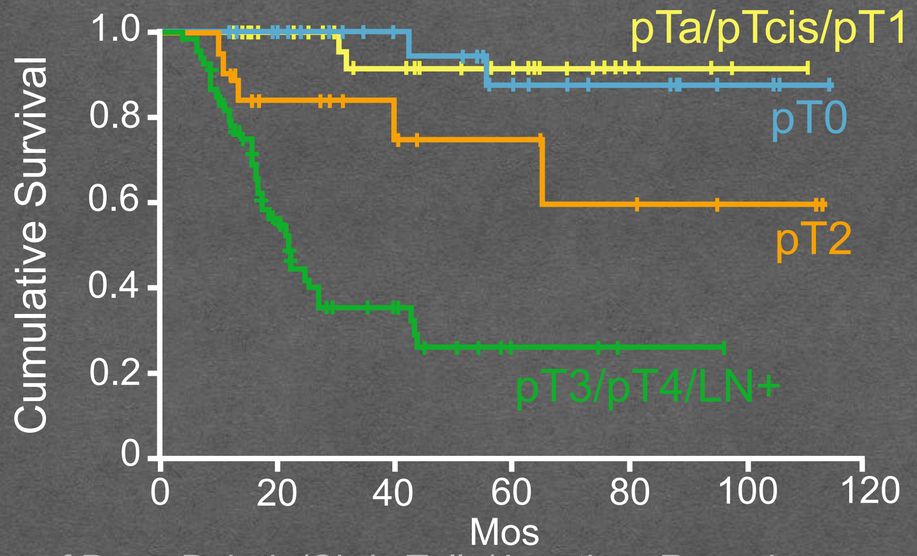
*vs 58% with cystectomy alone.

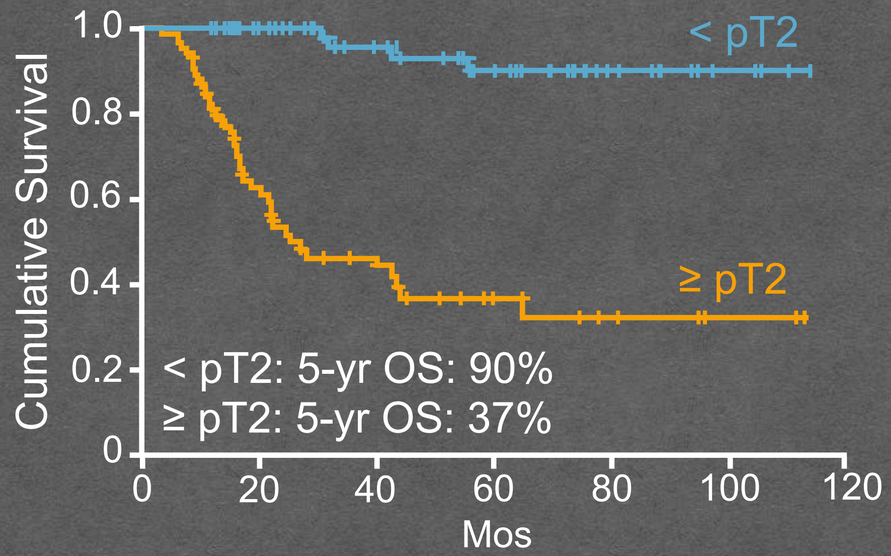

1. Dash A, et al. Cancer. 2008;113:2471-2477. 2. Tully CM, et al. ASCO GU 2014. Abstract 355.
3. Anari F, et al. Eur Urol Oncol. 2018;1:54-60. 4. Iyer G, et al. J Clin Oncol. 2018;36:1949-1956.
5. Blick C, et al. Cancer. 2012;118:3920-3927. 6. Plimack ER, et al. J Clin Oncol. 2014;32:1895-1901.
7. Choueiri TK, et al. J Clin Oncol. 2014;32:1889-1894.

# Pathologic Down-Staging Associated With High Cure Rates

| Pathologic Stage | SWOG 8710 (n = 126) | MSK (n = 154) | Dash et al (n = 42) | Yeshchina et al (n = 37) | Choueiri et al (n = 39) | Plimack et al (n = 44) |
|---|---|---|---|---|---|---|
| Regimen | MVAC | GC | GC | GC | ddMVAC | ddMVAC |
| pT0N0, % | 38 | 20 | 26 | 25 | 26 | 38 |
| < pT2N0, % | 44 | 44 | 36 | 50 | 49 | 53 |
| ≥ pT2, % | 56 | 56 | 64 | 50 | 51 | 47 |

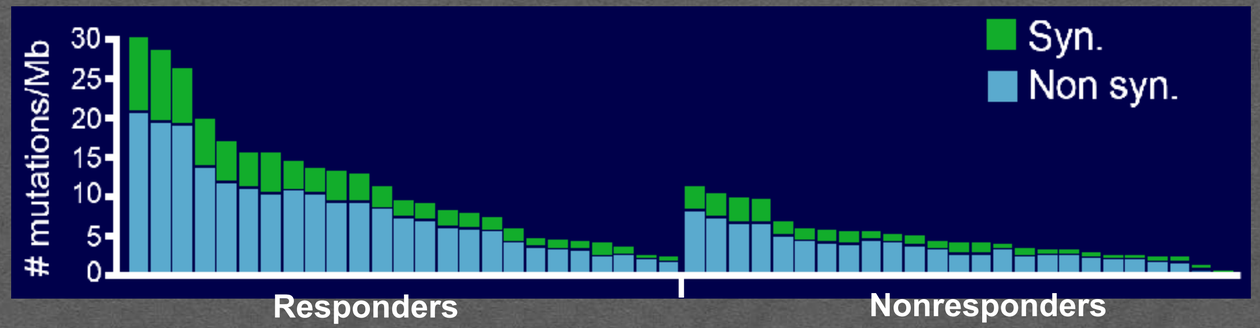
< pT2 = superficial, nonmuscle-invasive disease (pTa, pTis, pT1)



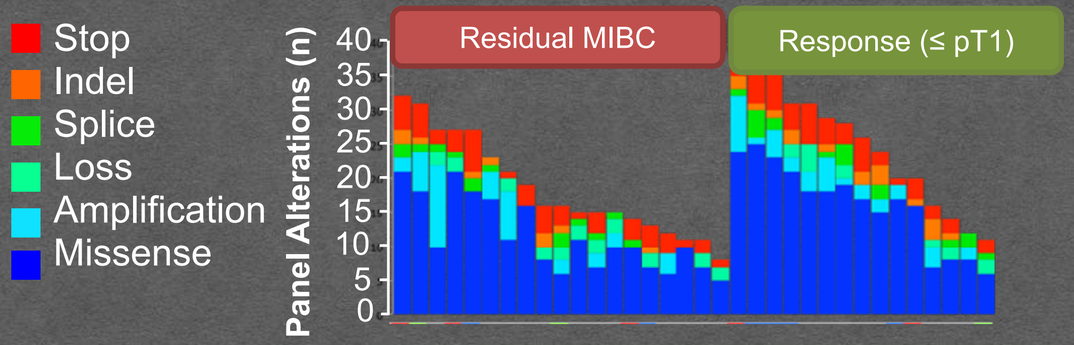




Courtesy of Dean Bajorin/Chris Tully/Jonathan Rosenberg.

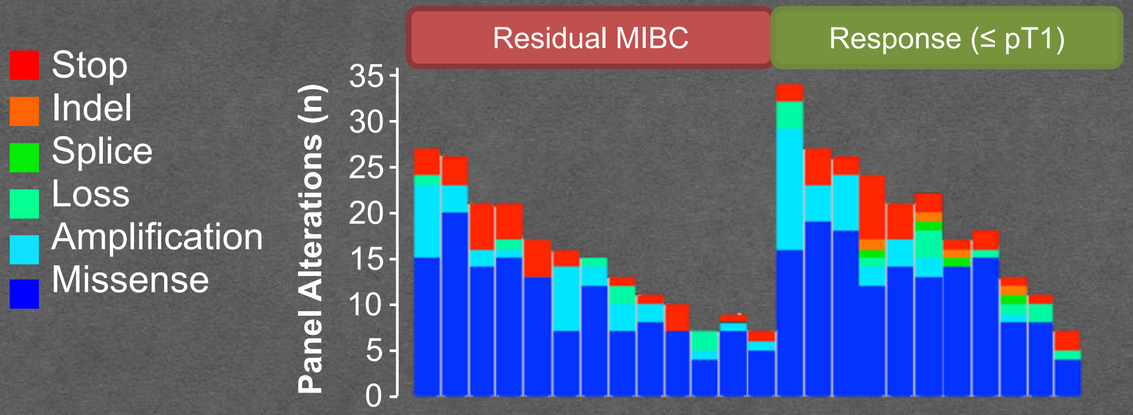
# More Alterations Correlates With Greater Probability of Response to Cisplatin-Based Neoadj Chemo




MSKCC/DFCI Discovery Cohort[1]
Higher total number of alterations in responders (pT0/Tis) vs nonresponders (≥ pT2)
(9.7 vs 4.4 mutations/Mb; *P* = .0003)



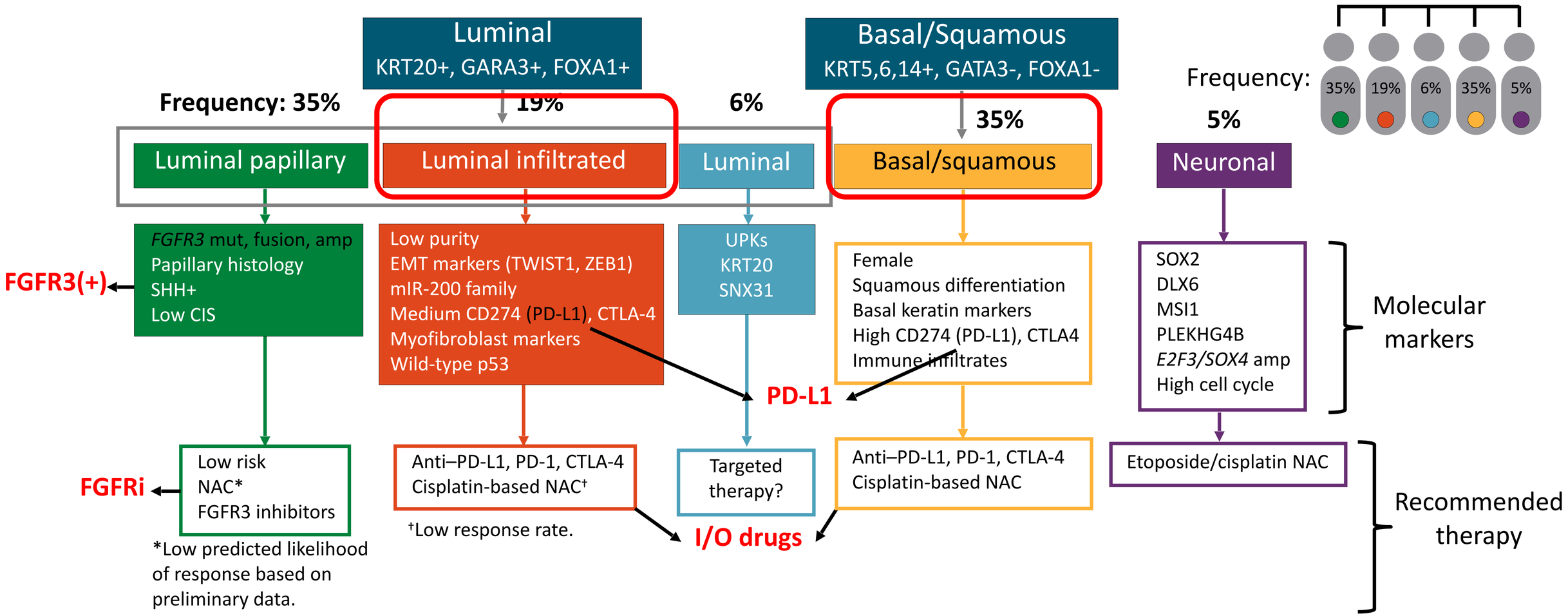

FCCC AMVAC Discovery Cohort[2]
Higher total number of alterations in responders (pT0) vs other (mean no. alterations: 25.4 vs 18.7; *P* = .024)




FCCC DDGC Validation Cohort[2]
Higher total number of alterations in responders (pT0) vs other (mean no. alterations 22.7 vs 15.3; *P* = .018)

1. Van Allen EM, et al. Cancer Discovery. 2014;4:1140-1153.
2. Plimack ER, et al. Eur Urol. 2015;68:959-967.

# A New Classification of Urothelial Cancer by Molecular Markers




*FGFR3*-positive UC defines a unique molecular subtype largely different from T-cell–inflamed UC.

Robinson GA. Cell. 2017;171:540.

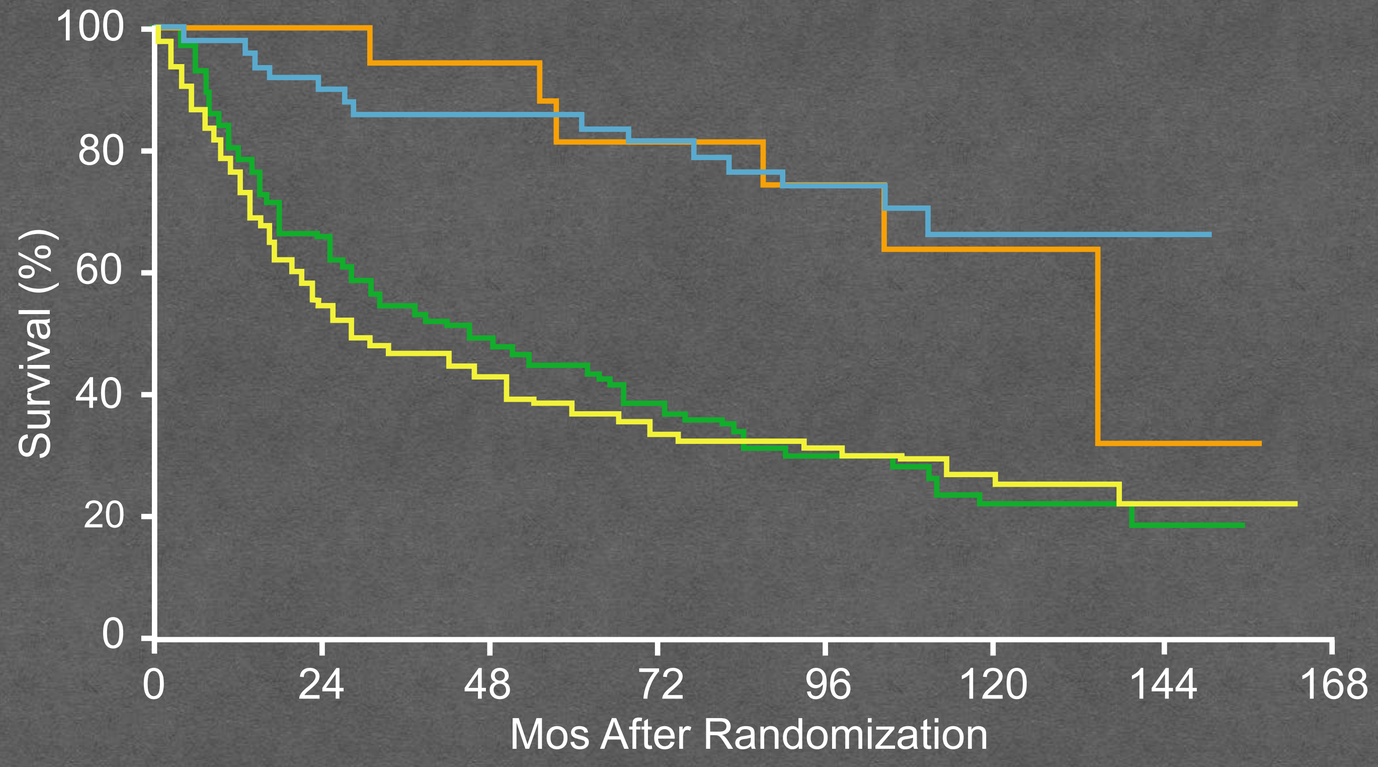
# Clinically Useful Biomarkers in Urothelial Cancer

- *FGFR* mutation/fusion status
  - Any metastatic treatment-refractory setting
- PD-L1 expression status
  - First-line (platinum-naive) metastatic setting only
    - PD-1/L1 therapy associated with a survival benefit regardless of PD-L1 status in second line

# Phase III Trial of Neoadjuvant MVAC Followed by Radical Cystectomy: 5-Yr Survival

- MVAC x 3 followed by cystectomy vs immediate cystectomy (N = 317)
  - pT0: 38% with MVAC vs 15% with cystectomy alone
  - 5-yr survival (pT0): 85%

| | Deaths, n | Median survival, yrs |
|---|---|---|
| MVAC + cystectomy, pT0 | 14 | NR |
| Cystectomy, pT0 | 6 | 11.3 |
| MVAC + cystectomy, RD | 76 | 3.8 |
| Cystectomy, RD | 94 | 2.4 |




Grossman HB, et al. N Engl J Med. 2003;349:859-866.

## Ongoing Clinical Trials With Checkpoint Inhibitors in Urothelial Cancer

### Neoadjuvant Trials

| Treatments | Phase | ClinicalTrials.gov ID |
|---|---|---|
| Pembrolizumab | II | NCT02736266 |
| Pembrolizumab with gemcitabine ± cisplatin | I/II | NCT02365766 |
| Pembrolizumab with gemcitabine/cisplatin | II | NCT02690558 |
| Nivolumab plus urelumab or nivolumab alone | II | NCT02845323 |
| Atezolizumab | II | NCT02662309 |

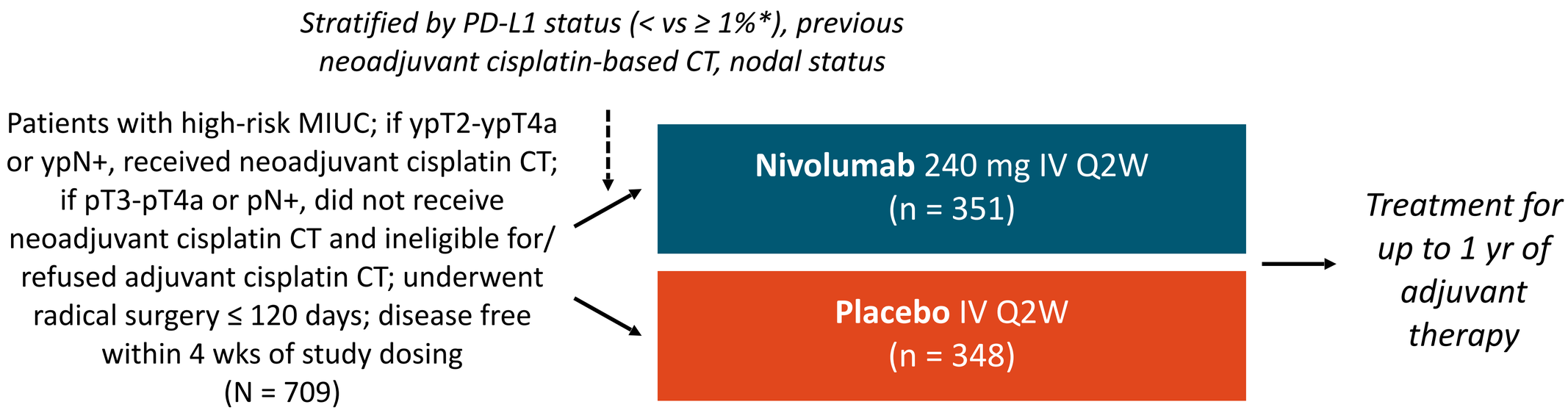
### Adjuvant Trials

| Trial Name | Treatments | Population | Primary Endpoint | ClinicalTrials.gov ID |
|---|---|---|---|---|
| IMvigor0101 | Atezolizumab vs observation | With neoadjuvant: ypT2-4a or ypN+ (ypT2-4 or ypN+ for UTUC)<br>Without neoadjuvant: pT3-T4a or pN+ (pT3-4 or pN+ for UTUC) | DFS | NCT02450331 |
| CheckMate 274 | Nivolumab vs placebo | With neoadjuvant: ypT2-pT4a or ypN+<br>Without neoadjuvant: ypT3-pT4a or ypN+ | DFS | NCT02632409 |
| AMBASSADOR | Pembrolizumab vs observation | With neoadjuvant: ≥ pT2 and/or N+<br>Without neoadjuvant: ≥ pT3 or pN+ | DFS, OS | NCT03244384 |

*UTUC, upper tract urothelial carcinoma.*

# CheckMate 274: Adjuvant Nivolumab vs Placebo After Radical Surgery ± Neoadjuvant CT in High-Risk MIUC

- First analysis of international, randomized, double-blind phase III trial




- **Primary endpoints:** DFS is ITT population, DFS in all randomized patients with PD-L1 ≥ 1%

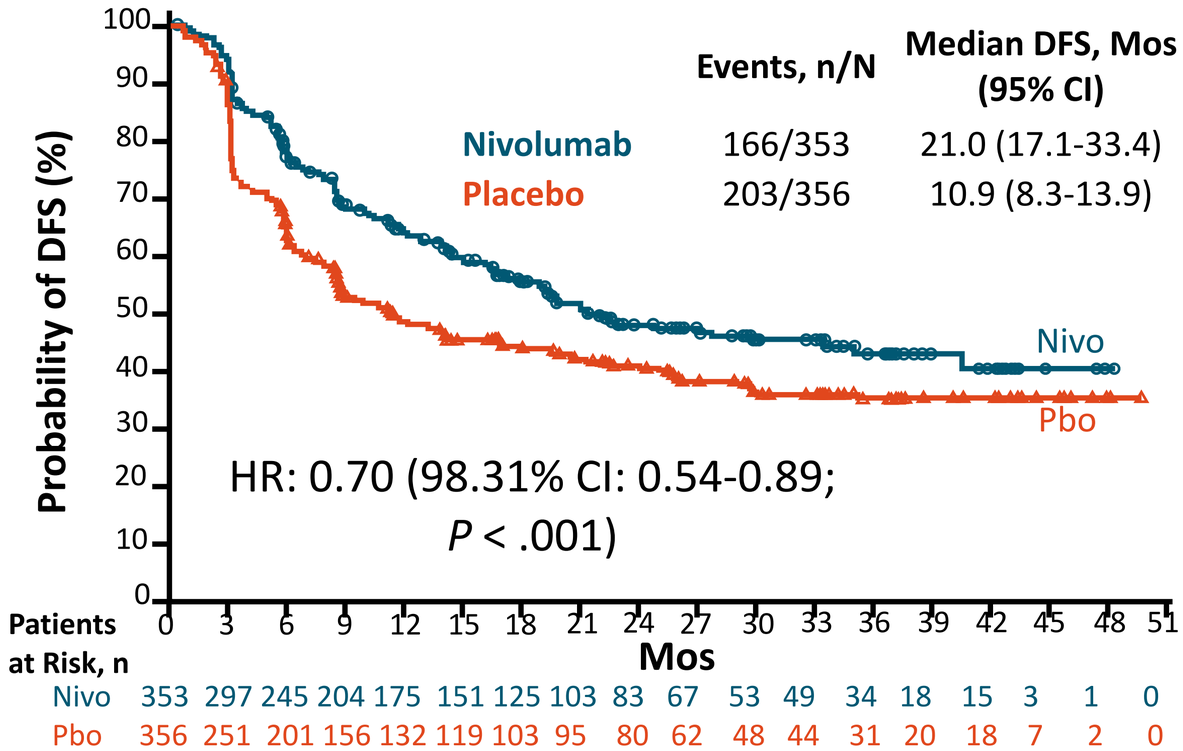
- **Secondary endpoints:** nonurothelial tract recurrence-free survival, disease-specific survival, OS†
- **Exploratory endpoints:** distant metastasis–free survival, safety, HRQoL

*Per PD-L1 IHC 28-8 PharmDx assay.
†OS data immature at time of analysis.

Bajorin. ASCO GU 2021. Abstr 391. NCT02632409.

# CheckMate 274: DFS in ITT and PD-L1 ≥ 1% Populations (Primary Endpoints)

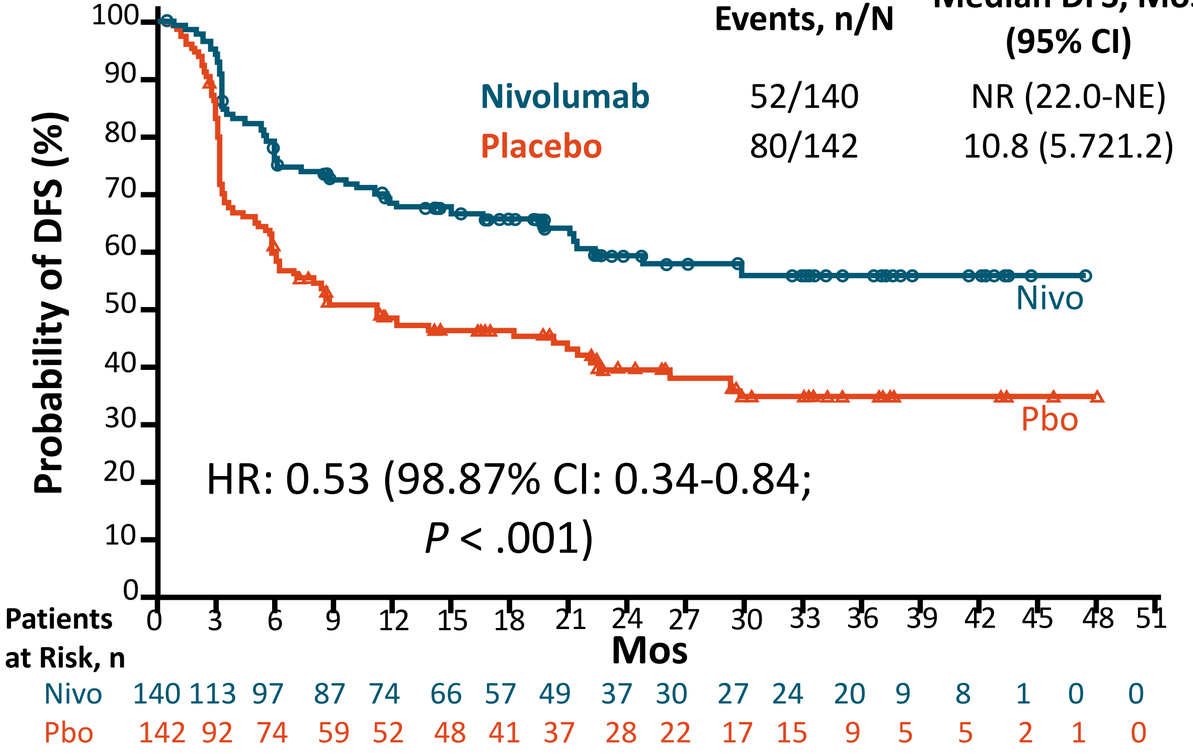
## ITT




Patients at Risk, n

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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%




Patients at Risk, n

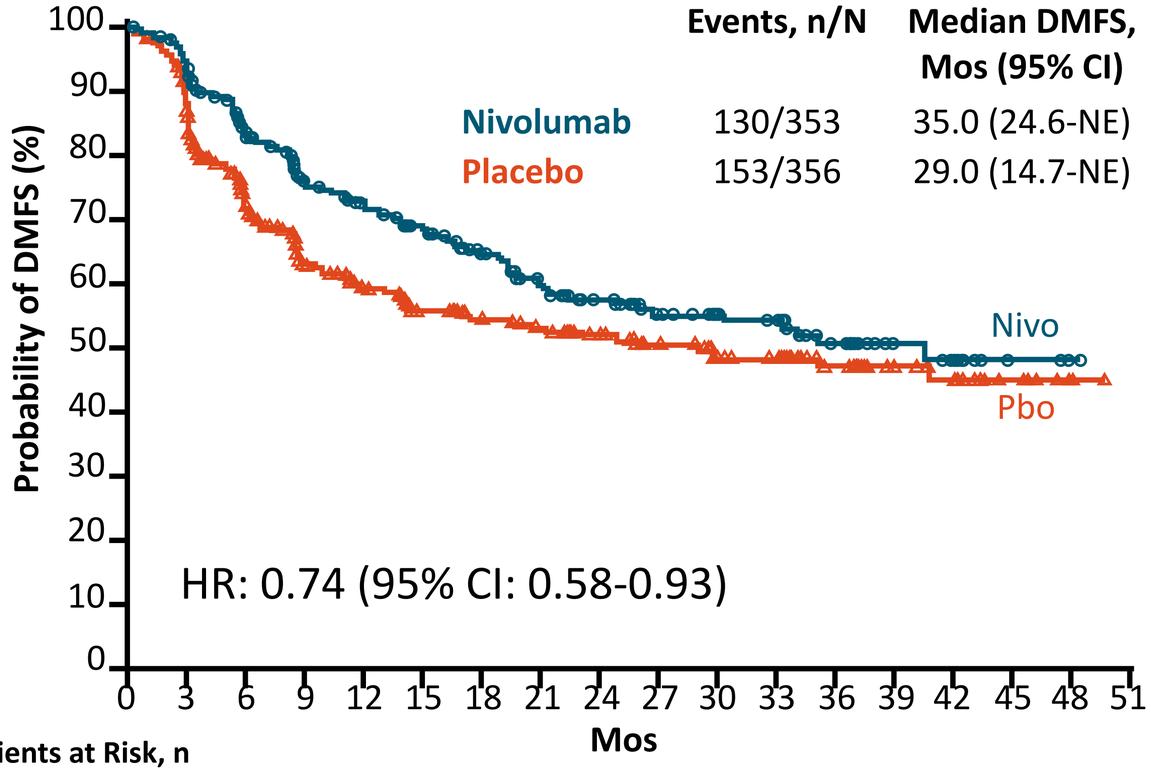
| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo | 140 | 113 | 97 | 87 | 74 | 66 | 57 | 49 | 37 | 30 | 27 | 24 | 20 | 9 | 8 | 1 | 0 | 0 |
| Pbo | 142 | 92 | 74 | 59 | 52 | 48 | 41 | 37 | 28 | 22 | 17 | 15 | 9 | 5 | 5 | 2 | 1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

- Study met its primary endpoints: nivolumab significantly prolonged DFS vs placebo in the ITT population and patients with PD-L1 ≥ 1% (both *P* < .001)

Bajorin. ASCO GU 2021. Abstr 391.

# CheckMate 274: Distant Metastasis–Free Survival

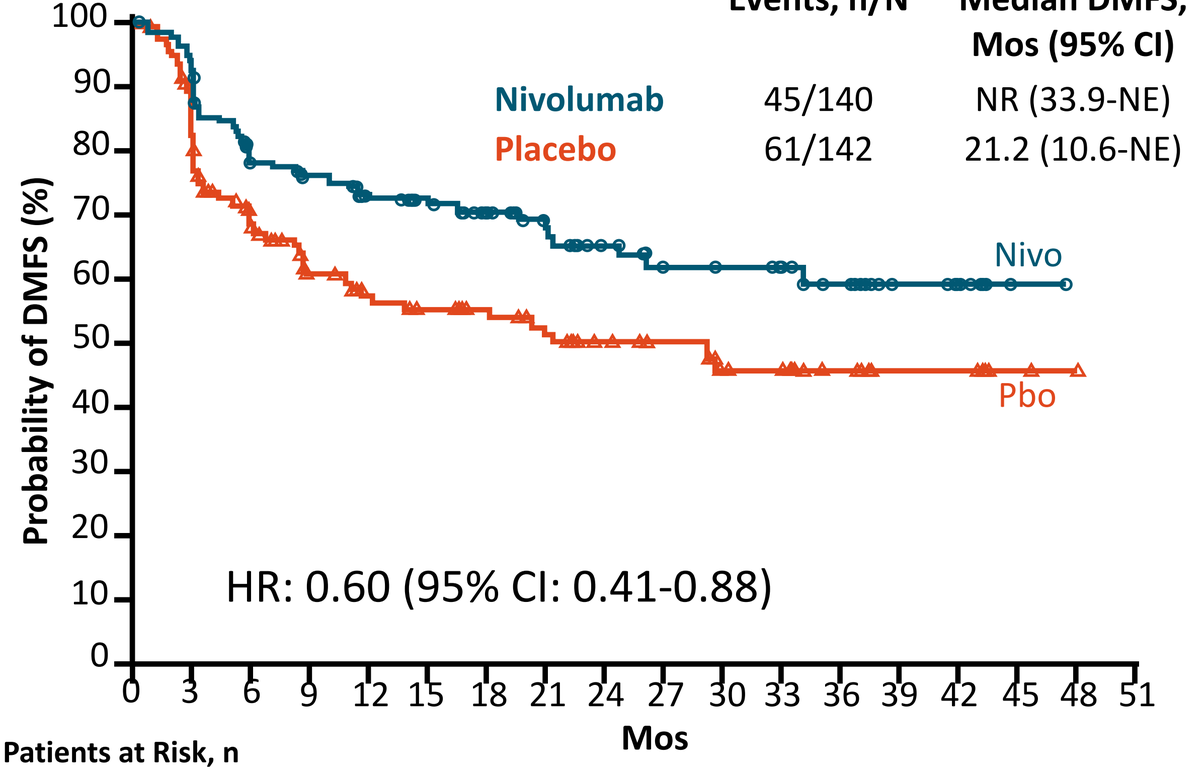
## ITT




**Patients at Risk, n**

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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%




**Patients at Risk, n**

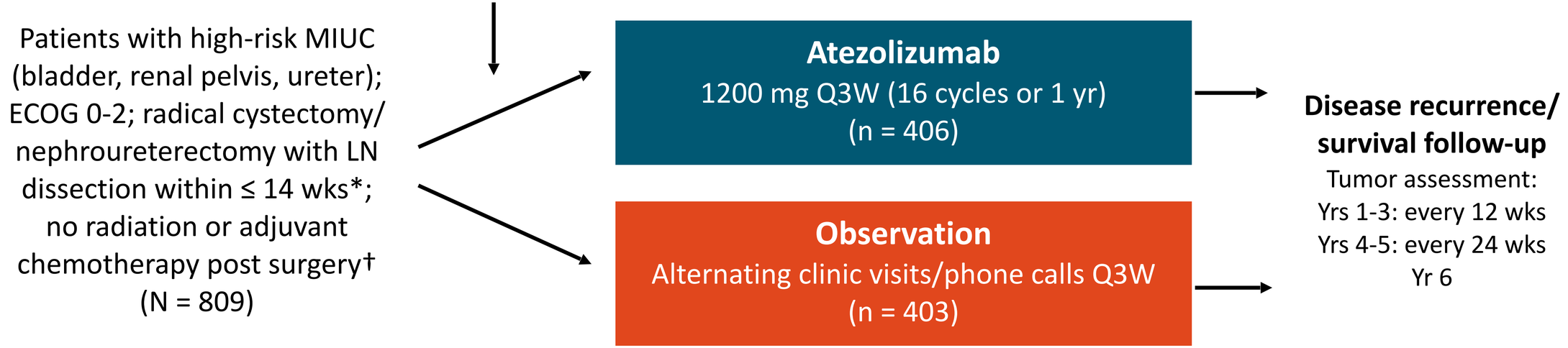
| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo | 140 | 113 | 99 | 89 | 77 | 69 | 60 | 51 | 39 | 31 | 29 | 25 | 20 | 9 | 8 | 1 | 0 | 0 |
| Pbo | 142 | 95 | 76 | 60 | 52 | 48 | 41 | 37 | 28 | 23 | 18 | 16 | 10 | 6 | 6 | 2 | 1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

Bajorin. ASCO GU 2021. Abstr 391.

# IMvigor010: Study Design

- International, open-label, randomized phase III study

*Stratified by: number of resected LNs (< 10 vs ≥ 10), prior neoadjuvant (yes vs no), LN status (+ vs -), tumor stage (≤ pT2 vs pT3/pT4), PD-L1 (IC0/1 vs IC2/3)*

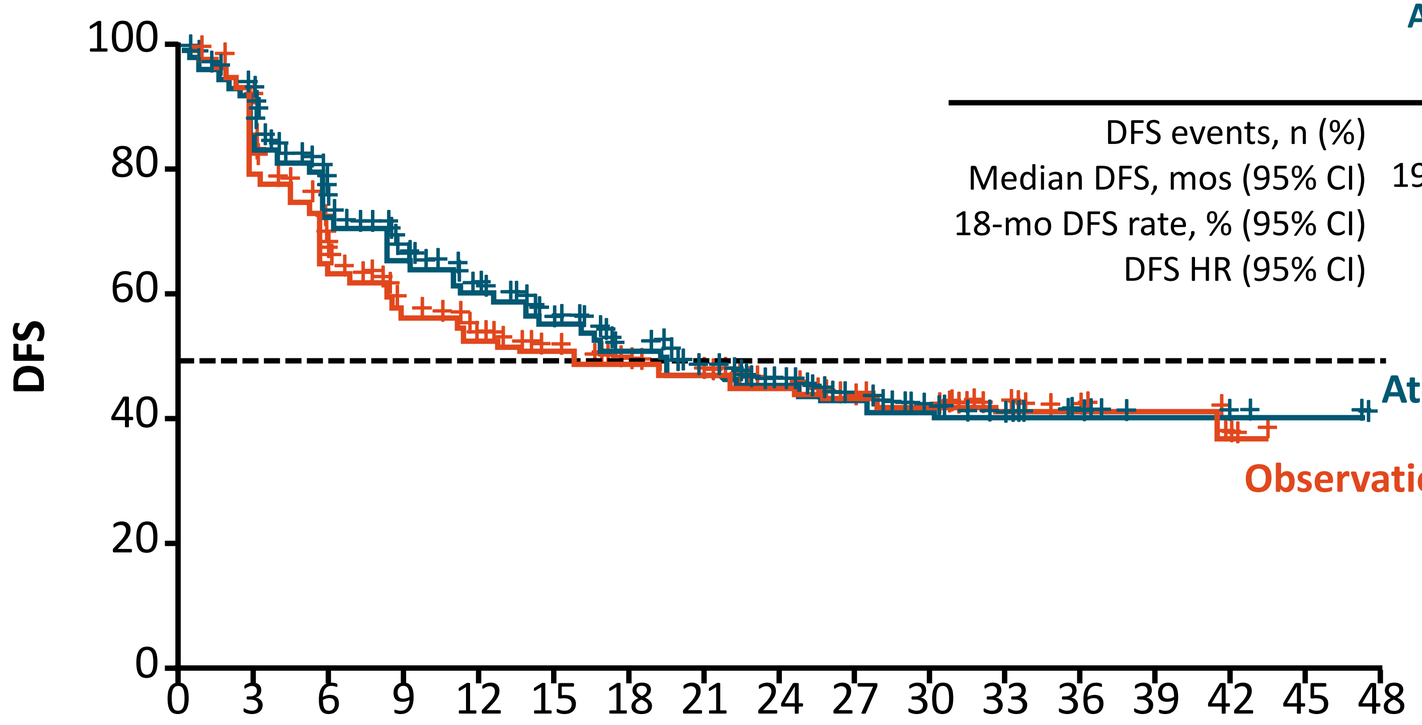



*Upper tract UC staging eligibiity cirteria: For patients given neoadjuvant chemotherapy: ypT2-T4a or ypN+. For patients *not* given neoadjuvant chemotherapy: pT3-T4a or pN+. †To be enrolled, patients who were not given neoadjuvant chemotherapy also must have been ineligible or declined adjuvant cisplatin-based therapy.

- Primary endpoint: DFS (ITT)
- Secondary endpoints: OS (ITT), safety; exploratory: biomarkers including PD-L1 status

Data cutoff: November 30, 2019

# IMvigor010: Similar DFS With Adjuvant Atezolizumab vs Observation in High-Risk MIUC (ITT; Primary Endpoint)




| | Atezolizumab (n = 406) | Observation (n = 403) |
|---|---|---|
| DFS events, n (%) | 212 (52) | 208 (52) |
| Median DFS, mos (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) | |

**Patients at Risk, n**

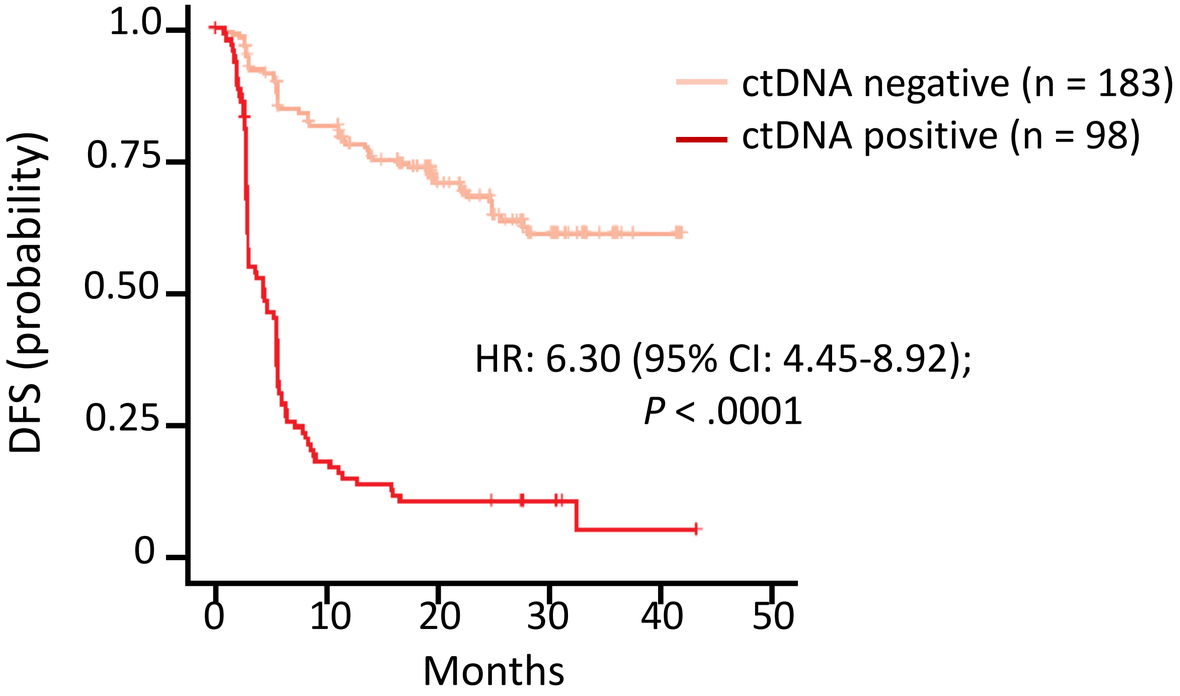
| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 406 | 332 | 281 | 248 | 223 | 201 | 169 | 142 | 115 | 92 | 67 | 52 | 15 | 10 | 3 | 2 |
| Observation | 403 | 305 | 240 | 211 | 188 | 177 | 156 | 131 | 109 | 87 | 67 | 42 | 17 | 12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

- No significant difference in DFS was observed in any clinical subgroup, including PD-L1 expression level

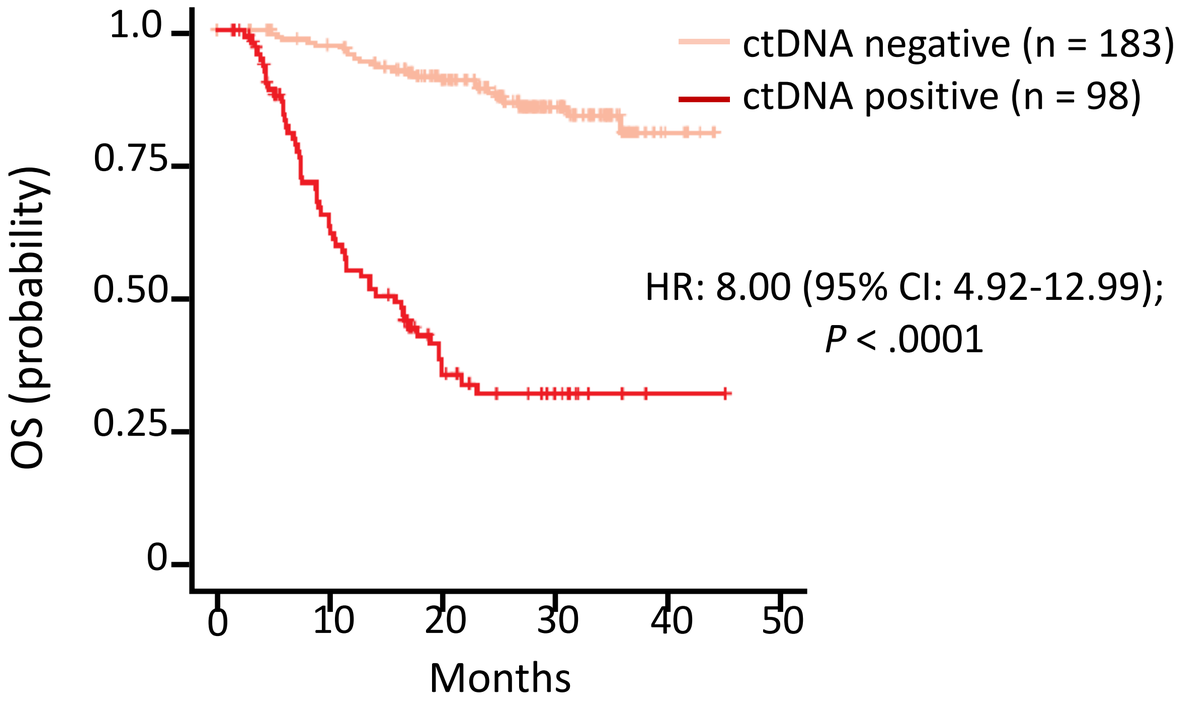
Hussain. ASCO 2020. Abstr 5000.

# IMvigor010: Patients With ctDNA(+) Tumors Have Poor Prognosis

## Observation arm: DFS



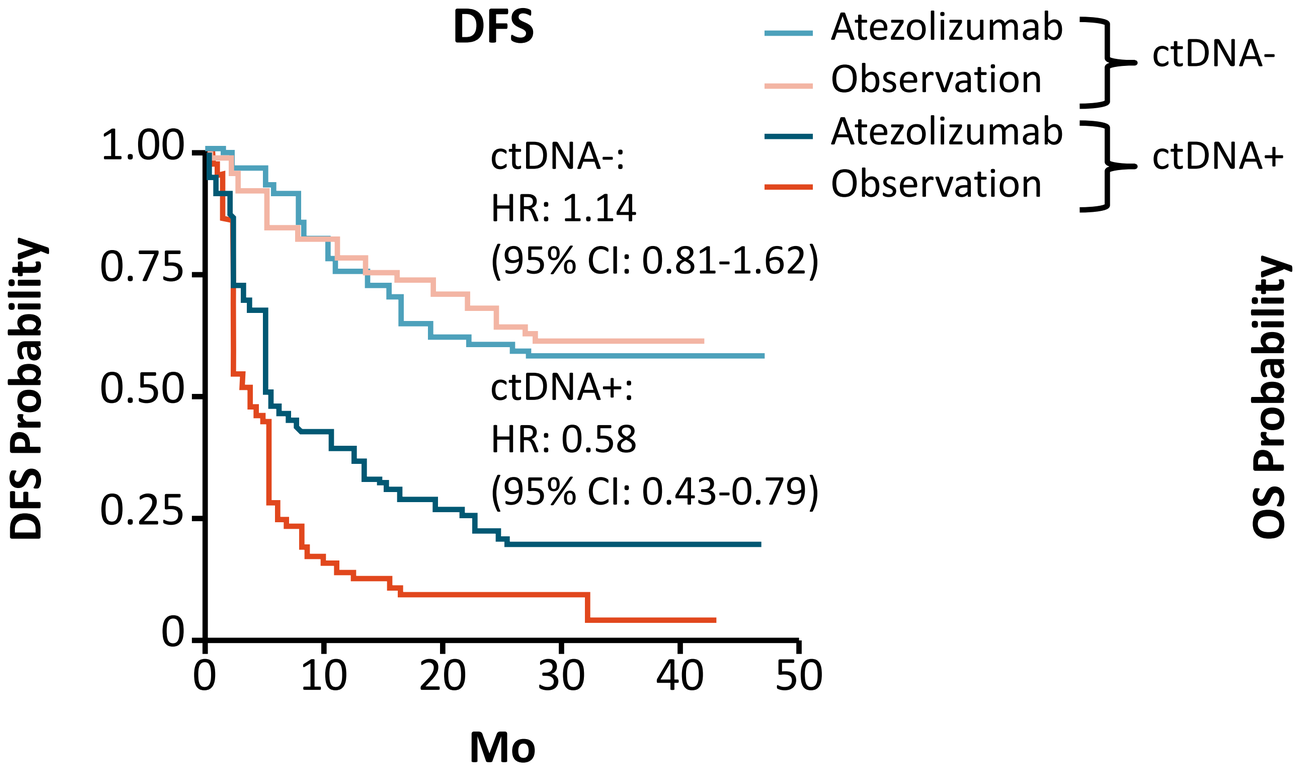

## Observation arm: OS

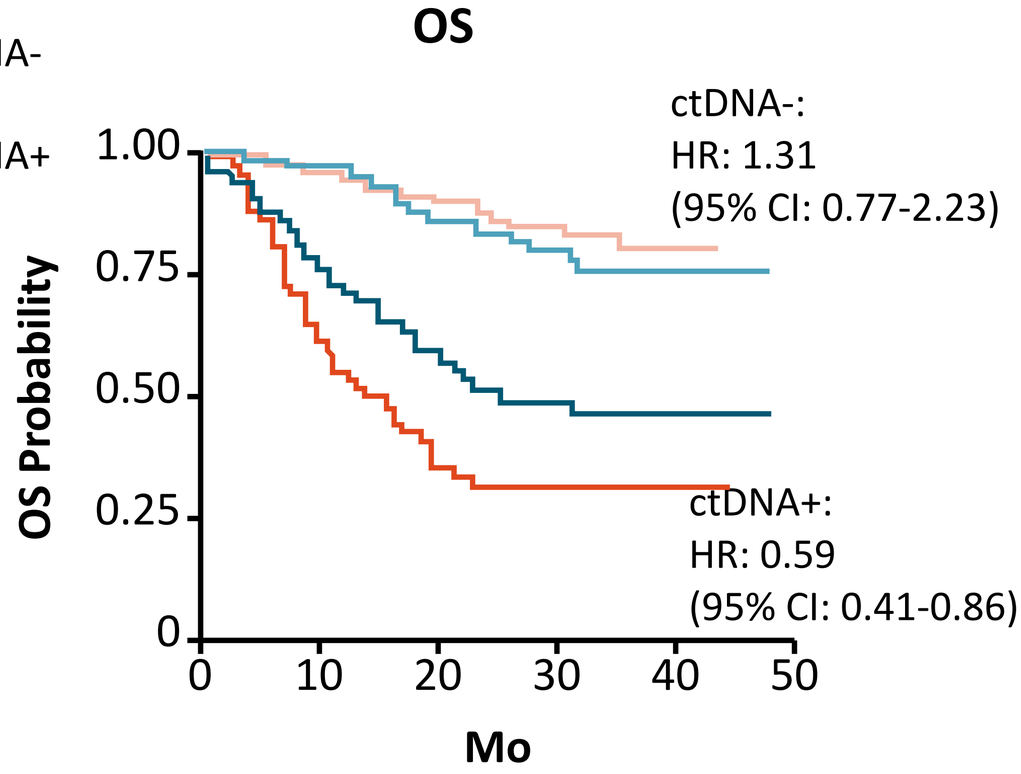



- IMvigor010 confirmed the prognostic value of ctDNA status

Powles. ESMO Immuno-Oncology 2020. Abstr 11.

# IMvigor010: Survival Outcomes With Atezolizumab vs Observation by Postsurgical ctDNA Status




| | Atezolizumab (n = 300) | Observation (n = 281) |
|---|---|---|
| **Median DFS, mo** | ctDNA-: NR<br>ctDNA+: 5.9 | ctDNA-: NR<br>ctDNA+: 4.4 |

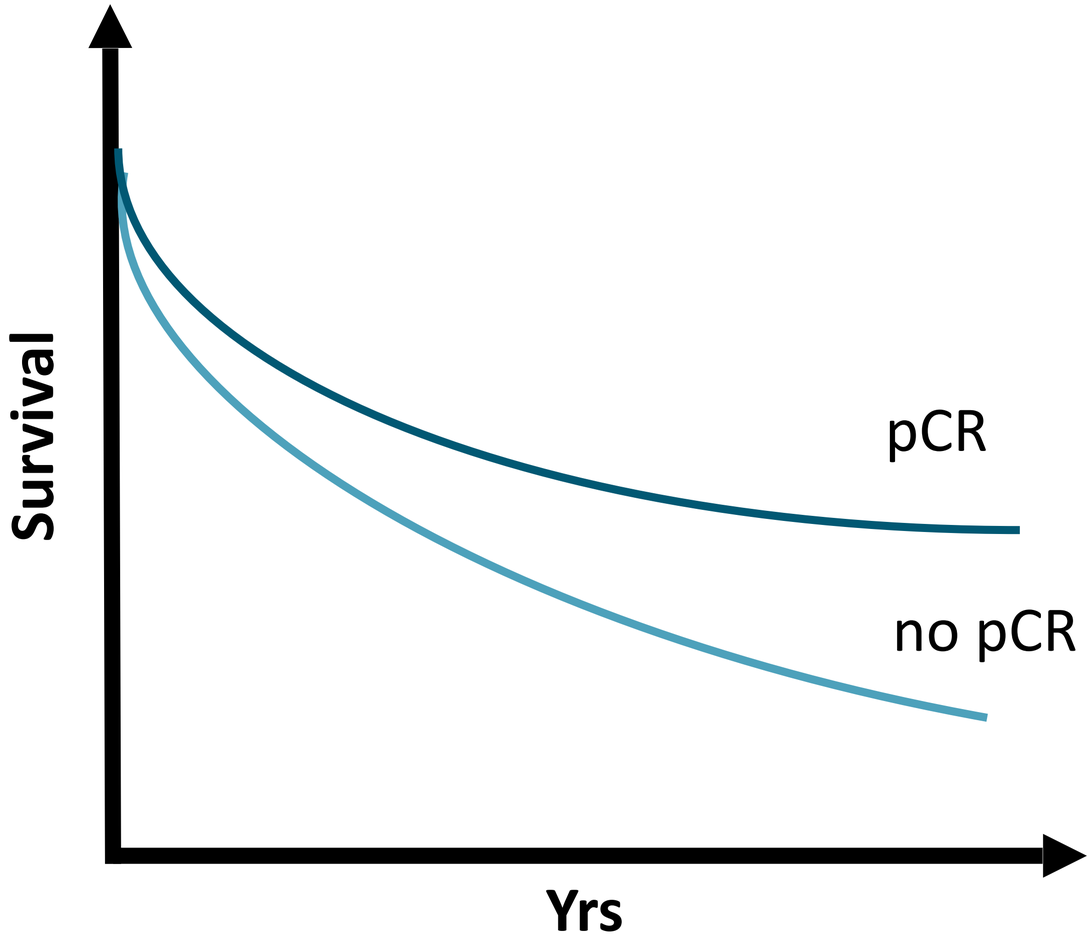
| | Atezolizumab (n = 300) | Observation (n = 281) |
|---|---|---|
| **Median OS, mo** | ctDNA-: NR<br>ctDNA+: 25.8 | ctDNA-: NR<br>ctDNA+: 15.8 |

Powles. Nature. 2021;595:432.

# Background Trials of Neoadjuvant Checkpoint Inhibition Muscle Invasive Bladder Cancer

- Standard management for T2-4aN0-1M0 bladder cancer: cystectomy
  - Cisplatin-based neoadjuvant chemotherapy increases pathologic CR rate and significantly improves OS (HR: 0.87; 95% CI: 0.79-0.96)[1]
  - Ineligibility for cisplatin-based therapy common in this population
  - Pathologic CR rate for TURBT without neoadjuvant therapy: 15%
- PD-1/PD-L1 antibody approved by FDA for treatment of cisplatin-ineligible locally advanced or metastatic UC

# pCR as a Potential Individual Level Surrogate Endpoint




Potential **individual-level** surrogate endpoint

# ABACUS and PURE-01: Phase II Trials of Neoadjuvant Checkpoint Inhibition Muscle Invasive Bladder Cancer

**ABACUS:**

**Atezolizumab**

1200 mg Q3W x 2 doses

(N = 95)[1]

**PURE-01:**

**Pembrolizumab**

200 mg Q3W x 3 doses

(N = 50)[2]

**Cystectomy**

- Current study designed to assess safety and efficacy in patients with operable bladder cancer who are **ineligible for neoadjuvant therapy**

1. Powles. Nat Med. 2019;[Epub]. 2. Necchi. J Clin Oncol. 2018;36:3353.

# ABACUS: pCR Rate and CD8+ Cell Count (Coprimary Endpoints)

| pCR Rate, n/N (%; 95% CI) | Evaluable Population (n = 68) |
|---|---|
| All patients | 20/68 (29; 19-42) |
| PD-L1 positive* | 10/25 (40; 21-61) |
| PD-L1 negative* | 5/31 (16; 5-34) |
| T2 disease at baseline | 17/48 (35) |
| T3 or T4 disease at baseline | 3/20 (15) |

*PD-L1 analysis in 56 of 68 patients.

- In cisplatin-ineligible patients with operable bladder cancer, 2 cycles of neoadjuvant atezolizumab was active and well tolerated
- pCR occurred in 29% (95% CI: 19% to 42%)
  - 40% (95% CI: 21% to 61%) in PD-L1–positive patients
  - 16% (95% CI: 5% to 34%) in PD-L1–negative patients
- Atezolizumab treatment associated with increased expression of CD8+ and PD-L1

Powles T, et al. ASCO 2018. Abstract 4506.

# PURE-01: Pathologic Response to Pembrolizumab

| Pathologic Response, n (%) | First-Stage Patients (n = 43) |
|---|---|
| pCR* (primary endpoint) | 17 (39.5) |
| Pathologic downstaging to pT < 2 | 22 (51.2) |
| Treatment failure | |
| ▪ ypT2-4 ypN0 | 7 (16.3) |
| ▪ ypTany ypN+ | 9 (20.9) |
| ▪ Clinical failure | 5 (11.6) |
| ▪ Clinical PD (RECIST v1.1) | 0 |

*pCR = pT0.

Necchi A, et al. ASCO 2018. Abstract 4507.

# PURE-01: Biomarkers for Pathologic Response to Pembrolizumab

- Median PD-L1 CPS percentage and TMB levels trended higher in patients with pCR vs non-pCR
- 42% of patients had deleterious genomic alterations in DDR genes
- Genomic alterations in *RB1* and *PBRM1* were significantly associated with achieving pCR
  - Patients with *RB1* and *PBRM1* alterations also had higher TMB levels
- Significantly higher gene expression levels pretreatment in patients who would attain pCR vs non-pCR for *IFNG*, *CXCL9*, *CXCR6*, *PD-L1*, *PD-L2*, and *IDO1* (all $P < .0001$)
- High pCR rate in subgroup with PD-L1 CPS ≥ 20% and genomic alterations in DDR genes or *RB1*

| Response, n (%) | First-Stage Patients (n = 43) | PD-L1 CPS ≥ 20% (n = 22) | Genomic Alterations in DDR and/or *RB1* (n = 25) | PD-L1 CPS ≥ 20% and Genomic Alterations in DDR and/or *RB1* (n = 10) |
|---|---|---|---|---|
| pCR | 17 (39.5) | 11 (50.0) | 15 (60.0) | 9 (90) |

Necchi A, et al. ASCO 2018. Abstract 4507.

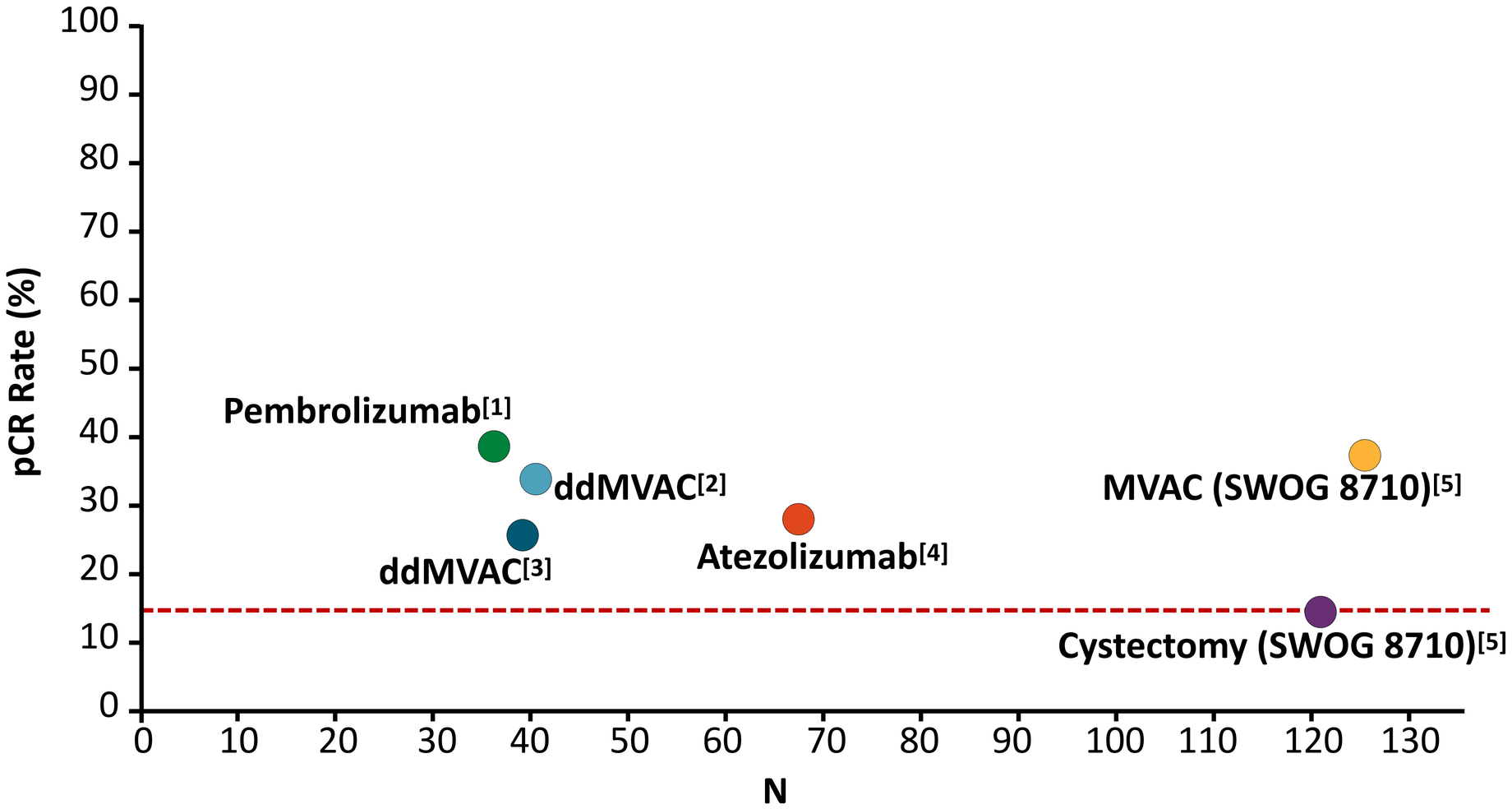
# PURE-01: Changes in Biomarkers Post Pembrolizumab

| Biomarker | Patients With Matched Tissue Samples (n = 18) | | *P* Value |
|---|---|---|---|
| | Pre-Pembrolizumab | Post-Pembrolizumab | |
| Median PD-L1 CPS, % | 10 | 30 | .1809 |
| Median TMB, mut/Mb | 10.1 | 4.4 | .0036 |

- In patients with matched tissue samples pre- vs post-pembrolizumab
  - PD-L1 CPS percentage increased
  - Median TMB levels significantly decreased
  - Significant increases observed for genes involved in promoting T-cell–mediated immunity (ie, IFN-γ signaling, immune cell recruitment, and T-cell maturation and differentiation) and also for genes involved in adaptive resistance (ie, *IDO1*, inhibitory receptors and ligands)

Necchi A, et al. ASCO 2018. Abstract 4507.

# pCR Rate With PD-1/PD-L1 Blockade Similar to Cisplatin-Based NAC




1. Necchi. ASCO 2018. Abstr 4507. 2. Anari. Eur Urol Oncol. 2018;1:54. 3. Choueiri. JCO. 2014;32:1889.
4. Powles. ASCO 2018. Abstr 4506. 5. Grossman. NEJM. 2003;349:859.

# Recent Clinical Trials of Neoadjuvant Checkpoint Inhibition in MIBC

| | ABACUS: Atezolizumab (n = 95)[1] | PURE-01: Pembrolizumab (n = 50)[2] | Durva + Tremelimumab (N = 28)[3] | NABUCCO: Nivo + Ipi (N = 24)[4] |
|---|---|---|---|---|
| Eligibility | T2-T3b<br>N+ not allowed<br>T4b allowed | T2-T3b<br>N1 allowed (4%)<br>T4b not allowed | cT2-3aN0M0<br>N+ not allowed<br>T4a allowed | cT3-4aN0M0 (58%) *or*<br>T1-4aN1-3M0 (42%) |
| Cisplatin ineligible, % | 100 | 8 | 100 | 54 |
| Pts who received NAC, % | 0 | 10 | 0 | 0 |
| Duration of neoadjuvant ICP therapy, cycles (wks) | 2 (6) | 3 (9) | 2 (8) | 3 (9) |
| Primary endpoint | pCR, TILs | pCR | Safety | Feasibility to resect within 12 wks |
| pCR, % | 31 | 42 | 37.5 | 46 |
| pCR in PD-L1 pos, % | 37.1* | 54.3† | -- | 73† (pCR or CIS/pTa) |
| pCR in PD-L1 neg, % | 24.5* | 13.3† | -- | 33† (pCR or CIS/pTa) |

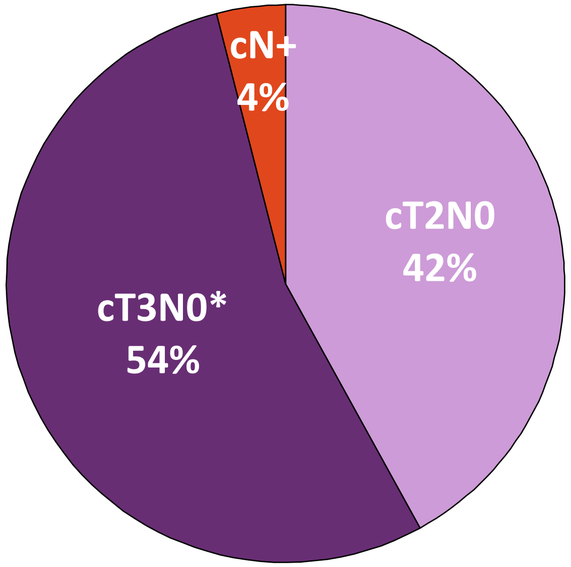
*PD-L1 positivity defined as IC ≥ 5% in SP142 assay. †PD-L1 positivity defined as CPS ≥ 10% by 22C3 assay.

1. Powles. Nat Med. 2019;25:1706. 2. Necchi. JCO. 2018;36:3353. 3. Gao. Nat Med. 2020;26:1845. 4. van Dijk. Nat Med. 2020;26:1839.

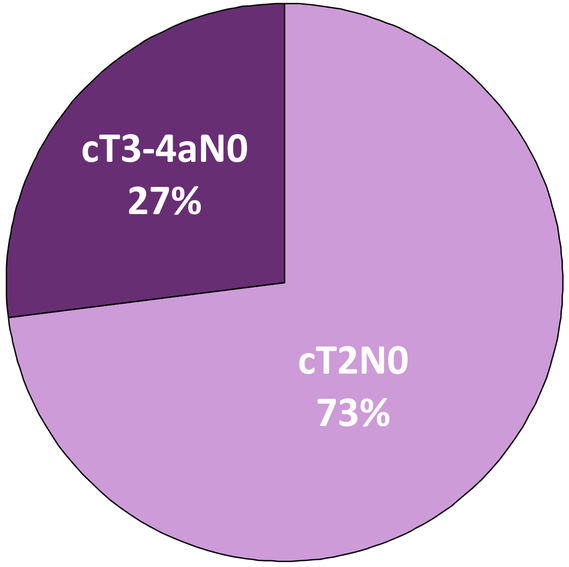
## Substantial Heterogeneity in Baseline Clinical Stages Complicates Comparisons Across Neoadjuvant Trials:

**ABACUS and PURE-01: Phase II Trials of Neoadjuvant Checkpoint Inhibition Muscle Invasive Bladder Cancer. Phase I Trials of Neoadjuvant PD-1/PD-L1 + CTLA-4 Blockade: Durvalumab + Tremelimumab in MIBC. Nivolumab + Ipilimumab in MIBC (NABUCCO).**

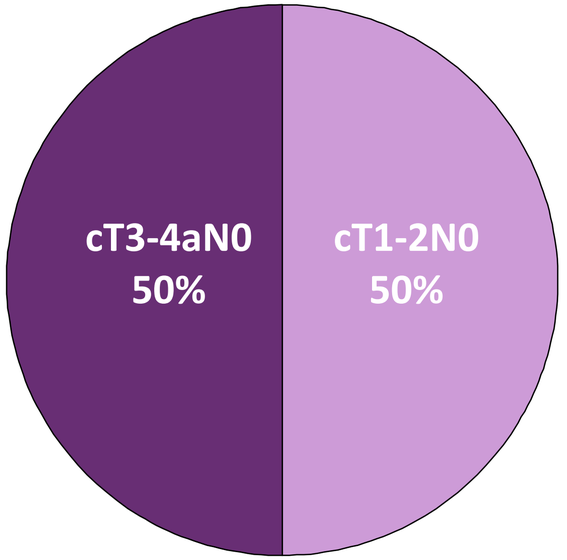
**Pembrolizumab[1]**
**pCR: 42%**



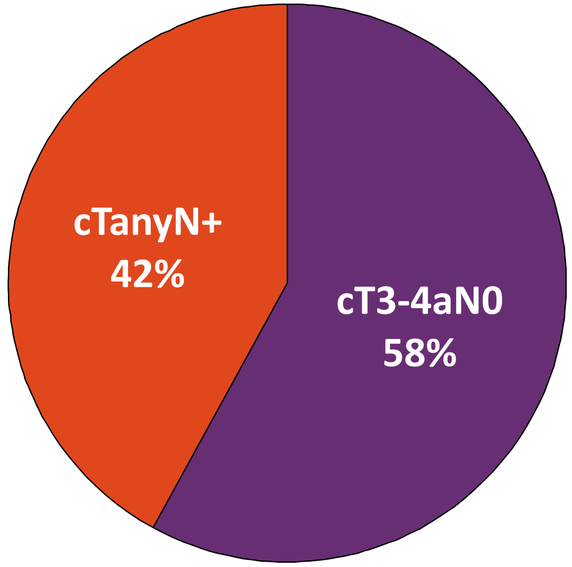

**Atezolizumab[2]**
**pCR: 29%**




**Durvalumab + tremelimumab[3]**
**pCR: 42%**



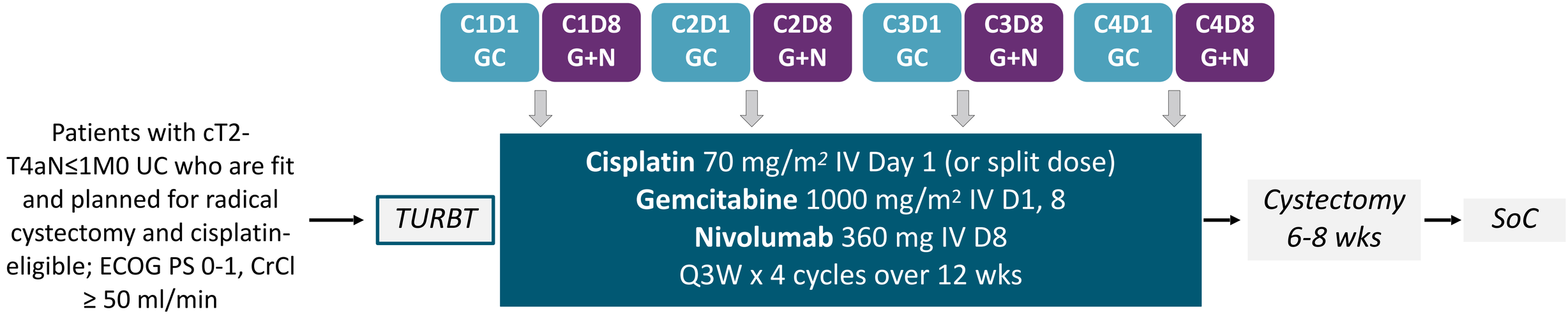

**Ipilimumab + Nivolumab[4]**
**pCR: 46%**




1. Necchi. J Clin Oncol 2018;36:3353. 3. Gao. ASCO 2019. Abstr 4551. 4. Van der Heijden. ESMO 2019. Abstr 904PD.

# BLASST-1: Neoadjuvant Gemcitabine/Cisplatin + Nivolumab in MIBC Undergoing Cystectomy

- A multicenter phase II trial




- Primary endpoints: pathologic response (pathologic non-muscle-invasive rate < pT2N0)
- Secondary endpoints: safety and PFS at 2 yrs

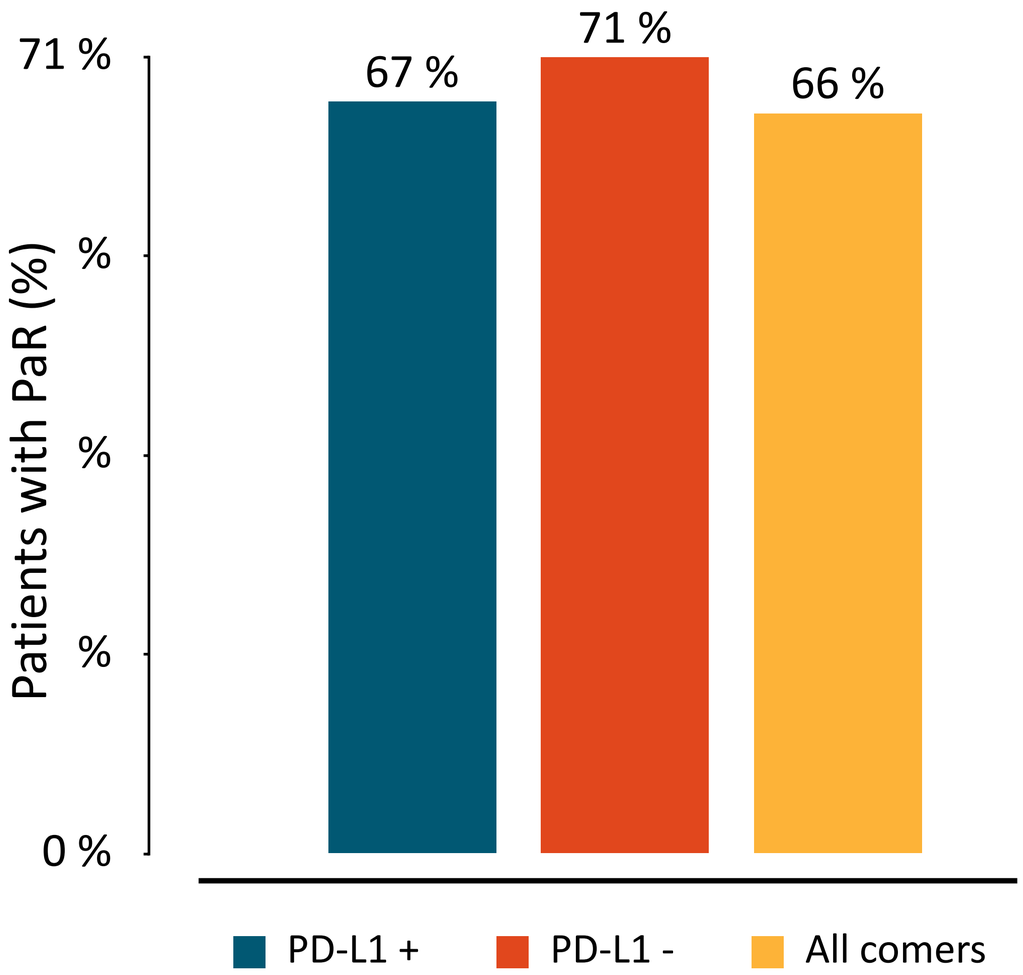
Gupta. ASCO GU 2020. Abstr 439.

# BLASST-1: pCR With Neoadjuvant Gem/Cis + Nivolumab

| Endpoint | Patients, n (%) (N = 41) |
|---|---|
| Pathologic non-muscle-invasive rate (PaR; < pT2N0) | 27 (66) |
| • pT0 | 14 (51.8) |
| • pT1 | 2 (7.4) |
| • pTa* | 5 (18.5) |
| • pTis | 6 (22.2) |
| pCR (pT0,pTis) | 20 (49) |

*1 patient with T4N1 disease had a down staging to pTaN0

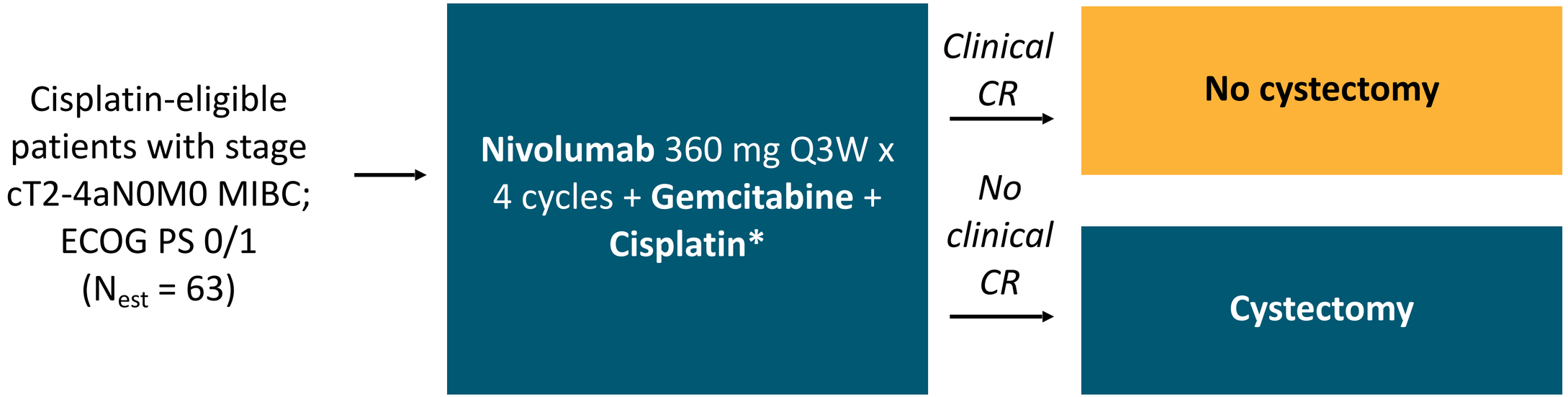
- 15/39 (39%) were PD-L1 positive
- 10/15 PD-L1–positive patients had PaR (67%)
- 17/24 PD-L1 – negative patients had PaR (71%)




Gupta. ASCO GU 2020. Abstr 439.

# Can We Identify Patients With MIBC Who Can Be Treated Curatively Without Cystectomy?

- Open-label phase II trial



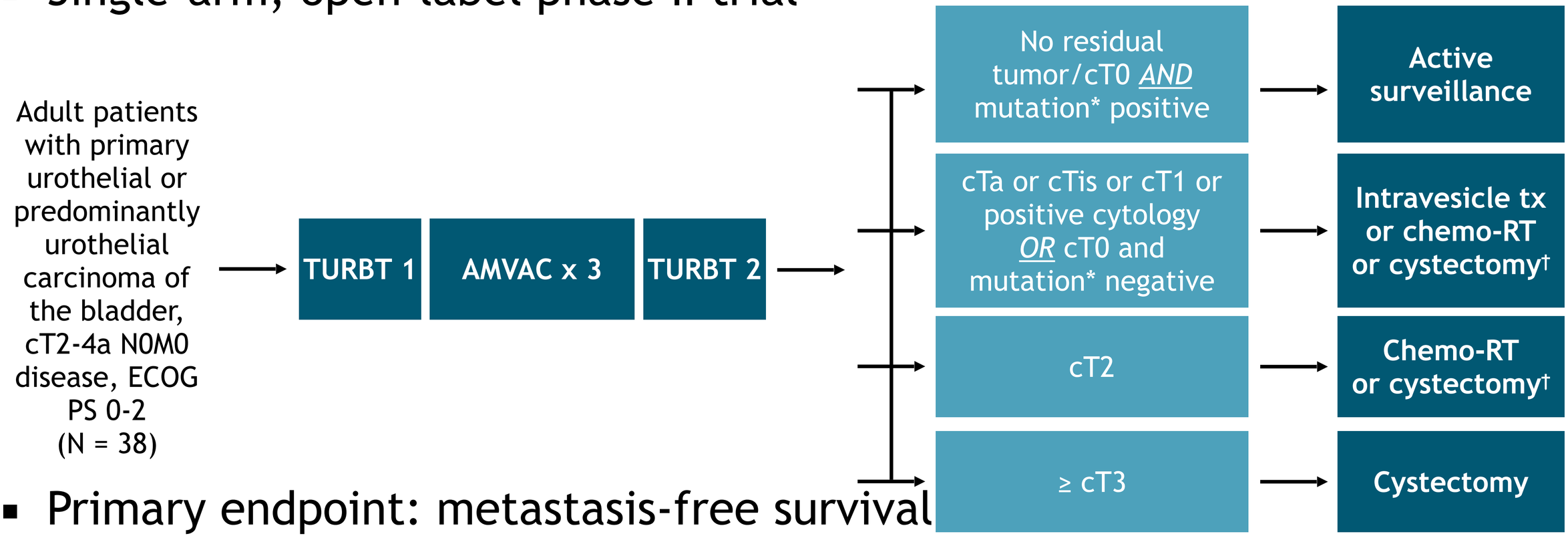

*70 mg/m$^2$ cisplatin on Day 1 and 1000 mg/m$^2$ gemcitabine on Days 1 and 8 of each 21-day cycle x 4 cycles.

- Primary endpoint: pCR rate, ability of pCR to predict benefit
- Secondary endpoints: safety, OS, RFS, biomarker assessment

NCT03558087.

# RETAIN BLADDER: Risk-Adapted Treatment After Neoadjuvant CT for Bladder Cancer

- Single-arm, open-label phase II trial




- Primary endpoint: metastasis-free survival

*Any alteration in ATM, RB1, FANCC, ERCC2.
†Patient and physician choice.

Geynisman DM, et al. ASCO GU 2018. Abstract TPS537. ClinicalTrials.gov. NCT02710734.

# KEYNOTE-057: Pembrolizumab in Patients With High-Risk NMIBC Unresponsive to BCG

- Single-arm, open-label, phase II study

Patients with high-risk NMIBC who are unresponsive to BCG who are ineligible for or refuse cystectomy

**Cohort A:** CIS with or without papillary disease* (high-grade Ta or T1) (n = 130)

**Cohort B:** papillary disease* (high grade Ta or any T1) without CIS (n = 130)

→ **Pembrolizumab**
200 mg Q3W for up to 24 mos

→ Eval with cystoscopy, cytology with or without biopsy Q12W x 2 yrs, then Q24W x 2 yrs and once yrly thereafter

CT urogram Q24W x 2 yrs or more frequently as clinically indicated

→ *If no persistence or recurrence of HR NMIBC*, treat until PD, toxicity, death or completion of 2 yrs of treatment
OR
Discontinue *if HR NMIBC present at any assessment*

*Patients with papillary disease must have fully resected disease at study entry.

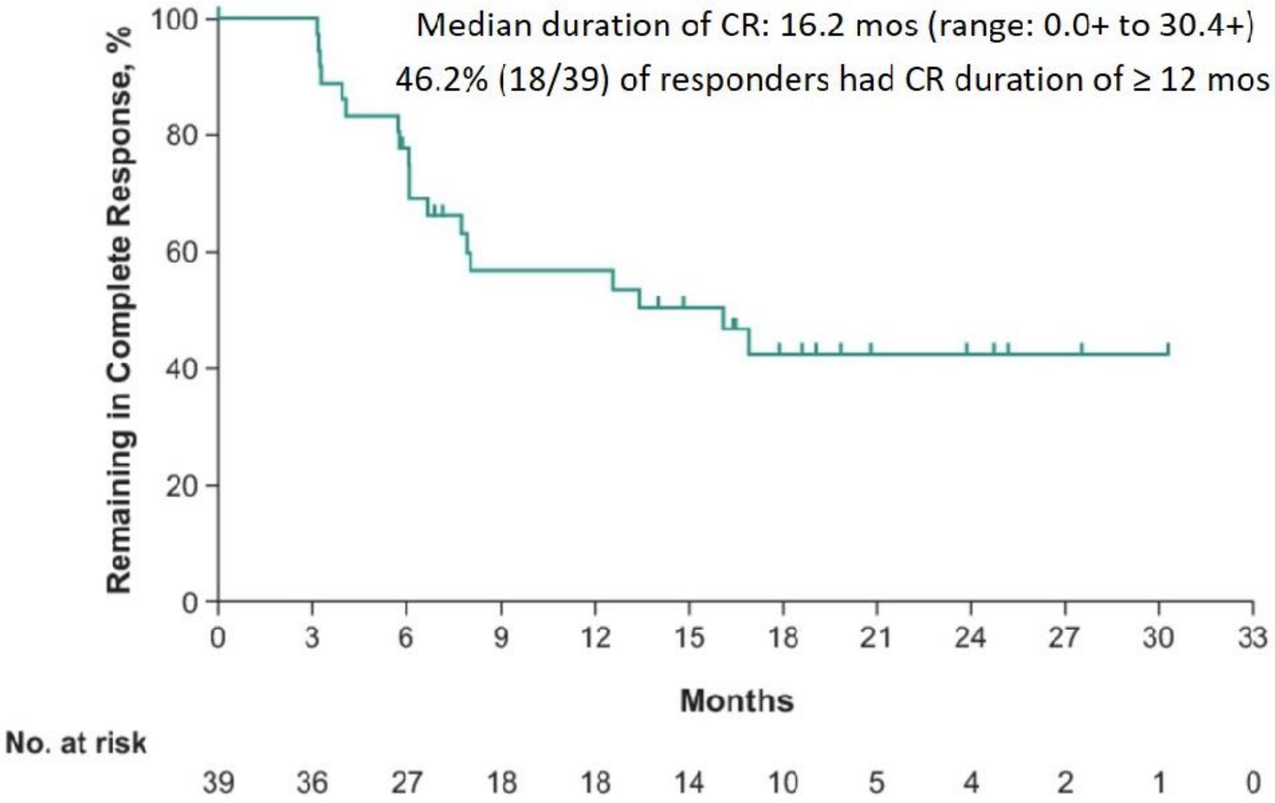
- Primary endpoint: CR (absence of HR NMIBC) in Cohort A; DFS in Cohort B
- Secondary endpoints: CR (absence of any disease, high or low risk NMIBC) in cohort A, DoR in cohort A, safety

De Wit. ESMO 2018. Abstr. Balar ASCO 2020. Abstr 5041.

# KEYNOTE-057: ORR at First Evaluable Assessment

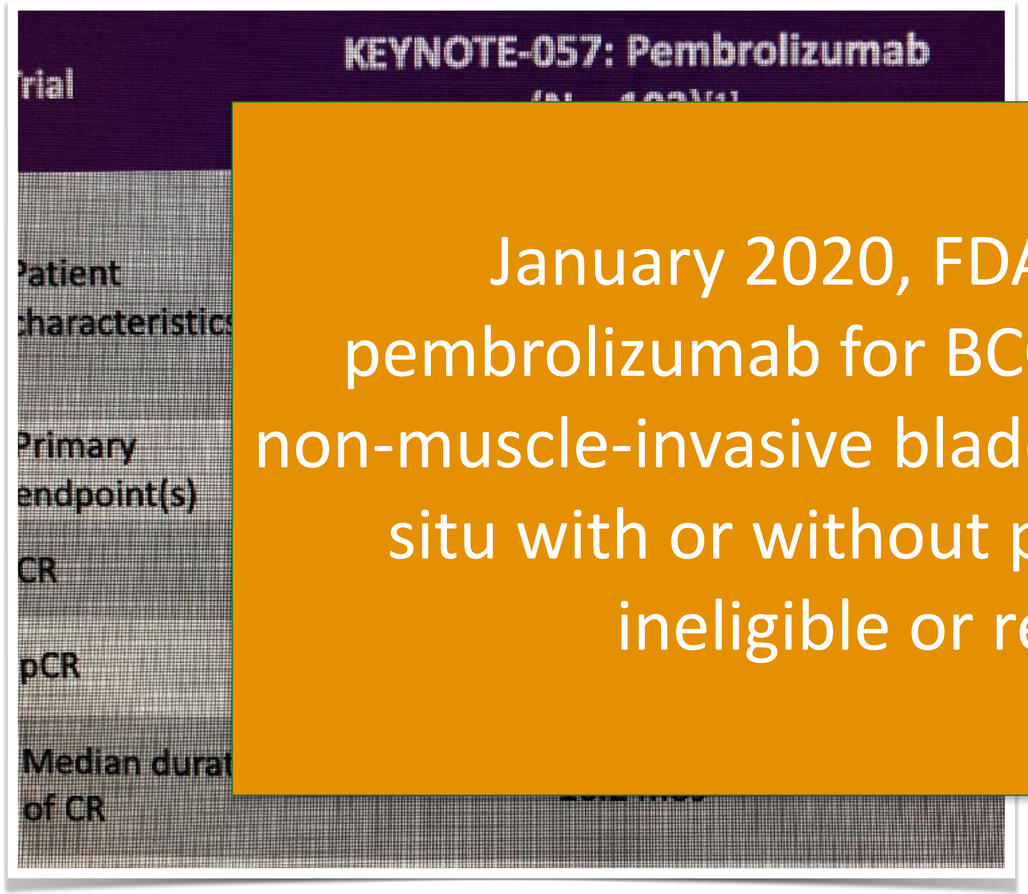
| Trial | KEYNOTE-057: Pembrolizumab (N = 103)[1] |
|---|---|
| Patient characteristics | Ineligible for/refuse cystectomy<br>CIS (TIS) alone (71.8%)<br>CIS (TIS) with high-grade Ta (15.5%)<br>CIS withT1 (12.6%) |
| Primary endpoint(s) | CR, DFS |
| CR | 40.6% |
| pCR | -- |
| Median duration of CR | 16.2 mos |

## DoR in Patients With CR

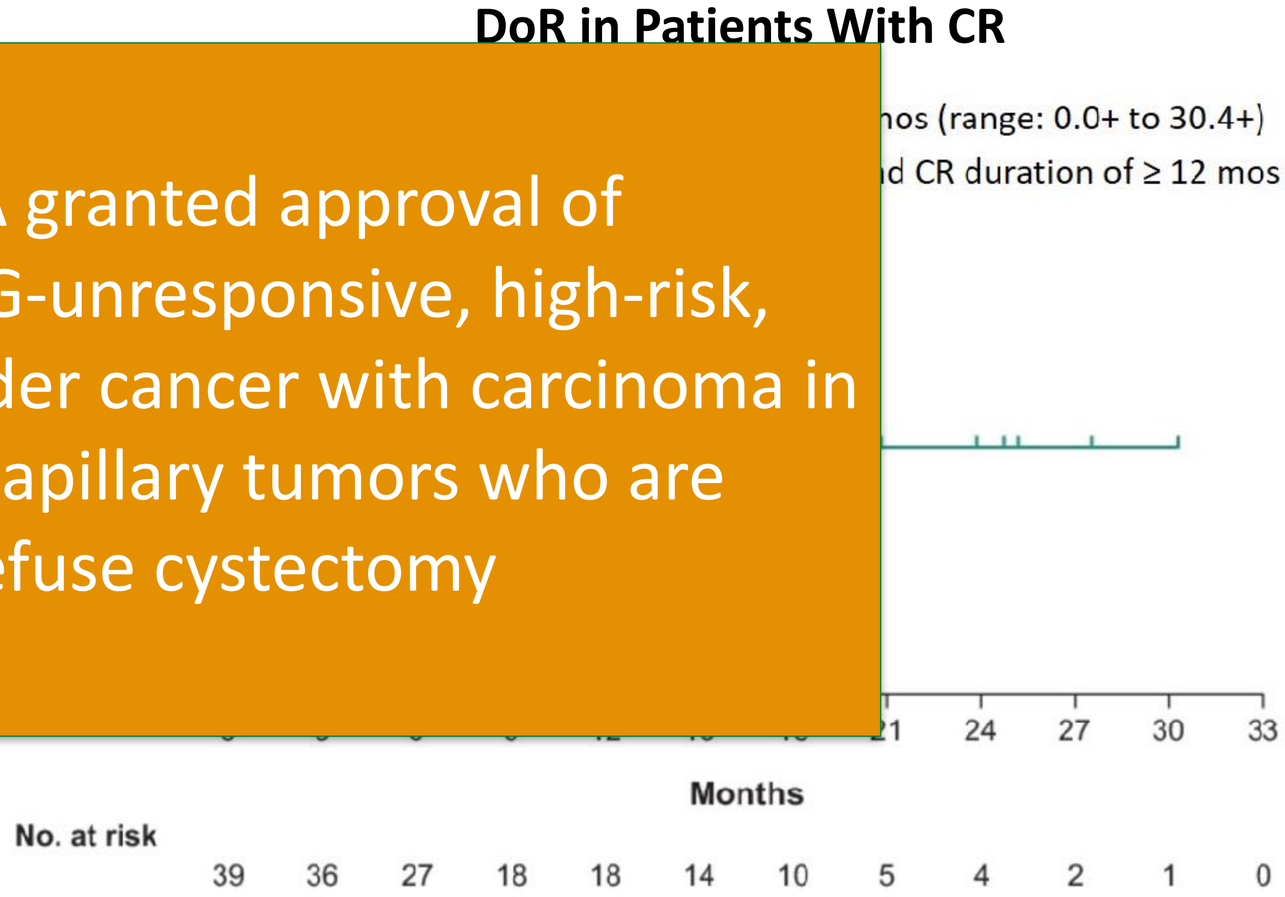



Balar ASCO 2020. Abstr 5041.

# KEYNOTE-057: ORR at First Evaluable Assessment

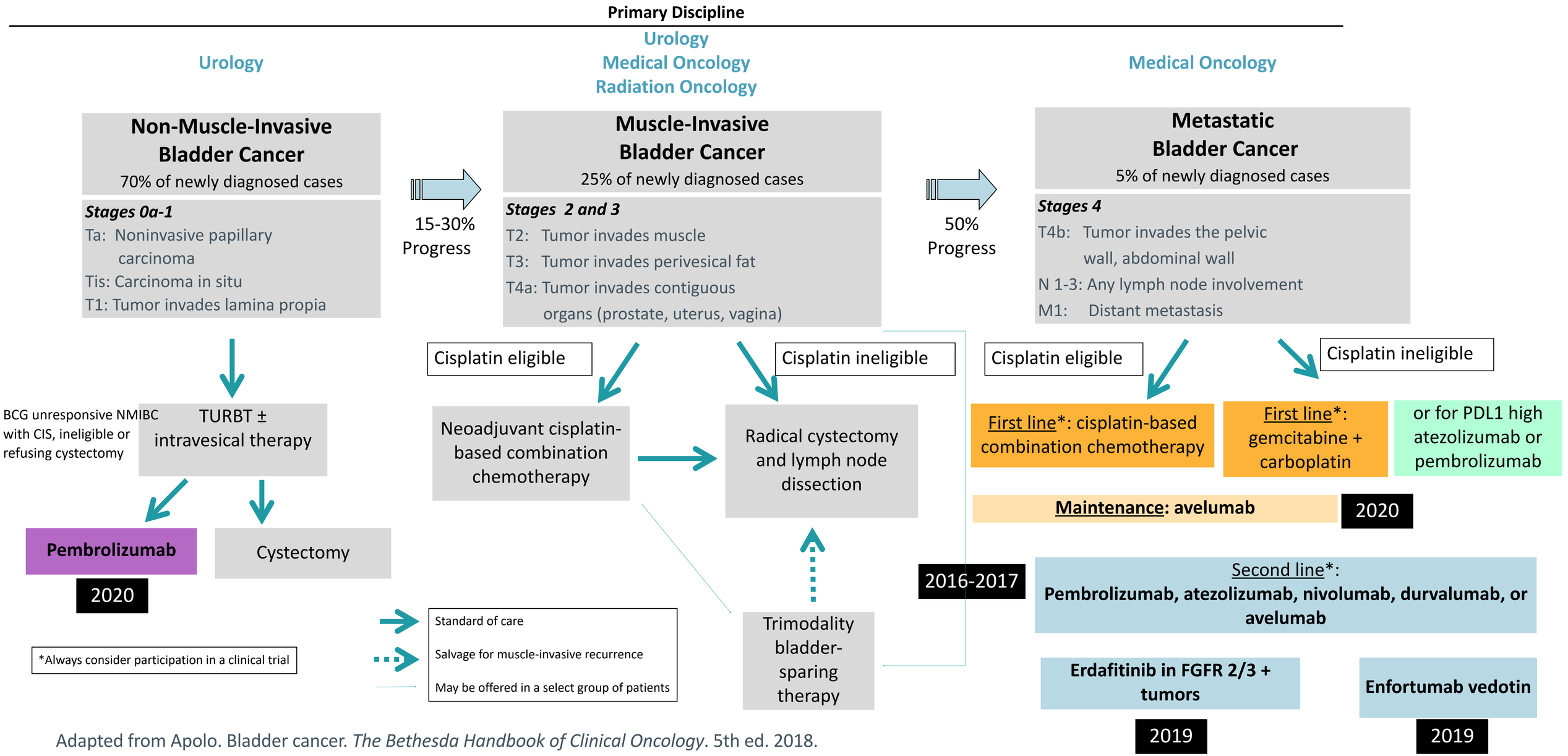



January 2020, FDA granted approval of pembrolizumab for BCG-unresponsive, high-risk, non-muscle-invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible or refuse cystectomy




Balar ASCO 2020. Abstr 5041.

# Bladder Cancer Management by Stage




Adapted from Apolo. Bladder cancer. *The Bethesda Handbook of Clinical Oncology*. 5th ed. 2018.

# Bladder Cancer: Spectrum of Disease

## The Future?