GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

UROTHELIAL CELL CANCER

Indications and regimens for neoadjuvant systemic treatment

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LEARNING OBJECTIVES

- To understand the additional value of neoadjuvant systemic treatment for patients with urothelial cell cancer (UCC)
- To determine the optimal treatment regimen for individual patients
- To select patients with UCC for neoadjuvant systemic treatment
- To be aware of future developments

OUTLINE

Neoadjuvant systemic treatment for patients with UCC:

- Why?
- Which?
- When?
- What's next?

DEFINITION

In UCC, neoadjuvant treatment...

- is administered for advanced disease
- is administered prior to the main therapy (i.e. surgery)
- has the potential to downstage the tumour ('induction therapy')
- can induce a pathological complete response
- has the potential to reduce tumour-associated symptoms (e.g. pain, haematuria)
- has the potential to facilitate surgery
- has the potential to target (micro)metastatic disease
- has the potential to improve progression-free and overall survival
- has curative intention in combination with local therapy (i.e. surgery)

STATEMENT

- UCC is a transitional cell cancer of the urinary tract including the bladder, ureter, urethra, and urachus
- Tumours of the urinary bladder account for 90–95% of UCC[1], whereas upper urinary tract UCCs account for 5–10%[2]
- Literature on neoadjuvant systemic treatment for UCC not originating from the bladder is very limited[3,4]
- The current ESMO E- Learning is therefore focused on bladder UCC

1. Ploeg M, *et al.,* World J Urol 2009; 2. Rouprêt M, *et al.,* Eur Urol 2011; 3. Martin *et al.,* Cancer 2010; 4. Rouprêt M, *et al*., Eur Urol 2017.

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHY?

BACKGROUND (1)

- Radical cystectomy with extended lymphadenectomy is the standard treatment of muscle-invasive bladder cancer (MIBC)[1,2]

- To improve patient outcome neoadjuvant chemotherapy (NAC) has been added to surgery[3-5]

1. Hautmann RE, *et al.,* Eur Urol 2012; 2. Gakis G, *et al*., Eur Urol 2013; 3. MRC/EORTC, Lancet 1999; 4. Grossman HB, *et al.,* NEJM 2003;
5. Advanced Bladder Cancer Meta-analysis Collaboration, Cochrane Database Syst Rev 2005 and Eur Urol 2005.

BACKGROUND (2)

- Bladder preserving strategies for MIBC can be considered when[1]:
  - A patient is medically unfit for surgery
  - A patient prefers bladder preservation (with the option of a radical cystectomy as salvage therapy)

- Bladder preserving strategies include transurethral resection of the bladder tumour (TURBT), radiotherapy, chemotherapy, or a combination of these[1-4]

1. Bellmunt J, *et al.,* Ann Oncol 2014; 2. Coppin CM, *et al*., J Clin Oncol 1996; 3. Hoskin PJ, *et al.,* J Clin Oncol 2010; 4. James ND, *et al.,* NEJM 2012.

RATIONALE: SURVIVAL (OS)

Meta-analysis[1,2] to evaluate the effect of NAC on overall survival (OS):

- 3005 patients from 11 randomised clinical trials were included
- Patients had clinical stage cT2-T4a MIBC
- Patients were treated with definitive treatment +/- NAC
- Local definitive treatment consisted of surgery, radiotherapy or both

Platinum-based combination chemotherapy had a significant benefit on OS:

- Hazard ratio (HR) 0.86 (95% CI 0.77 to 0.95, $p = 0.003$)
- 14% reduction in the risk of death
- 5% absolute benefit at 5 years (OS increased from 45% to 50%)
- Effect was irrespective of the type of local treatment

1. Advanced Bladder Cancer Meta-analysis Collaboration, Cochrane Database Syst Rev 2005; 2. Eur Urol 2005.

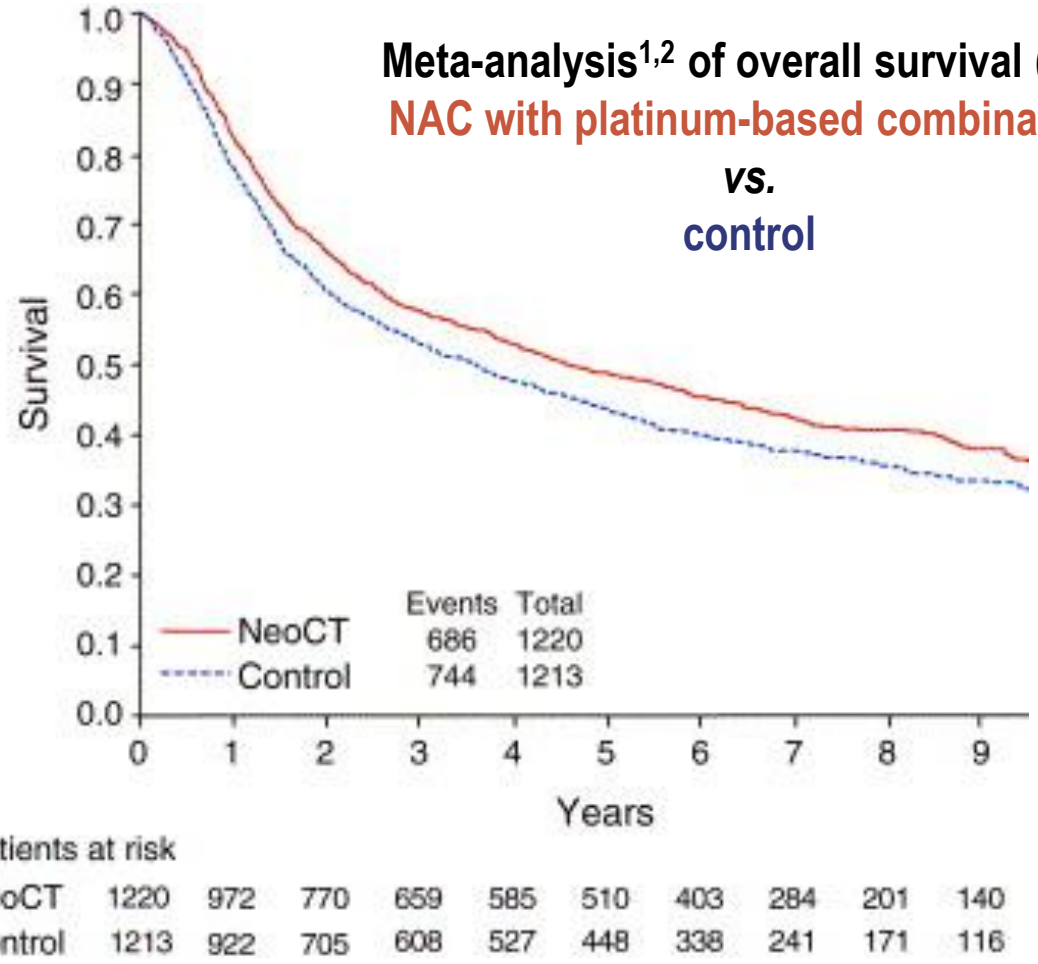
RATIONALE: SURVIVAL (OS)

Meta-analysis[1,2] of overall survival (OS)

NAC with platinum-based combination

vs.

control



1. Advanced Bladder Cancer Meta-analysis Collaboration, Cochrane Database Syst Rev. 2005;(2):CD005246;

2. Reprinted from European Urology, 48 (2), Vale CL, Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration, 202-206. Copyright 2005. With permission from Elsevier.

MORE BENEFIT TO BE EXPECTED?

Compared to the published meta-analyses, the survival is expected to be better in current practice, because of:

1. Optimised cisplatin-based chemotherapy schedules

2. Improved surgery with extended lymphadenectomy

3. Improved radiation techniques with improved treatment planning

RATIONALE: SURVIVAL (DFS)

Meta-analysis[1,2] to evaluate the effect of NAC on disease-free survival (DFS):

- 3005 patients from 11 randomised clinical trials were included
- Patients had clinical stage cT2-T4a MIBC
- Patients were treated with definitive treatment +/- NAC
- Local definitive treatment consisted of surgery, radiotherapy or both

Platinum-based combination chemotherapy <u>also</u> had a significant benefit on DFS:

- Hazard ratio (HR) 0.78 (95% CI 0.71–0.86, $p<0.0001$)
- 9% absolute improvement at 5 years

1. Advanced Bladder Cancer Overview Collaboration, Cochrane Database Syst Rev. 2005;(2):CD005246; 2. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration.Eur Urol. 2005;48(2):202-5.

RATIONALE: RESPONSE

Meta-analysis[1] to evaluate the effect of NAC on tumour response:

- 886 patients from 13 clinical trials were included
- Patients had MIBC
- Patients were treated with NAC and radical cystectomy, without any postoperative treatment

- Pathologic complete response (pCR; pT0N0M0 stage) was 28.6%
- Patients with pCR after NAC had a better overall and recurrence-free survival than patients without pCR:
  - Relative risk (RR) for overall survival = 0.45
  - RR for recurrence-free survival = 0.19

1. Petrelli F, *et al.,* Eur Urol 2014.

CLINICAL PRACTICE

- In clinical practice, the majority of patients with resectable UCC do not receive NAC at all[1]

- Reasons for withholding NAC include:
  - Cisplatin-ineligibility
  - Comorbidities
  - Advanced age
  - Potential toxicity
  - Perception of modest benefit
  - Potential harm from delayed radical cystectomy

1. Reardon ZD, *et al.,* Eur Urol 2015.

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHY NOT ADJUVANT?

ADJUVANT CLINICAL TRIALS

- There is no high level evidence for adjuvant therapy, as randomised trials of adjuvant therapy are incomplete or underpowered

First Author	Eligibility	Regimen	Total patients randomly assigned	Completed accrual	Improved survival
Bono	pT2-T4a	Cisplatin plus methotrexate	90	Yes	No
Freiha	P3b-4, N0 or N+	CMV	55	No*	No
Otto	pT3	MVEC	108	Yes	No
Skinner	pT3-4 or N+	Multiple cisplatin-based combinations	102	No*	No
Lehmann	PT3-4a and/or pN+	MVAC or MVEC	49	No*	No
Studer	Multifocal recurrent pT1 or pT2-T4a	Cisplatin	91	No†	No
Stadler	pT1/T2 N0M0	MVAC	114	Yes	No
Cognetti	pT2 grade 3, N0-2; pT3-4, N0-2, any grade; or pN1-2, any T, any grade	GC	194	No	No
Paz-Ares	pT3-4 and/or pN+	PCG	142	No	Yes
Sternberg	pT3-4 and/or pN+	GC, MVAC, or DD-MVAC	284	No	No

CMV, cisplatin, methotrexate and vinblastine; DD-MVAC, dose-dense methotrexate, vinblastine, doxorubicin and cisplatin; GC, gemcitabine plus cisplatin; MIBC, muscle-invasive bladder cancer; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; MVEC, methotrexate, vinblastine, epirubicin and cisplatin; PCG, paclitaxel, cisplatin and gemcitabine.
*Stopped early because interim analysis favoured adjuvant chemotherapy.
†Stopped early because interim analysis favoured control arm of no adjuvant chemotherapy

Sonpavde G, et al., J Clin Oncol. 2016;34(8):780-5.

META-ANALYSIS ADJUVANT TRIALS

Meta-analysis to evaluate the effect of adjuvant therapy on survival[1]:

- 945 patients from 9 randomised trials were included

Adjuvant chemotherapy appeared to have a significant benefit on:

- Overall survival: HR of 0.77 (95% CI 0.59 - 0.99, $p = 0.049$)
- Disease-free survival: HR 0.66 (95% CI 0.45 - 0.91, $p = 0.014$)

- These results were confirmed by an updated meta-analysis[2]

1. Leow JJ, *et al.,* Eur Urol 2014; 2. Sternberg CN, *et al*., Lancet Oncol 2015.

ADJUVANT THERAPY IN THE CLINIC

- There is insufficient evidence for routine use of adjuvant chemotherapy for MIBC, as randomised trials of adjuvant therapy are incomplete or underpowered[1,2]
  - It is likely that high-risk patients (e.g. extravesical disease) who have not received NAC, will benefit most from adjuvant chemotherapy[2]
  - In selected cases, adjuvant chemotherapy may be considered[2], however high-level evidence is lacking

1. Leow JJ, *et al.,* Eur Urol 2014; 2. Sonpavde G, *et al.,* J Clin Oncol 2016.

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHICH?

SCHEDULES FOR NAC IN UCC

- There is only high-level evidence for NAC consisting of 4 cycles of cisplatin-based combinations, including[1,2]:
  - Accelerated M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin)

  OR
  - Gemcitabine-cisplatin
- Based on randomised clinical trials in advanced and metastatic UCC, overall and progression-free survival are similar for MVAC and gemcitabine-cisplatin, whereas gemcitabine-cisplatin is associated with less toxicity[3]

1. Advanced Bladder Cancer Overview Collaboration, Cochrane Database Syst Rev. 2005;(2):CD005246; 2. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol. 2005;48(2):202-5. 3. Von der Maase H, *et al.,* J Clin Oncol 2005.

GEMCITABINE-CISPLATIN

SCHEDULE:

- Gemcitabine 1,000 mg/m^2 during 30-60 minutes on Days 1, 8, and 15
- Cisplatin 70 mg/m^2 on Day 2
- In clinical practice, gemcitabine on Day 15 is frequently cancelled

Von der Maase H, *et al.,* J Clin Oncol 2000 & 2005.

HIGH DOSE M-VAC (1)

- High dose or accelerated M-VAC consists of a 2-weekly regimen with G-CSF[1]
- In advanced and metastatic UCC, high dose M-VAC was compared with classic M-VAC[1]
- As compared with classic M-VAC, high dose M-VAC shows improved[1]:
  - Response rate (64% *vs*. 50%)
  - Progression-free survival (median 9.5 *vs.* 8.1 months)
  - Overall survival (OS rate at 5 years 21.8% *vs.* 13.5%)
- Therefore high dose M-VAC is preferred instead of classic M-VAC[1]

1. Sternberg CN, *et al.,* Eur J Cancer 2006.

HIGH DOSE M-VAC (2)

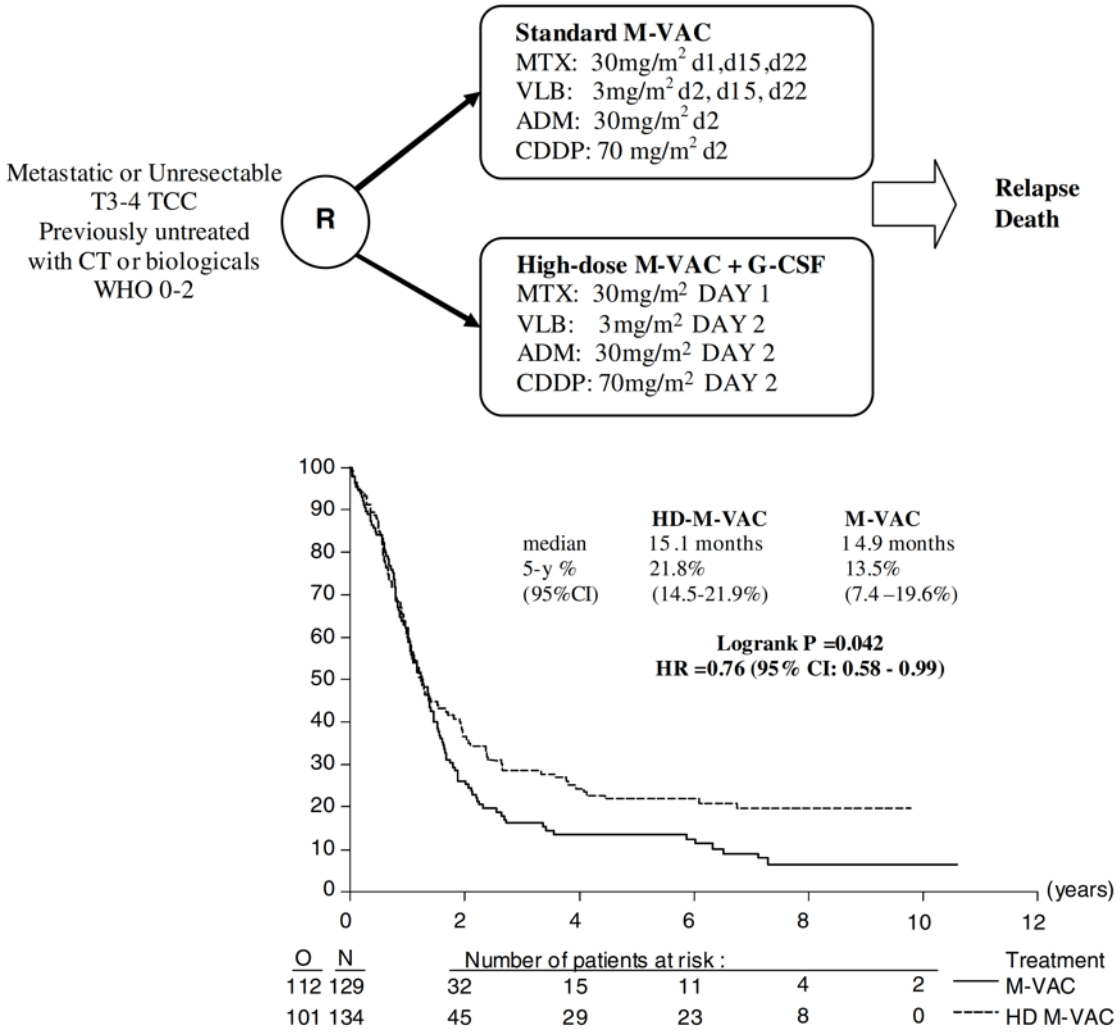


Fig. 3 – Overall survival.

Reprinted from Eur J Cancer 42(1), Sternberg CN, *et al.,* Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF *versus* classic M-VAC in advanced urothelial tract tumours, 50–4. Copyright 2006. with permission from Elsevier.

CARBOPLATIN-BASED OR NOT?

Carboplatin-based NAC is not considered standard of care for cisplatin-ineligible patients, because[1-3]:

1. Studies are lacking to support this

2. Cisplatin is superior

1. Petrioli R, *et al.,* Cancer 1996; 2. Bellmunt J, *et al.,* Cancer 1997; 3. Lokich J, *et al.,* Ann Oncol 1998.

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHEN?

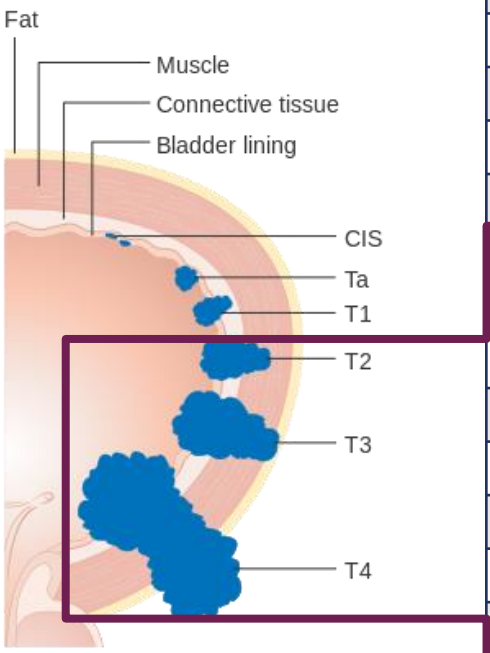
HOW TO SELECT PATIENTS?

1. Tumour characteristics

2. Patients characteristics

TUMOUR CHARACTERISTICS (1)

Patients with cT2-T4aN0M0[1] MIBC are eligible for NAC



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Definition of TNM

Primary Tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
pT2a	Tumour invades superficial muscle (inner half)
pT2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall

1. AJCC TNM staging 8th edition, New York: Springer; 2017.

TUMOUR CHARACTERISTICS (2)

Staging of disease should at least include the following:

- Biopsy-proven UCC (cystoscopy)
- Adequate abdominal imaging of local disease (CT or MRI)
- Local imaging before TURBT
- Additional imaging (i.e. CT of the chest) to exclude metastases in patients at high risk of metastases

1. Bellmunt J, *et al.,* Ann Oncol 2014.

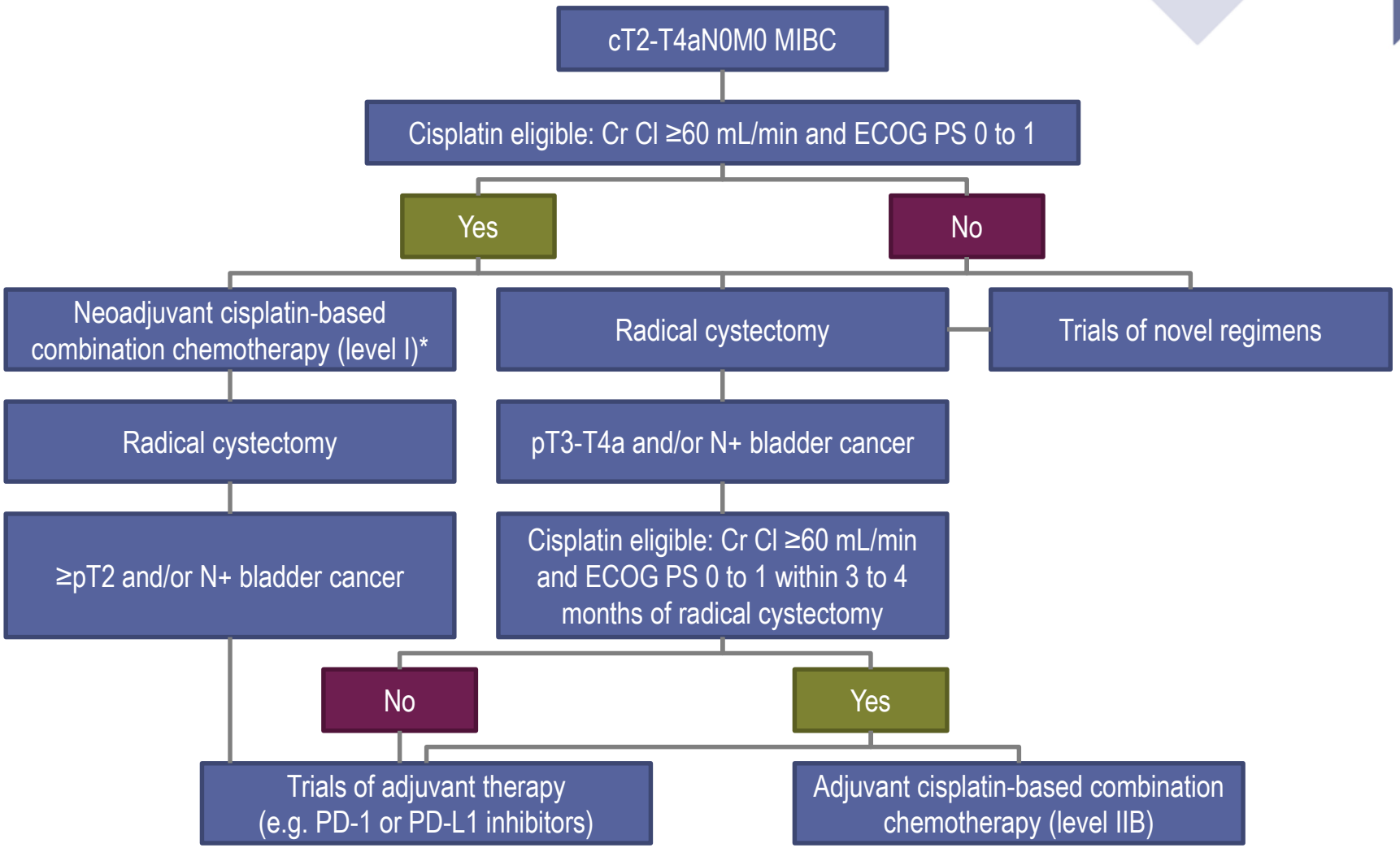
PATIENT CHARACTERISTICS

Patient characteristics important for NAC selection include[1,2]:

- Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1)
- Laboratory results including full blood count and renal function (e.g. risk of hydronephrosis!)
- Co-morbidity

1. Bellmunt J, *et al.,* Ann Oncol 2014; 2. Sonpavde G, *et al.,* J Clin Oncol 2016.

ALGORITHM CLINICAL PRACTICE



Suggested algorithm for the perioperative therapy of muscle-invasive bladder cancer (MIBC). Cr Cl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed death-1; PD-L1, programmed death-ligand 1. (*) Trials evaluating combinations of cisplatin-based chemotherapy with biologic agents should be considered.[1]

Sonpavde G, *et al.*, J Clin Oncol. 2016;34(8):780-5.

NEOADJUVANT SYSTEMIC TREATMENT FOR UCC

WHAT'S NEXT?

FUTURE PERSPECTIVES (1)

Ongoing and future clinical trials may evaluate whether neoadjuvant systemic therapy in UCC can be improved by:

- Checkpoint inhibitors (e.g. anti-PD1, PDL1, CTLA4)[1]
- Inhibitors of VEGF signaling (e.g. ramucirumab)[2]
- FGFR3 inhibitors[3]
- Other...[4,5]

1. Rijnders M, *et al.,* Eur Urol 2017; 2. Petrylak DP, *et al.,* Lancet 2017; 3. Tabernero J, *et al.,* J Clin Oncol 2015; 4. Felsenstein KM, & Theodorescu D, Nat Rev Urol 2017; 5. ClinicalTrials.gov.

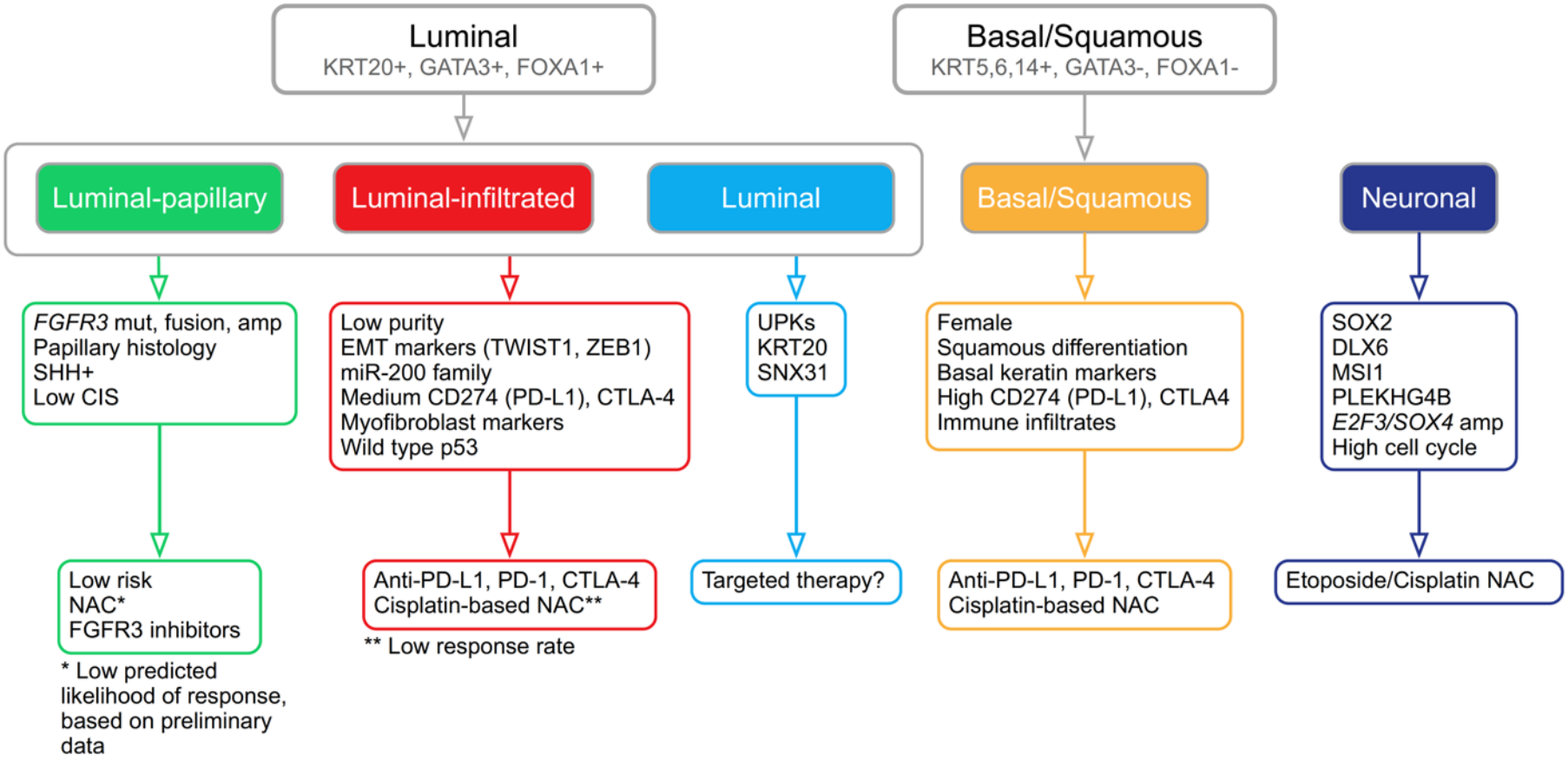
FUTURE PERSPECTIVES (2)

Clinical trials on the treatment of locally UCC will focus on[1]:

- Organ preservation strategies
- Adjuvant (systemic) therapy +/- neoadjuvant systemic therapy
- The development of new systemic therapies
- Introduction of (neo)adjuvant therapy at earlier disease stages
- More personalised therapy with better selection of patients

1. ClinicalTrials.gov

MOLECULAR CHARACTERISATION



CONCLUSIONS

- Based on the highest level of evidence, cisplatin-based NAC with subsequent radical cystectomy is the current standard of care for cT2-T4aN0M0 MIBC
- Cisplatin-based NAC needs to be considered for every patient with cT2-T4aN0M0 MIBC
- As the treatment options for patients with UCC are expanding, participation in clinical trials is recommended and should always be considered

THANK YOU!