

# Urothelial Cancer 2023

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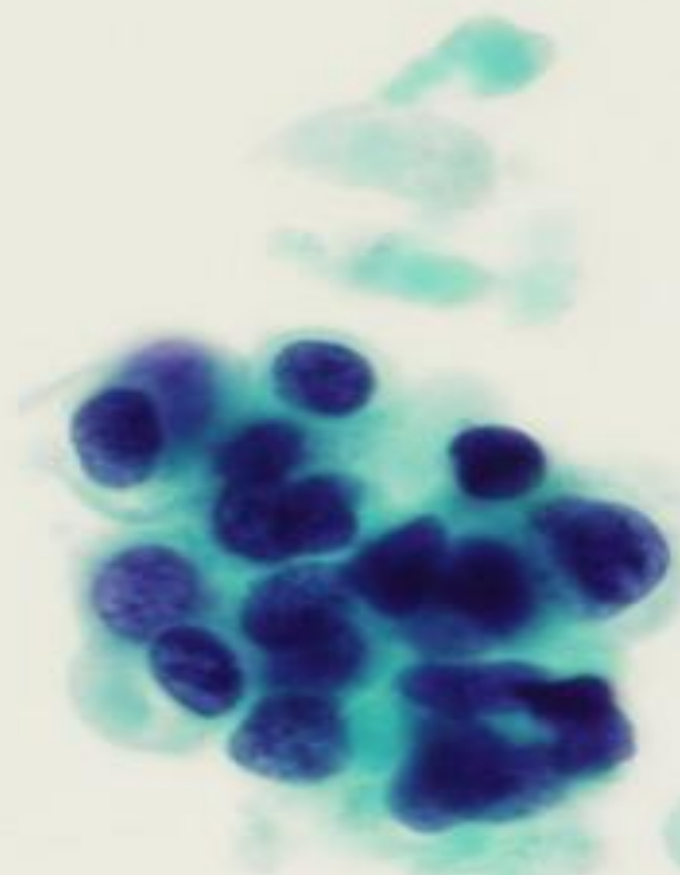
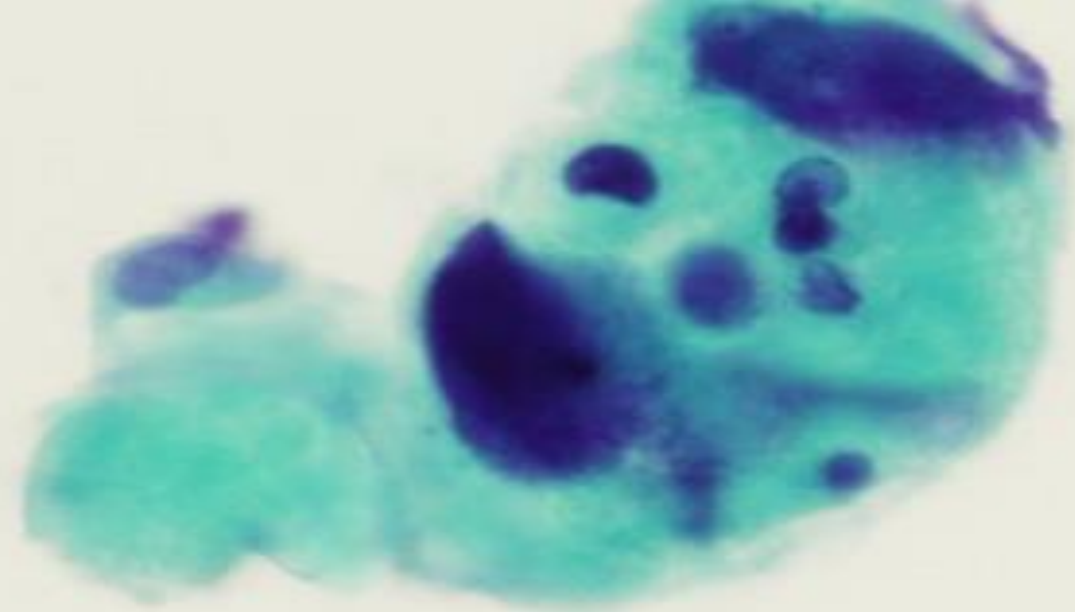
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## Aims

Review the latest ASCO abstract presented 2023

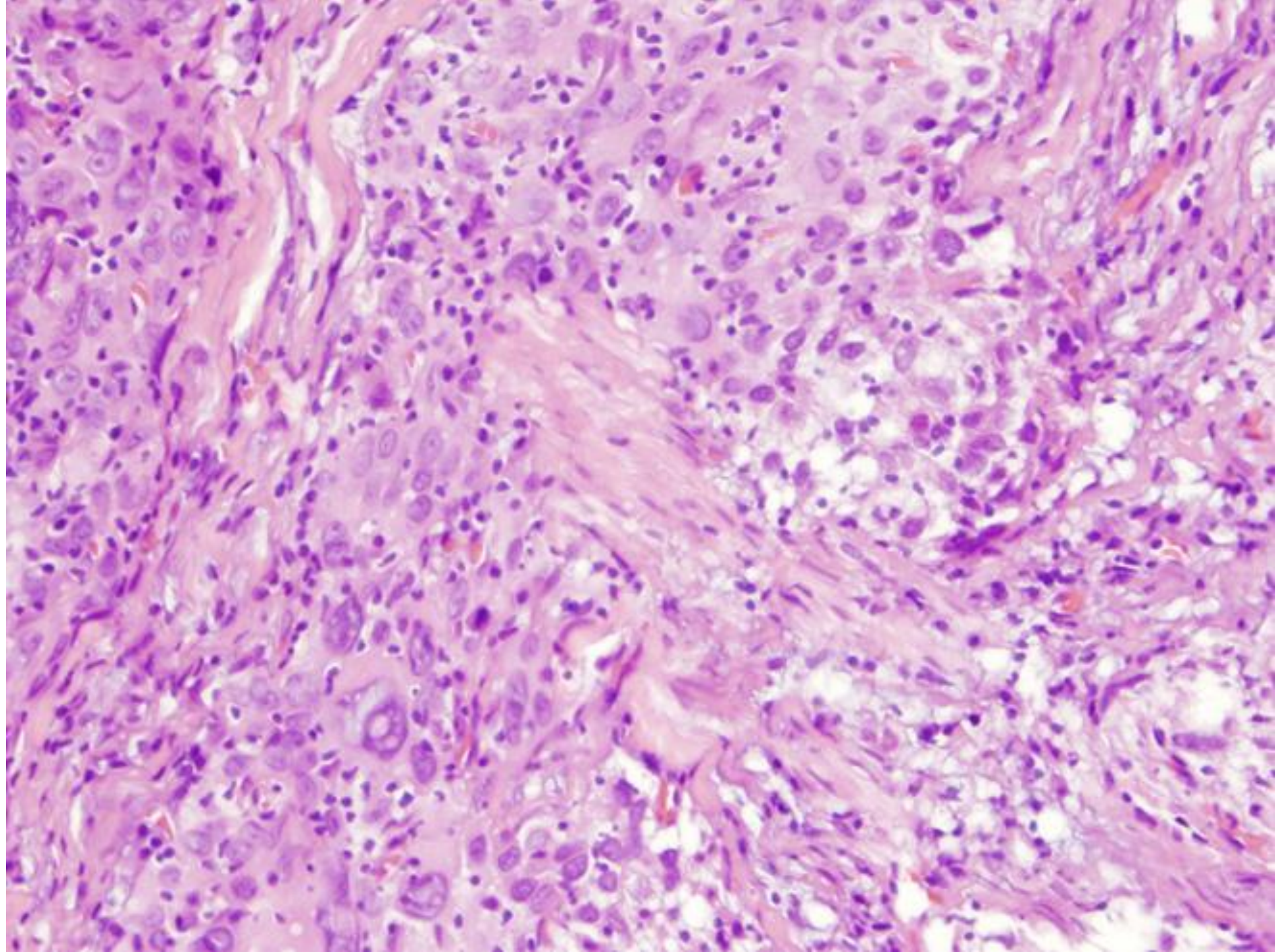
Elaborate and discuss the current standard of care for urothelial cancer and metastatic cancer management



## Pembrolizumab in superficial Bladder Cancer

Pembrolizumab was approved for treatment of patients with Bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

The recommended dose of pembrolizumab in patients with high-risk BCG-unresponsive non–muscle invasive bladder cancer is 200 mg via intravenous infusion over 30 minutes every 3 weeks until persistent or recurrent high-risk non–muscle invasive bladder cancer, disease progression, unacceptable toxicity,



Multicenter randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for muscle-invasive bladder cancer (MIBC): Overall survival (OS) data at 5 years in the GETUG/AFU V05 VESPER trial

Christian Pfister,  
Gwenaelle Gravis, Aude  
Flechon, Christine  
Chevreau, Hakim  
Mahammedi, Brigitte  
Laguerre, Aline Guillot,  
Florence Joly, Yves  
Allory, Valentin Harter,  
Stephane Culine





# Background

The optimal perioperative chemotherapy for patients (pts) with muscle-invasive bladder cancer remains open to discussion. The primary endpoint of the VESPER trial (NCT 018 12369) was previously reported with dd-MVAC improved 3 years PFS over GC schedule. In the neoadjuvant group, a better bladder local control and significant difference on 3y-PFS was observed in the dd-MVAC arm ( $p=0.025$ )



# Methods

Between February 2013 and February 2018, 500 pts were randomized in 28 French centers and received either 4 cycles of GC every 3 weeks or 6 cycles of dd-MVAC every 2 weeks before surgery (neoadjuvant group) or after surgery (adjuvant group). We report the final analysis of the VESPER phase III trial with the overall survival (OS) data after 5 years



# Results

437 pts (88%) received neoadjuvant chemotherapy, 60% of patients received the planned 6 cycles in the dd-MVAC arm, 84% received 4 cycles in the GC arm, thereafter 91% and 90% of patients underwent surgery, respectively.

Final median of follow-up was 5 years and 3 months and 190 deaths were reported within 5 years of follow-up.

OS at 5 years was improved in the dd-MVAC arm (64% vs 56%, HR=0.77 (95% CI, 0.58-1.03),  $p=0.078$ ), as was also disease-specific survival (DSS) (5-year rate: 72% vs 59%, HR=0.63 (95% CI, 0.46-0.86),  $p=0.004$ ).

The main cause of death was bladder cancer progression (83%), other causes included cardio-vascular events (4.2%), toxic deaths (2.1%), second cancers (2.1%), others (4.7%) and undocumented deaths (4.2%).

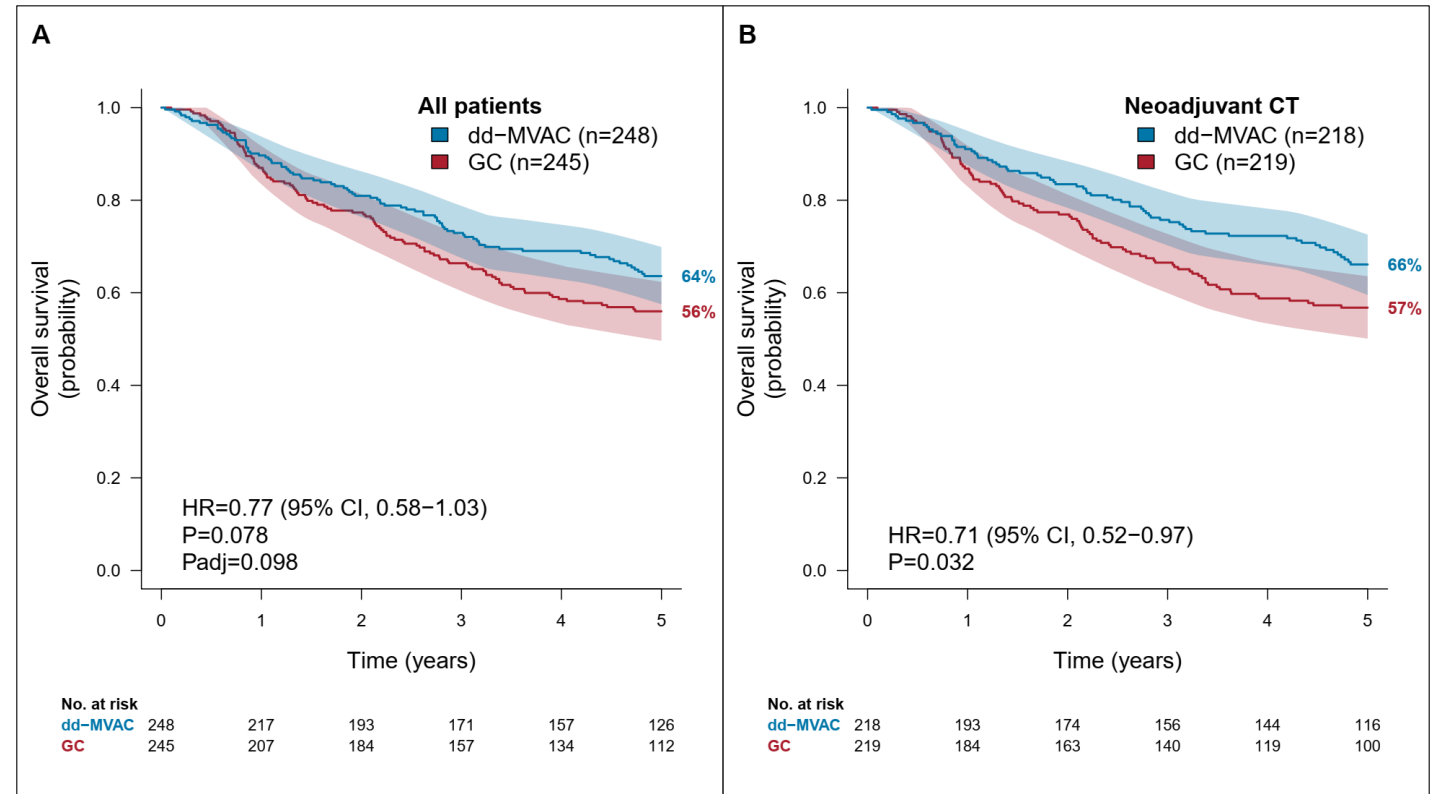
In the neoadjuvant group, OS was significantly superior in the dd-MVAC arm (5-year rate: 66% vs 57%, HR=0.71 (95% CI, 0.52-0.97),  $p=0.032$ ) as well as DSS (5-year rate: 75% vs 60%, HR=0.56 (95% CI, 0.39-0.80),  $p=0.001$ ).

In the adjuvant group, the results were not conclusive due to the limited sample size ( $n=56$ )

# Results (1)

## Overall Survival at 5 years

- C Pfister - 5-y OS Vesper



# Conclusion

Dose-dense MVAC provided a better OS at 5 years and improved significantly DSS over GC in the peri-operative setting of MIBC



# Surgery for muscle invasive

- Radical cystoprostatectomy in men
- Anterior pelvic exenteration in women
- Bilateral pelvic lymphadenectomy (PLND), standard or extended
- Creation of a urinary diversion
- Neoadjuvant chemotherapy

**SWOG S1011: A phase III surgical trial to evaluate the benefit of a standard versus an extended lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer**

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# Background

- S1011 tested the hypothesis that an extended lymphadenectomy (ELND) is associated with improved disease-free and overall survival (DFS, OS) compared to standard (S) LND in patients with localized muscle invasive bladder cancer

# Methods

- Eligible patients with cT2-4a N0-2 were stratified by receipt and type of neoadjuvant chemotherapy (NAC), T2 vs T3-4a and PS 0-1 vs 2. Patients were randomized 1:1 after intraoperative exploration determined they did not have disease outside the pelvis. All patients then underwent a standard bilateral pelvic LND including external and internal iliac and obturator LNs.
- If randomized to the experimental arm additional ELND up to at least the aortic bifurcation including common iliac (CI), pre-sciatic, and pre-sacral nodes was performed.
- We hypothesized that patients in the ELND arm would have a 10% improvement in 3-year DFS compared to an estimated 55% for patients in the SLND arm (HR = 0.72).

# Results

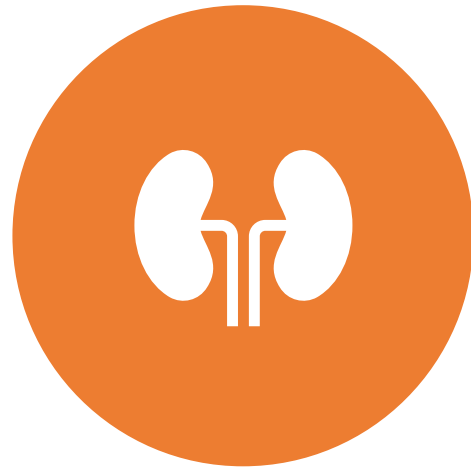
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- 36 surgeons at 27 sites in US and Canada were credentialed prior to enrolling patients, 658 were registered from 8/11-2/17, and 618 eligible patients were randomized to ELND (n=292) or SLND (n=300).
- Median f/up was 6.1 years in both arms. Median age was 69, 21% female, and 9% non-White. Clinical stage was balanced in both arms: T2 (71%) and T3-4a (29%). NAC was given to 57% in both. Pathologic T stage was <T2 in 39% in S and 37% in E and <sup>3</sup> T2 in 61% and 63%, respectively. Median lymph nodes removed was higher in ELND compared to SLND (41 vs 25), but there was no difference in node metastasis with 26% vs 24%, respectively



# Results

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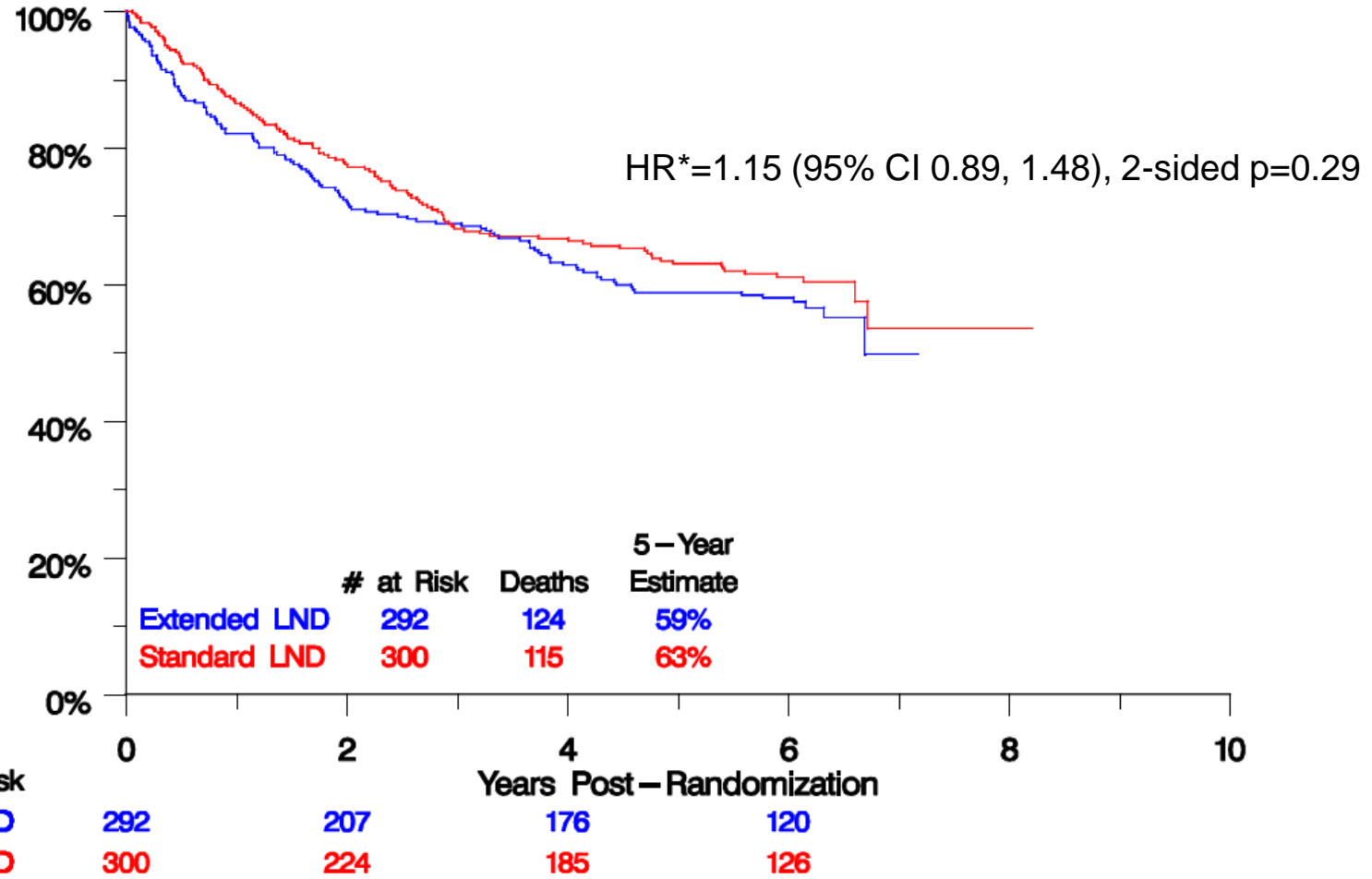
MORE ELND PATIENTS HAD N2 OR N3 DISEASE. ELND WAS ASSOCIATED WITH INCREASED G3-4 AES COMPARED TO SLND: 16% VS 8%. DEATHS WITHIN 90 DAYS OF RC OCCURRED IN 26 (4.4%) PATIENTS, INCLUDING 16 IN ELND VS 9 IN SLND. THERE WAS NO DIFFERENCE IN DFS BETWEEN E VS S ARMS (HR 1.10; 95% CI 0.87, 1.42), 1-SIDED LR P=0.82.



OS RESULTS WERE SIMILAR (HR 1.15 95% CI 0.89, 1.48), 1-SIDED LR P=0.87

## Overall Survival

All Eligible, Randomized Patients



# Conclusion

- Patients with MIBC undergoing RC and ELND had increased node yield and higher pathologic N stage, but no significant DFS or OS benefit compared to patients undergoing SLND. ELND was also associated with greater morbidity and higher peri-operative mortality

# Metastatic bladder cancer

Standard of care

Cisplatin  
/gemcitabine 4-6  
cycles

Average survival  
is 14 months

# Avelumab

- In a phase 3 trial, patients with unresectable locally advanced or metastatic urothelial cancer who did not have disease progression with first-line chemotherapy (four to six cycles of gemcitabine plus cisplatin or carboplatin) to receive best supportive care with or without maintenance avelumab. The primary end point was overall survival, assessed among all patients who underwent randomization (overall population) and among those with tumors positive for programmed cell death ligand 1 (PD-L1).

Powles T , Park Sh, Voog E. NEJM 2020;383:1218-1230

# Results

- Among all 700 patients who underwent randomization.
- Overall survival at 1 year was 71.3% in the avelumab group and 58.4% in the control group (median overall survival, 21.4 months vs. 14.3 months; hazard ratio for death, 0.69; 95% confidence interval [CI], 0.56 to 0.86;  $P=0.001$ ). Avelumab also significantly prolonged overall survival in the PD-L1–positive population; overall survival at 1 year was 79.1% in the avelumab group and 60.4% in the control group (hazard ratio, 0.56; 95% CI, 0.40 to 0.79;  $P<0.001$ ).

# Results

The median progression-free survival was 3.7 months in the avelumab group and 2.0 months in the control group in the overall population (hazard ratio for disease progression or death, 0.62; 95% CI, 0.52 to 0.75) and 5.7 months and 2.1 months, respectively, in the PD-L1–positive population (hazard ratio, 0.56; 95% CI, 0.43 to 0.73). The incidence of adverse events from any cause was 98.0% in the avelumab group and 77.7% in the control group; the incidence of adverse events of grade 3 or higher was 47.4% and 25.2%, respectively.



## New approval

April 3, 2023, the Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv with pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy





## Response rate

Major efficacy outcome measures were objective response rate (ORR) and duration of response (DoR) determined by blinded independent central review using RECIST v1.1. The confirmed ORR in 121 patients was 68% (95% CI: 59, 76), including 12% with complete responses. The median DoR for the dose escalation cohort + Cohort A was 22 months (range: 1+ to 46+) and for Cohort K was not reached (range: 1 to 24+)



## Side effects

Most common adverse reactions (>20%), including laboratory abnormalities, were increased glucose, increased aspartate aminotransferase, rash, decreased hemoglobin, increased creatinine, peripheral neuropathy, decreased lymphocytes, fatigue, increased alanine aminotransferase, decreased sodium, increased lipase, decreased albumin, alopecia, decreased phosphate, decreased weight, diarrhea, pruritus, decreased appetite, nausea, dysgeusia, decreased potassium, decreased neutrophils, urinary tract infection, constipation, potassium increased, calcium increased, peripheral edema, dry eye, dizziness, arthralgia, and dry skin.



## Standard dose

- Recommended enfortumab vedotin-ejfv dose when given with pembrolizumab is 1.25 mg/kg (up to a maximum of 125 mg for patients  $\geq 100$  kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. The recommended pembrolizumab dose, administered after enfortumab vedotin on the same day, is 200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months.