Systemic Therapy for Bladder Cancer in 2022: The Medical Oncologist's Perspective

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Presenter Disclosure

- **Faculty/Speaker:** Hanbo Zhang

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** Merck (honoraria), Novartis AAA and Pfizer (advisory boards).
  - **Consulting Fees:** None
  - **Other:** Employed by CCMB and U of M

Mitigating Potential Bias

- Using generic names of drugs
- Talking about approved indications of drugs

Equity Commitment

- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

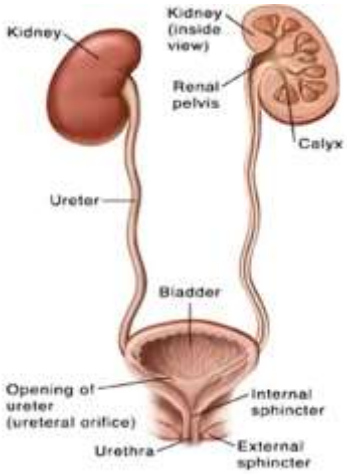
- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

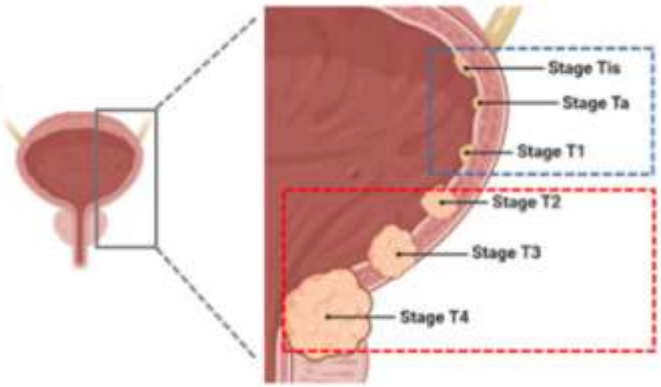
Learning Objectives

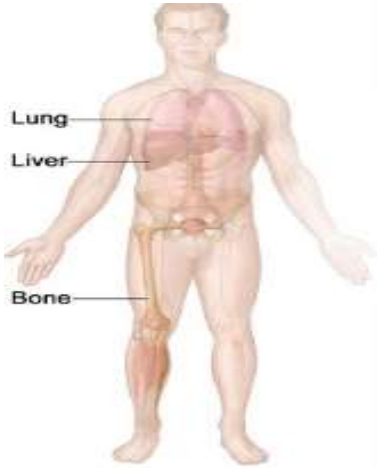
At the end of this session participants will be able to:

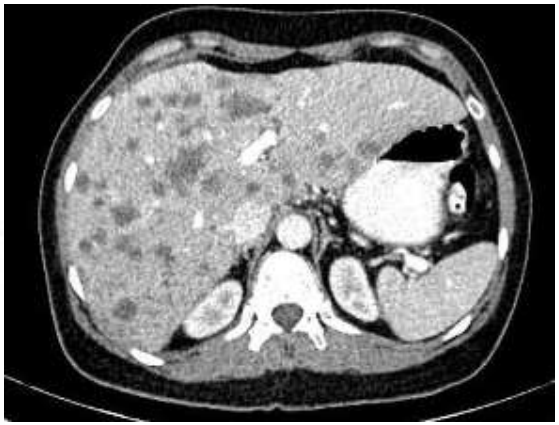
- Explain the roles of systemic therapy in management of muscle-invasive bladder cancer;
- State the current systemic therapy options for metastatic bladder cancer;
- Describe the management of toxicities of newer systemic therapy agents (immune checkpoint inhibitor, antibody drug conjugate, and FGFR inhibitor);

Urothelial Carcinoma (UC)





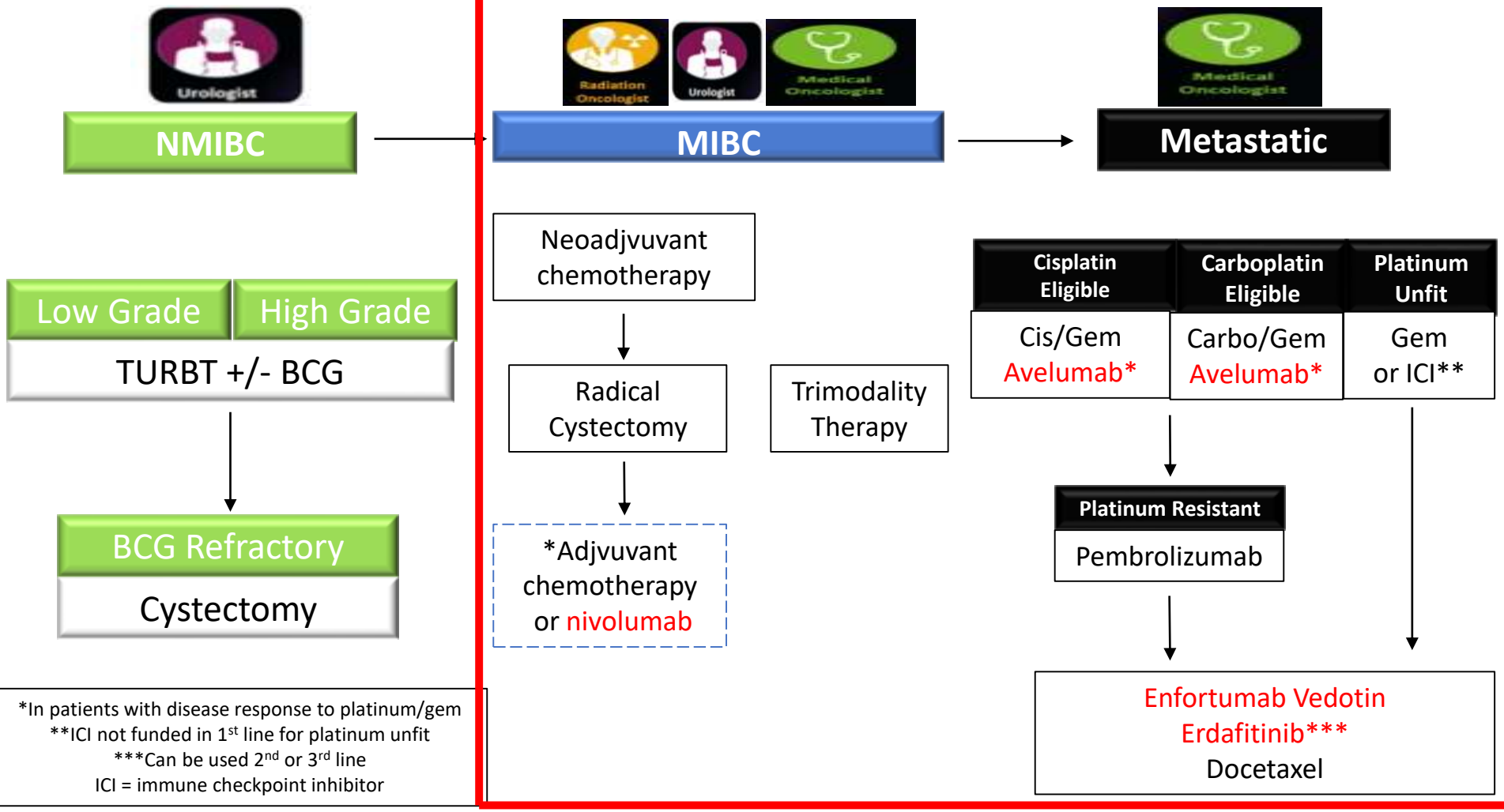




- Average age at diagnosis is 73
- Most common histologic subtype: urothelial carcinoma (UC)
- 70% are non-muscle invasive (NMIBC) (pTis, pTa, pT1)
- 25% are muscle invasive (MIBC) (pT2, pT3, pT4)
  - Many will develop recurrence
  - **5-year survival 50%**
- 5-10% are metastatic (N+, M+)
  - **5-year survival 6% (M+)**
  - Improving over time
    - 3-6 months prior to introduction of modern chemotherapy

Canadian Cancer Society 2021 ; American Cancer Society 2022

Disease Management Overview



*In patients with disease response to platinum/gem
**ICI not funded in 1st line for platinum unfit
***Can be used 2nd or 3rd line
ICI = immune checkpoint inhibitor

Evolution of Systemic Therapy

CancerCare Manitoba
ActionCancerManitoba

mUC: First Line Chemotherapy

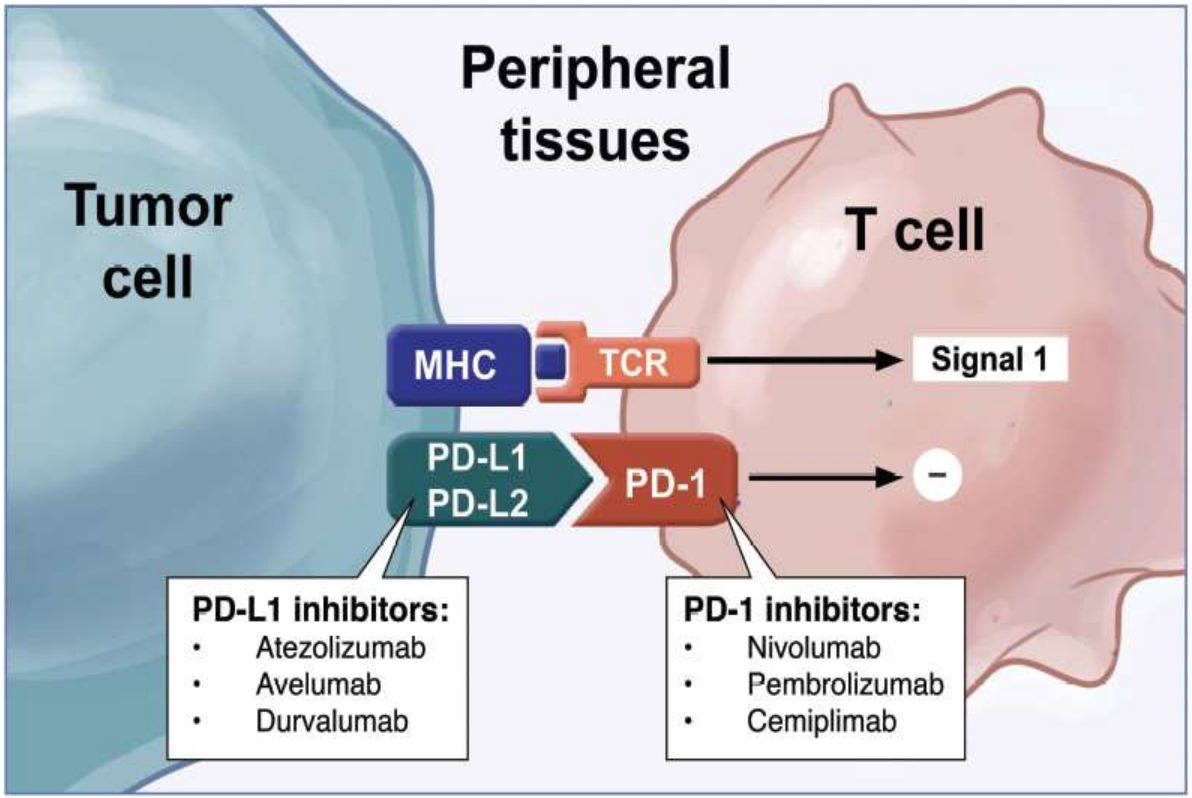
- First-line treatment remains platinum-based chemotherapy
- Active regimens, but short durability (PFS ~6-7 months)
  - **Cisplatin (Day 1) + Gemcitabine (Day 1+ 8) q3wks x 4-6 cycles**
    - median overall survival 14 months, response rate 46%
  - **Carboplatin (Day 1) + Gemcitabine (Day 1 + 8) q3wks x 4-6 cycles**
    - median overall survival 9 months, response rate 41%

- Cisplatin eligibility (need all):

  (ECOG 0-1, GFR >50-60mL/min, peripheral neuropathy < grade 2, audiometric hearing loss < grade 2 or heart failure < NYHA class III)

Von der Maase H, JCO 2005; De Santis M, et al. JCO 2012

Immune checkpoint Inhibitors (ICI) – role in metastatic UC

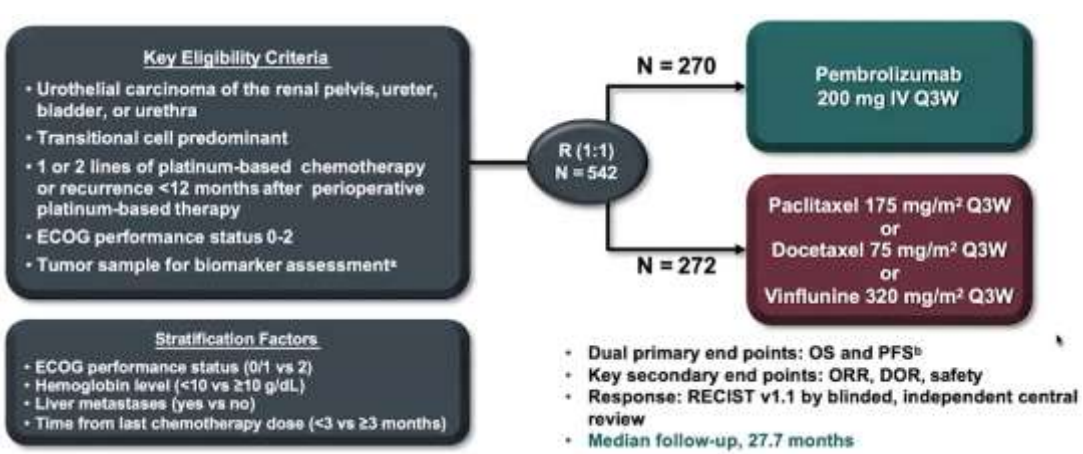


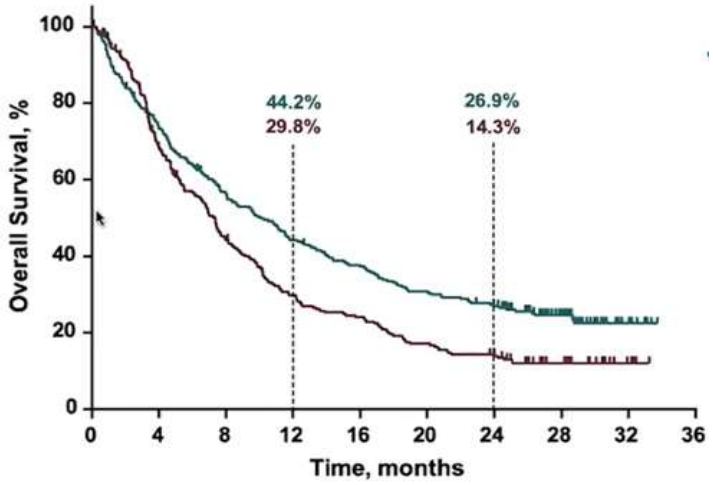
Abbreviations: MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1/2, programmed death-ligand 1 or 2; TCR, T cell receptor.

This article was published on February 17, 2017, at NEJM.org.

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

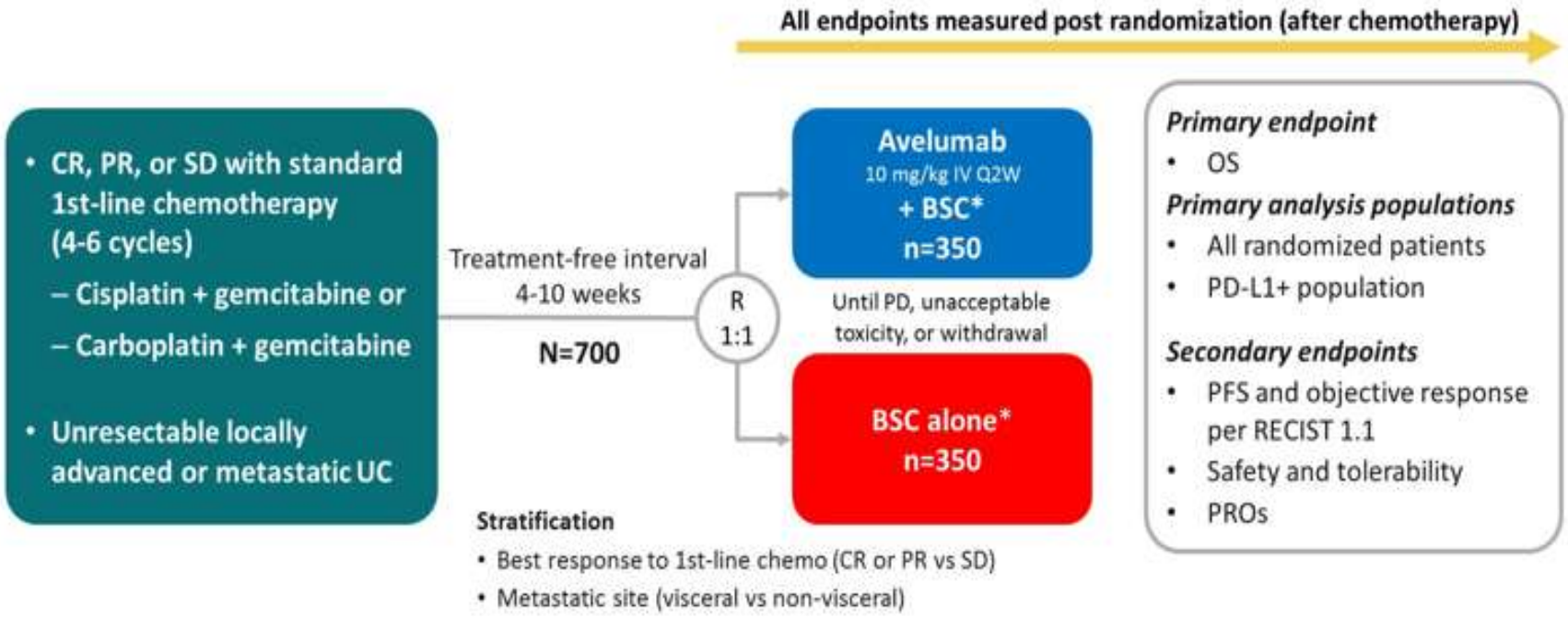




- Overall survival 10.1 months vs. 7.2 months (HR 0.73, p 0.0022).
- ORR: 21 %, median OS have not been reached at 5-year follow up.
- Part of Provincial Oncology Drug Formulary

Bellmunt et al. NEJM 2017

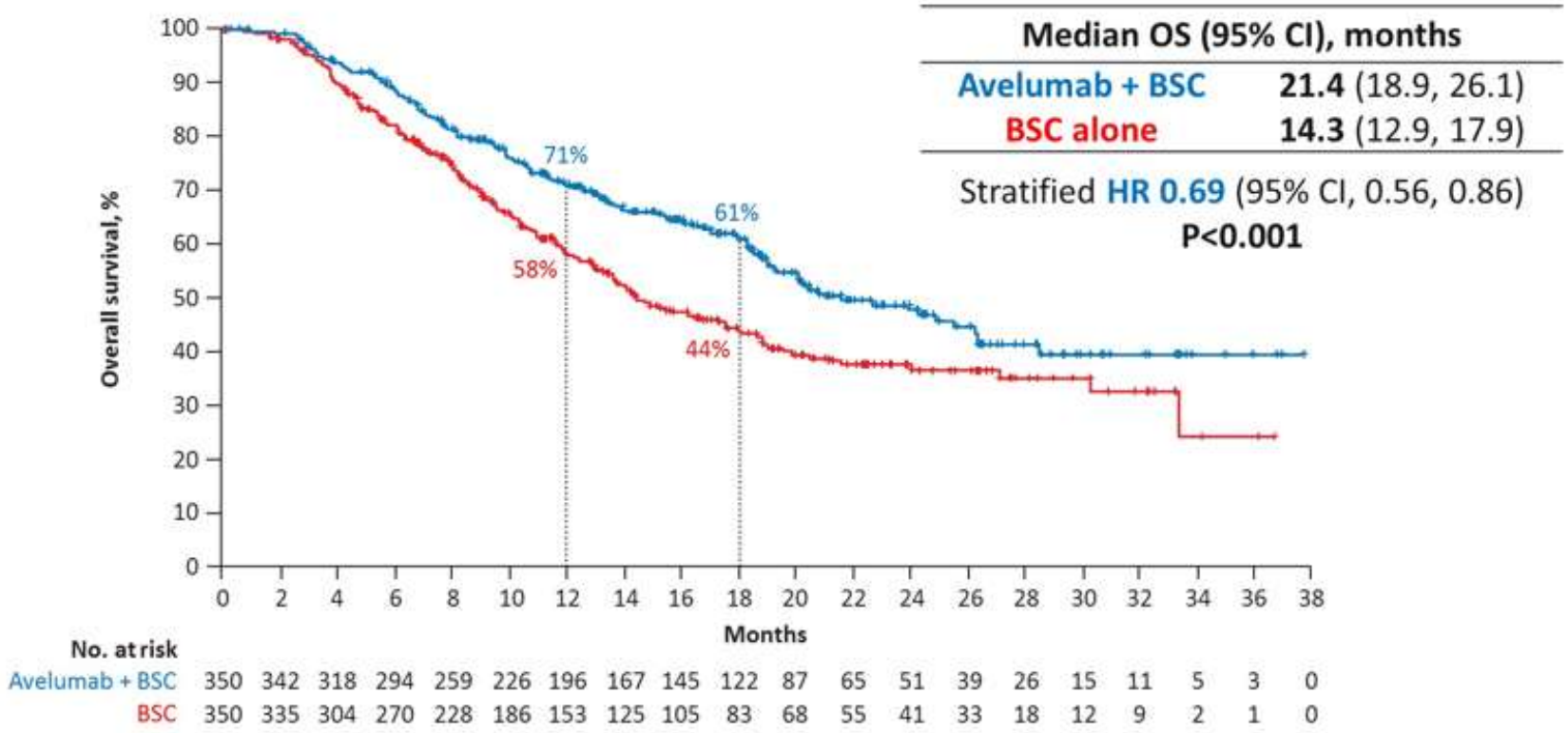
JAVELIN Bladder 100 - Avelumab



- Phase III, randomized, open-label trial investigating 1L maintenance with avelumab in patients whose disease had not progressed with platinum-based induction chemotherapy.

Powles T, et al; ASCO 2020

Overall survival



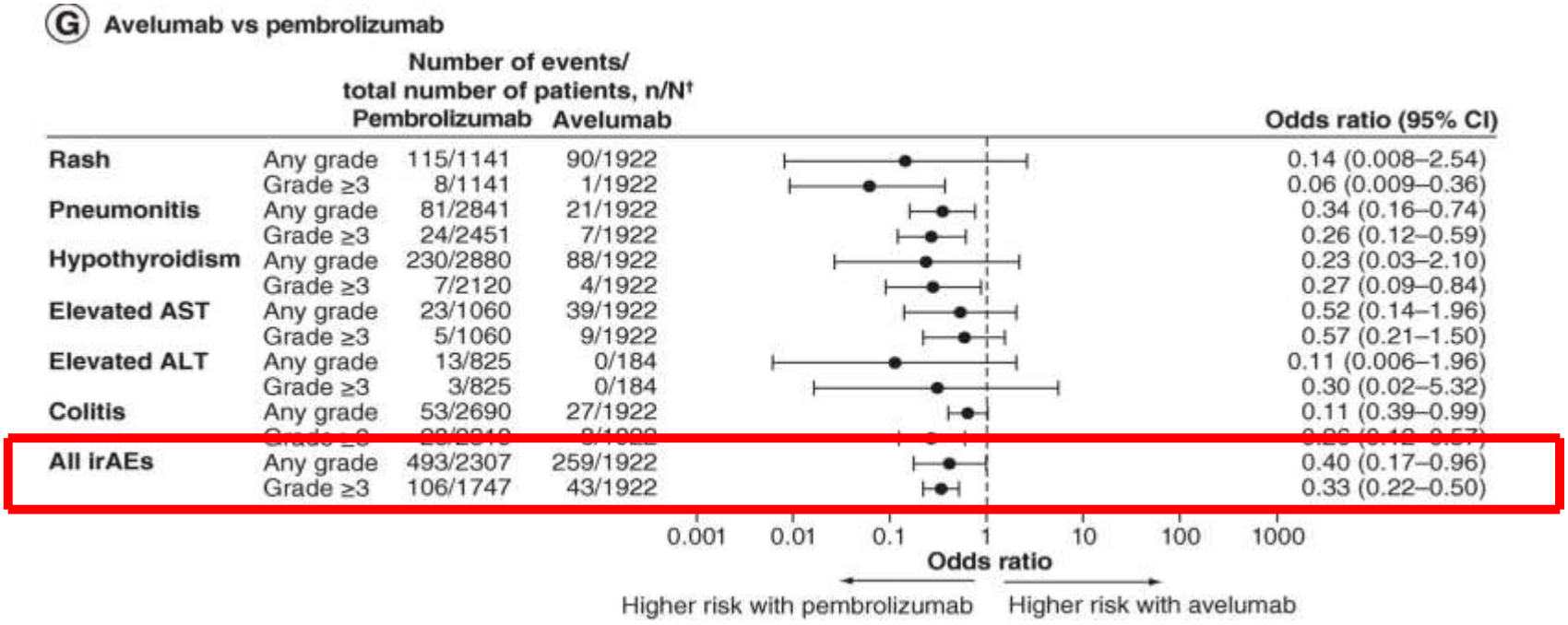
- At median follow-up of 38 months:
  - median OS **23.8 months**. Vs. **15 months**. HR 0.76 (0.63 – 0.92), P 0.0036

Powles T, et al; ASCO 2020/2022

Maintenance Avelumab

- For patients who have stable disease or response after 4-6 cycles of platinum-based chemotherapy
  - Health Canada Approved in Jan 2021
  - Added to Provincial Oncology Drug Program formulary as of April 1st, 2022.

Immune-related Toxicities



- Grade 3 or higher immune-related events 7% for avelumab, 15% for pembrolizumab.

Sonpavde et al. Future Oncology 2021

Avelumab Infusional Reactions

- Premedication: cetirizine 10 mg + acetaminophen 650 mg po 30 min prior to avelumab; at least for the first 4 infusions

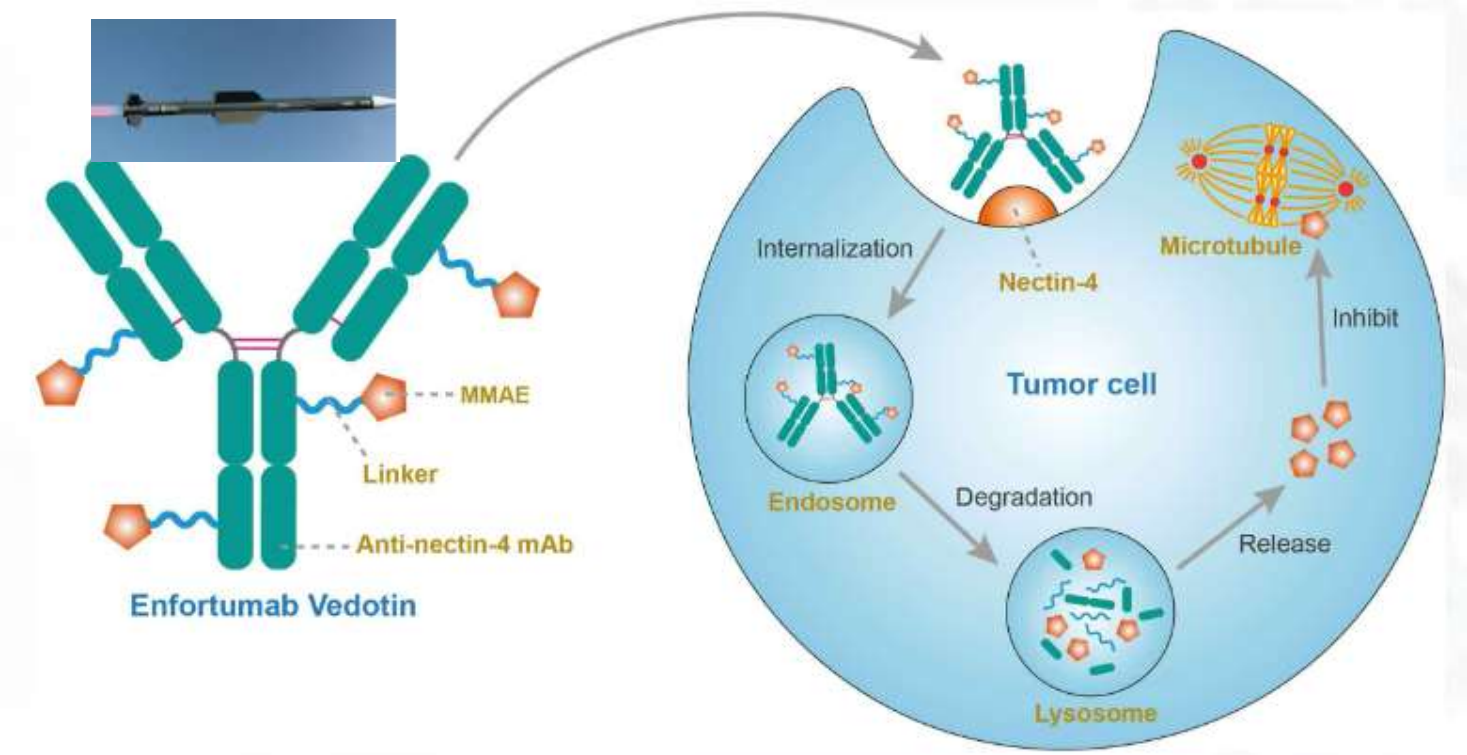
Table 1 Incidence of infusional reaction among selected PD-1 or PD-L1 inhibitors

Agent, (reference)	Grade 1, 2 (%)	Grade 3, 4 (%)	Total (%)
Avelumab, (7)	18.5	2.2	20.7
Atezolizumab, (4)	NR	NR	1.3
Durvalumab, (5)	1.5	0.3	1.8
Nivolumab, (9)	3.7	0.4	4.1
Pembrolizumab, (10)	4.5	0	4.5

NR, not reported.

Tanvetyanon, Trans Cancer Res; 2017
2022 PODP Regimen Reference Order

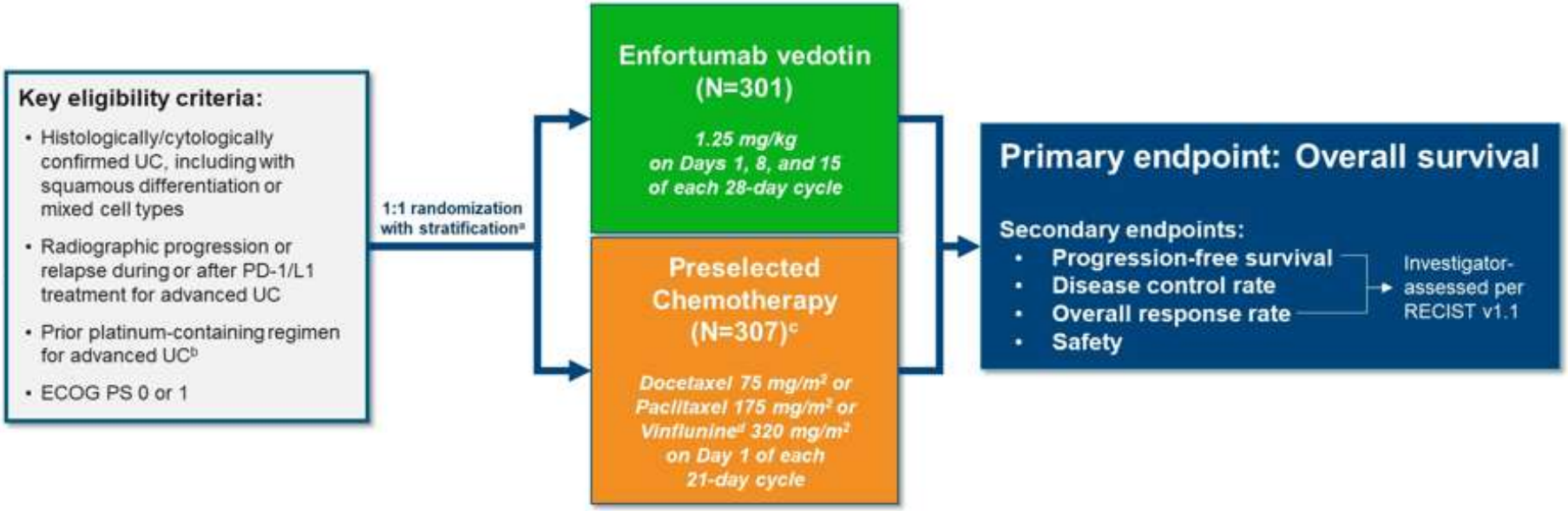
Enfortumab Vedotin



- Antibody-drug conjugate against Nectin-4 (cell adhesion molecule highly expressed on urothelial carcinoma cells)
- Monomethyl auristatin E (MMAE) – microtubule inhibitor.

Enfortumab Vedotin

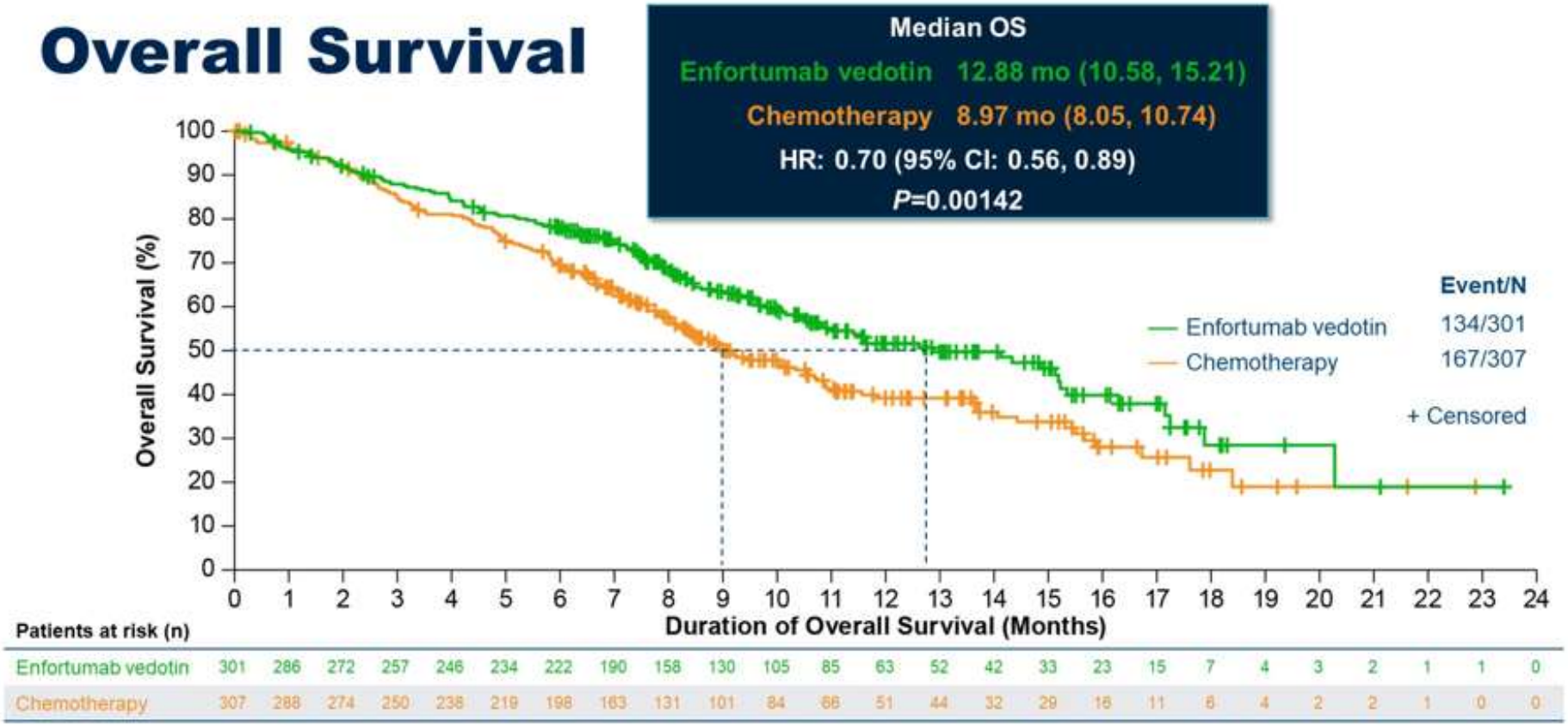
EV-301 Open-Label Phase 3 Trial Design



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

Powles et al. GU ASCO 2021

Overall Survival



- Overall response **40.6%** vs. **17.9%.**
- At median follow-up of 23.75 months:
  - median OS **12.91 months**. Vs. **8.94 months**. HR 0.70 (0.58 – 0.85), P = 0.00015

Powles et al. GU ASCO 2021; Rosenberg et al. JCO 2022

Enfortumab Vedotin - Status

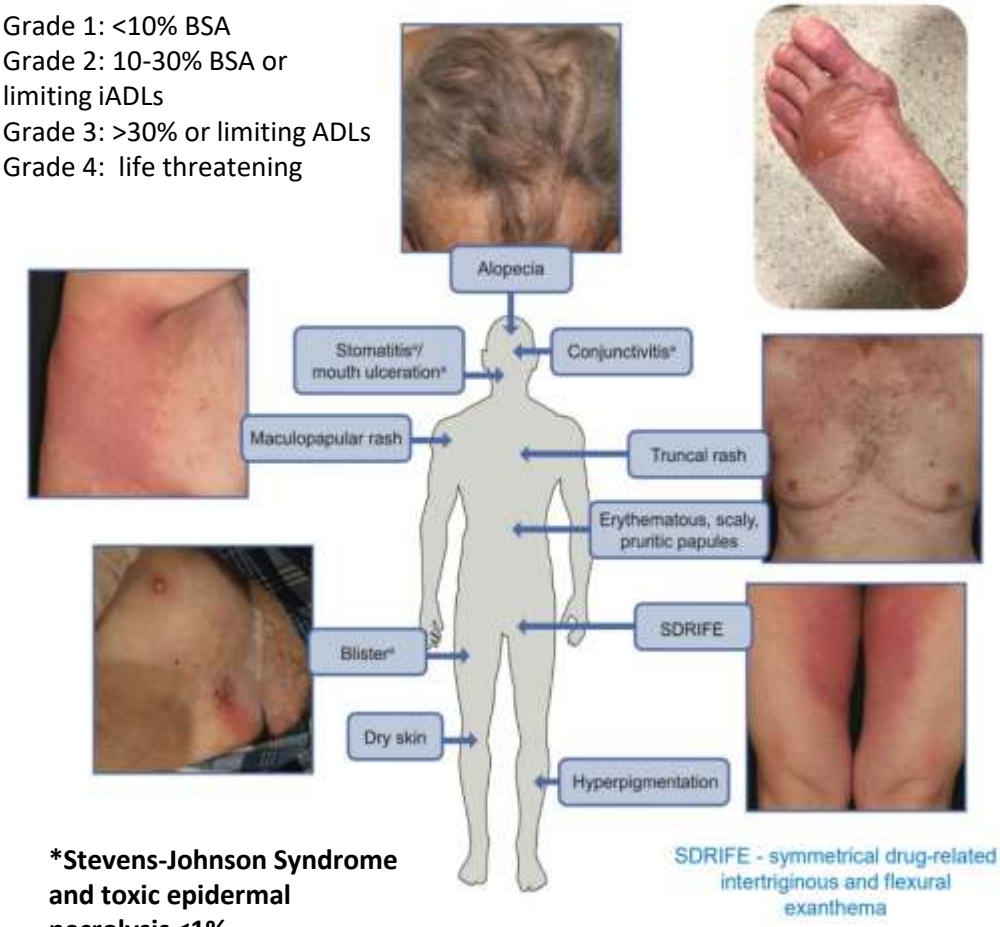
- Health Canada approved for treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and PD-1/PD-L1 inhibitor therapy.

- Recommendation for reimbursement with conditions by CADTH as of January 24, 2022

- Available through Compassionate Access Program

Skin Toxicities

Grade 1: <10% BSA
Grade 2: 10-30% BSA or limiting iADLs
Grade 3: >30% or limiting ADLs
Grade 4: life threatening



***Stevens-Johnson Syndrome and toxic epidermal necrolysis <1%**

- Skin Reactions (~50% of patients)
  - Pruritus +/- maculopapular rash most common
  - Severe ~10%
- Typically occur within 1st cycle
- Prevention (moisturizers, sunscreen)
- Rash/pruritis:
  - Grade 1-2 :topical corticosteroids and antihistamine
  - Grade 3: STOP DRUG. Oral corticosteroid (prednisone 0.5 mg/kg/day for 14 days)
  - Consult Dermatology for grade $\geq$ 3

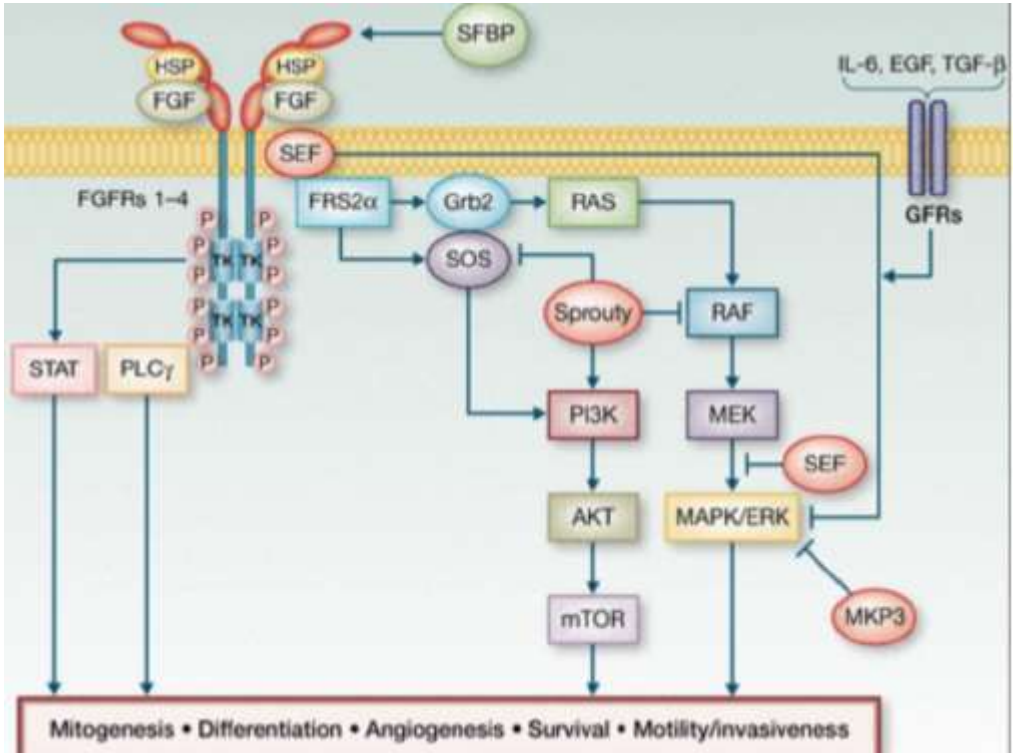
Lacouture et al. Oncologist 2022; 2022 BC Cancer Drug Manual Enfortumab Vedotin

Other Important Toxicities

- Peripheral Neuropathy (~50% of patients)
  - Primarily sensory
  - Severe (2-4%)
  - Median time to onset of grade 2: 3.8 months
  - Dose reduction for grade 2 and interruption for grade $\geq$ 3
- Ocular Disorders
  - Dry eyes (~40%, prophylaxis with artificial tears)
  - Keratitis (<1%; ophthalmic topical steroids, and consult ophthalmology)
  - Median time to onset: 1.9 months
- Hyperglycemia (severe 8%)
  - Optimize glucose control prior to starting treatment
  - Close monitoring of BG in patients with or at risk for diabetes mellitus
  - *Contact prescriber if BG > 13.9 mmol/L*

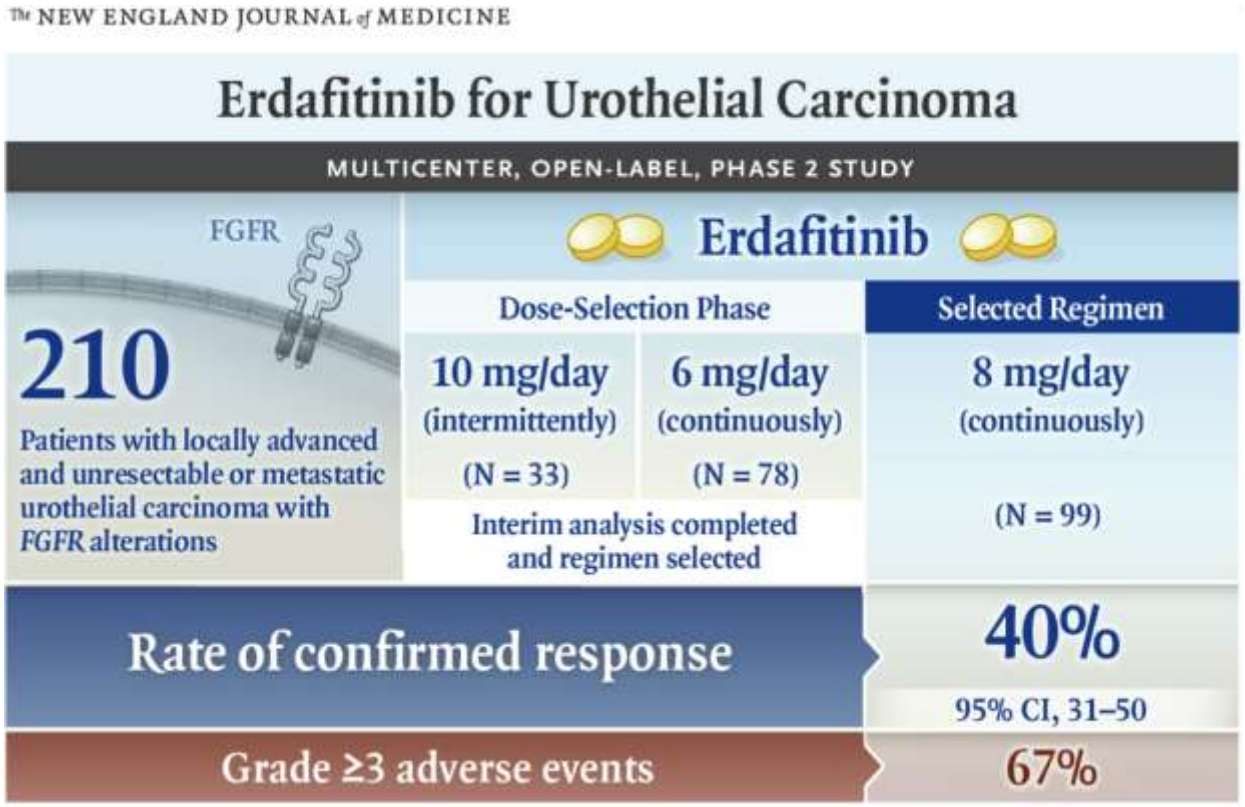
2022 BC Cancer Drug Manual Enfortumab Vedotin; 2022 PODP Regimen Reference Order

Erdafitinib – FGFR inhibitor



- Fibroblast Growth Factor receptors – regulate cell growth, survival, migration and differentiation.
- ~20% of mUC have FGFR2/3 alterations
  - More frequent in upper tract (37%)
- Erdafitinib is a potent small molecule tyrosine kinase inhibitor of FGFR 1-4.

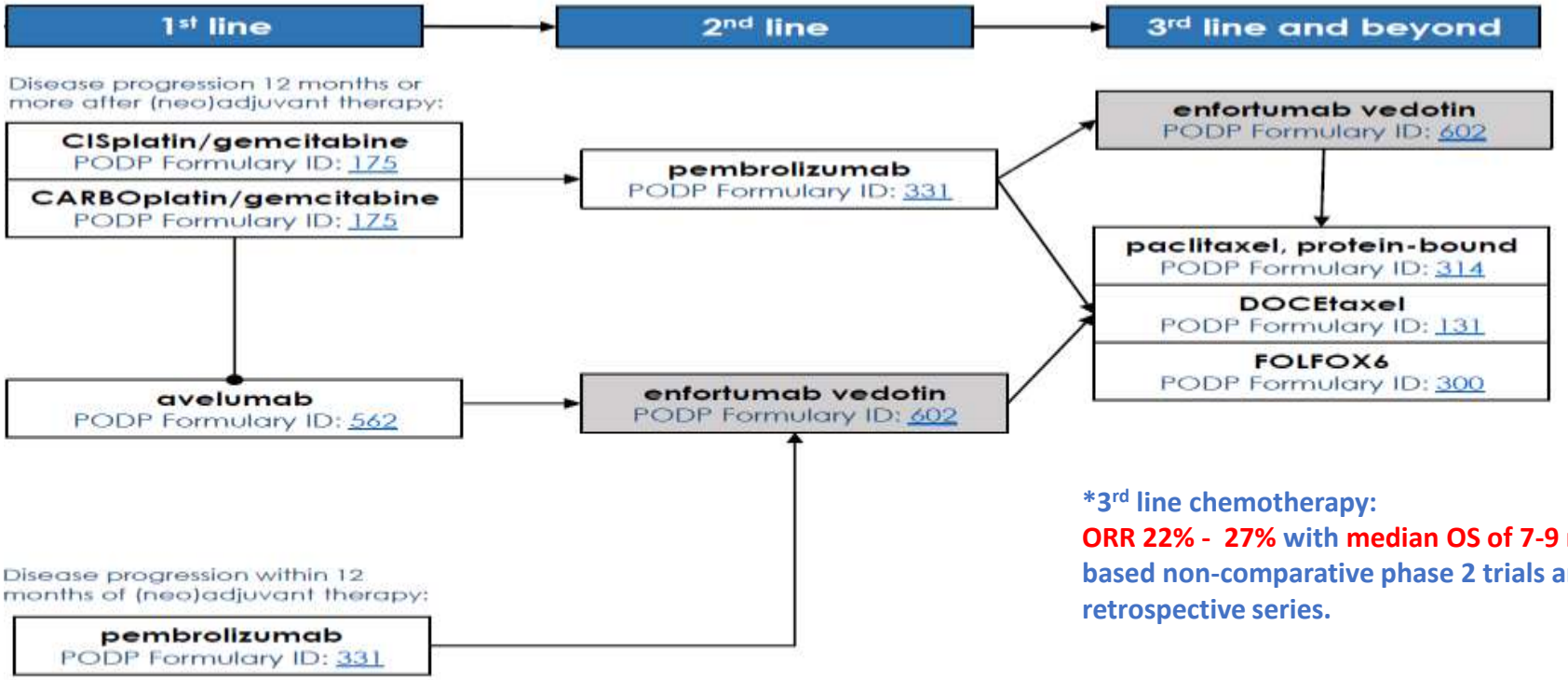
Erdafitinib – FGFR inhibitor



- Median PFS 5.5 months and OS 13.8 months
- FDA – approved for patients with mUC and selected FGFR2/3 alterations.
- Conditional approval by Health Canada
- Compassionate Access Program available
- Toxicities
  - Hyperphosphatemia
  - Stomatitis; Diarrhea
  - Dry mouth
  - Central serous retinopathy

Loriot et al. NEJM 2021

Treatment Algorithm for mUC



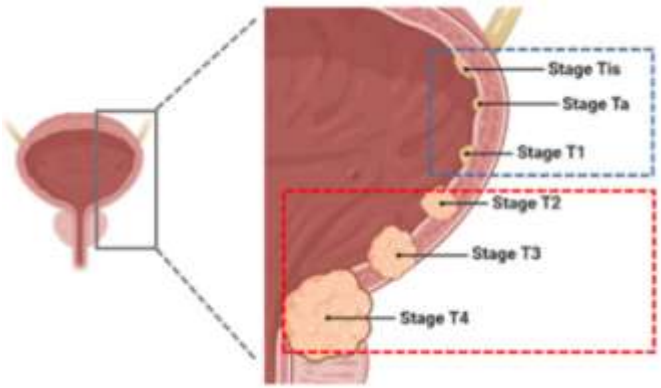
***3rd line chemotherapy:**
ORR 22% - 27% with median OS of 7-9 months based non-comparative phase 2 trials and retrospective series.

**** Erdafinitib can be given 2nd or 3rd line for patients with FGFR mutations/fusions**

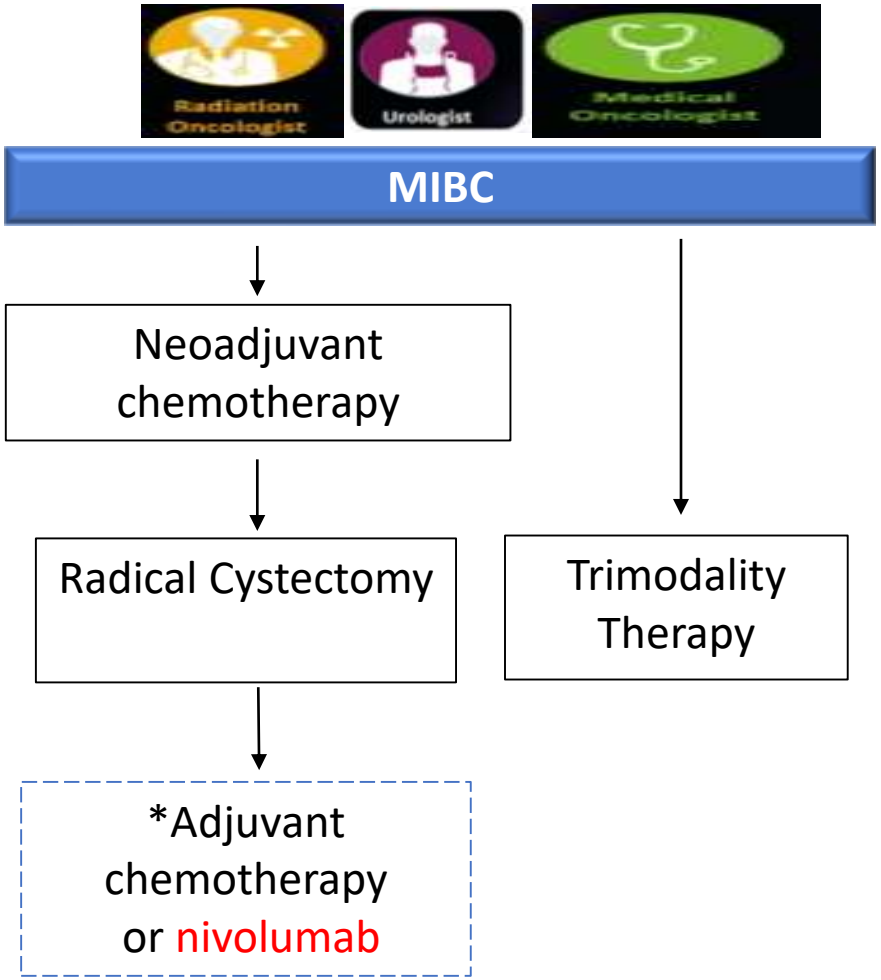
Version Date: March 2022

Provincial Oncology Drug Formulary Funding Algorithms: Urothelial Carcinoma March 2022; Sridhar et al. JAMA Oncol 2020; Dodagoudar at al. JJCO 2016

Muscle-invasive Bladder Cancer (MIBC)



- Goal of treatment is cure!
- Radical cystectomy with bilateral pelvic lymphadenectomy is gold standard treatment in North America
- 5-year overall survival ~50%



Bladder Preservation (Trimodality Therapy)

- Multimodality approach combining maximum TURBT with radiotherapy and concurrent radiosensitizing chemotherapy.
  - Weekly cisplatin (if GFR $\geq$ 60)
  - Mitomycin + 5-FU (PICC line required)
  - Weekly gemcitabine (frail patients)

- 5-year OS ~51-57%

- No completed definitive randomized trials that compare bladder preserving trimodality with radical cystectomy

Choudhury et al. JCO 2011; James et al. NEJM 2012; Tunio et al. IJROBP. 2012

Bladder Preservation (Trimodality Therapy)

- Ideal candidates for bladder preservation:
  - Unwilling to undergo or unable to tolerate radical cystectomy
  - No hydronephrosis
  - Urothelial histology
  - T2-T3a
  - No extensive CIS
  - Solitary lesion
  - Tumour smaller < 5 cm
  - Visibly complete TURBT
  - Proper bladder capacity and function
- Intensive process:
  - Frequent cystoscopy to evaluate response to therapy
  - Frequent follow-up to monitor for local recurrence or new primary tumours

Kulkarni et al. CUAJ 2019; Jiang et al. Bladder Cancer 2020

Neoadjuvant Chemotherapy for MIBC

- Standard of care prior to radical cystectomy (level 1 evidence)
- Advanced Bladder Cancer Meta-analysis Collaboration (11 RCTs of **cisplatin-based** neoadjuvant chemotherapy)
  - 5% improved of 5-year survival (50% vs. 45%)
- Pathologic complete response (pCR) 30-40%
  - 5-year cancer-specific survival ~90%
- Does not increase surgical morbidity

ABC Meta-analysis collaborators. Eur Urol 2005; Zargar et al. J Urol 2016

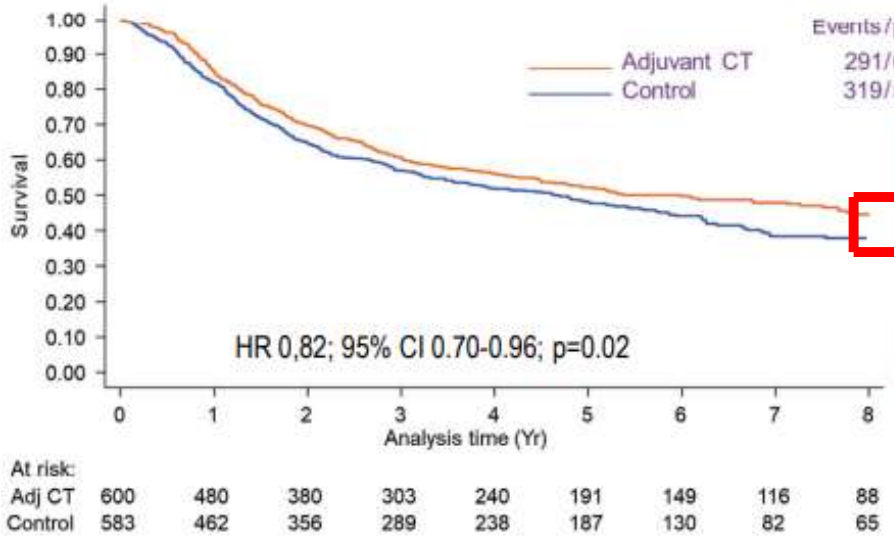
Neoadjuvant Chemotherapy for MIBC

- Regimens:
  - Cisplatin + Gemcitabine x 4 cycles
    - Day 1 (cis+gem), Day 8 (gem) q 21 days
    - Most commonly used regimen
  - Dose-dense MVAC (methotrexate, cisplatin, vinblastine, doxorubicin) x 6 cycles
    - Day 1 (M), Day 2 (VAC) q14 days
    - younger, fit with good PS, needs G-CSF prophylaxis
    - VESPER phase 3 RCT (ddMVAC x 6 vs. GC x 4)
      - 3-year PFS (66% vs. 56%, HR 0.77)
      - Higher rates of nausea/vomiting, asthenia, anemia and febrile neutropenia in ddMVAC compared to GC
- No evidence for carboplatin-based chemotherapy.

Pfister et al. Annals of Oncology 2021.

Adjuvant Chemotherapy for MIBC

- Less preferred compared to neoadjuvant, but can be considered in patients with T3/T4 or N+ disease who didn't have neoadjuvant chemo.
- ~30% patients have post cystectomy complications + slow recovery -> poor candidates for chemotherapy
- Updated ABC Meta-analysis in 2022 (10 RCTs of adjuvant cisplatin-based chemotherapy)



	local Tx + AC	Local Tx alone +/- CTX on relapse
5yr survival (%)	56	50
Adjusted 5yr survival (%)	59	50
5yr recurrence free survival** (%)	61	50

*Adjusted for age, sex, pT stage and N stage
** based on 1075 participants (9RCTs)

Advanced Bladder Cancer Collaborators. European Urology 2022

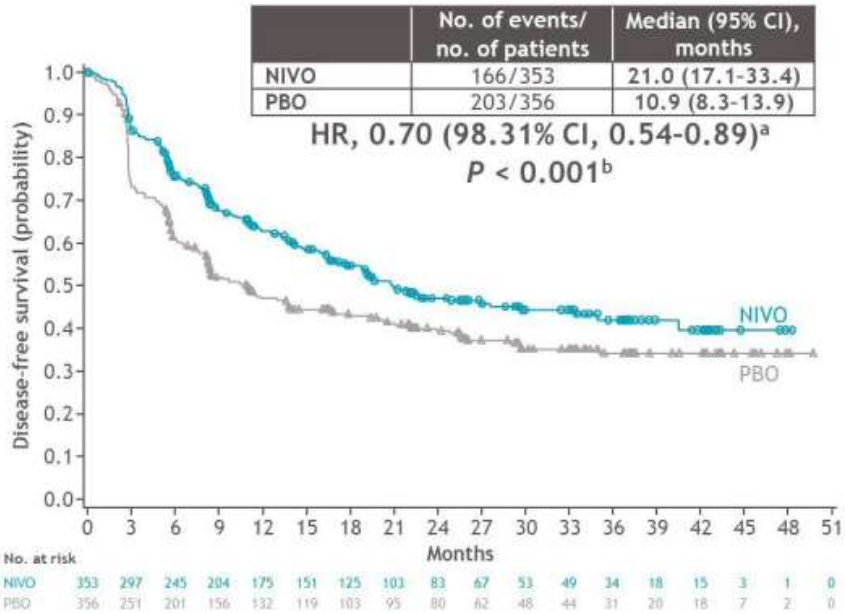
Adjuvant Nivolumab – Checkmate 274

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma

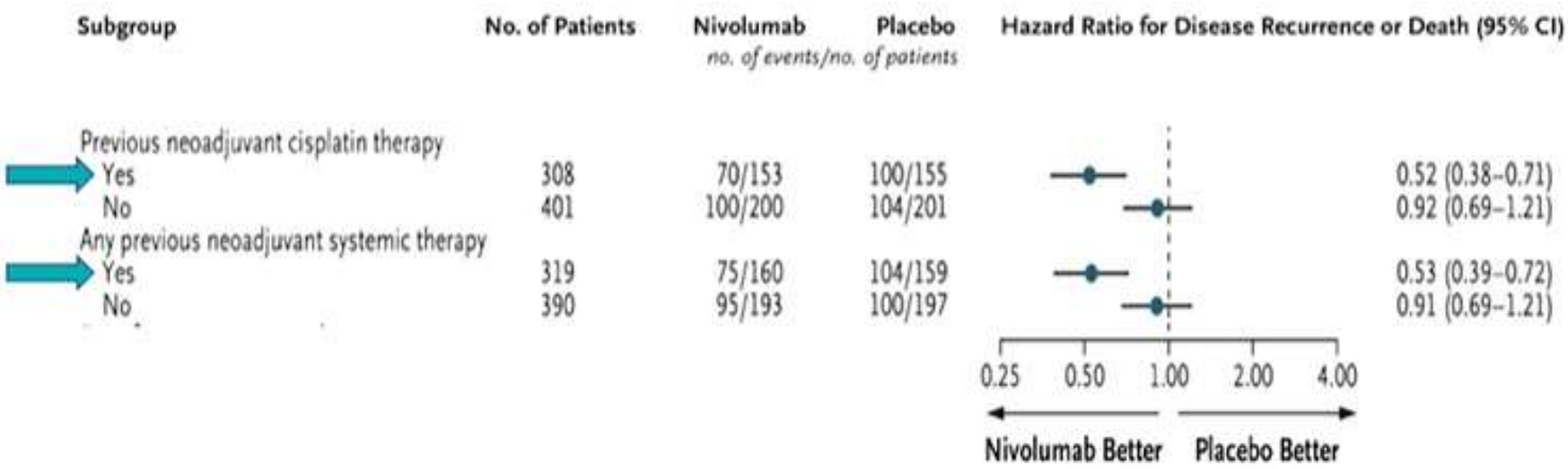
D.F. Bajorin, J.A. Witjes, J.E. Gschwend, M. Schenker, B.P. Valderrama, Y. Tomita, A. Bamias, T. Lebret, S.F. Shariat, S.H. Park, D. Ye, M. Agerbaek, D. Enting, R. McDermott, P. Gajate, A. Peer, M.I. Milowsky, A. Nosov, J. Neif Antonio, Jr., K. Tupikowski, L. Toms, B.S. Fischer, A. Qureshi, S. Collette, K. Unsal-Kacmaz, E. Broughton, D. Zardavas, H.B. Koon, and M.D. Galsky



- N = 709
- Randomized to nivolumab 240 mg IV q2weeks x 1 year vs. placebo
- Either received neoadjuvant chemotherapy and had persistent muscle-invasive disease
- OR did not received neoadjuvant chemotherapy, had p T3 – T4 p N+, and declined/ineligible for adjuvant chemotherapy

Bajorin et al. NEJM 2021

Adjuvant Nivolumab – Checkmate 274



- Adjuvant nivolumab more beneficial in patients previously received neoadjuvant chemotherapy

Adjuvant Therapy for MIBC

- Health Canada approved nivolumab for adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after radical resection

- Compassionate Access Program available

- BOTTOM LINE:
  - Nivolumab for patients who had neoadjuvant chemo but still muscle invasive disease!
  - Chemo vs. nivolumab need to be discussed with patients who DID NOT have neoadjuvant chemo but has high risk disease (lymph node involvement, T3/T4)

Take Home Messages

- Outcomes are improving in patients with advanced bladder cancer
- Toxicity and quality of life is crucial as patients are living longer
- We've made progress in precision oncology
- Multidisciplinary care is crucial in treatment of muscle-invasive bladder cancer