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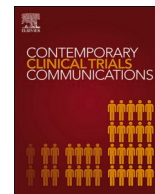
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## Short communication

## Design of a randomized controlled phase III study of dose dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as peri-operative chemotherapy for patients with locally advanced transitional cell cancer of the bladder. The French GETUG/AFU V05 VESPER trial

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## ABSTRACT

The main objective of the French GETUG/AFU V05 VESPER randomized phase III study was to assess the efficacy of dd-MVAC and GC in term of progression-free survival in patients for whom chemotherapy has been decided, before or after surgery.

A total of 500 patients have been randomized in 28 reference centers. Inclusion criteria were urothelial carcinoma without neuro-endocrine variant, disease defined by a T2, T3 or T4a N0 (pelvic lymph node  $\leq 10$  mm on CT scan) M0 staging for patients receiving neoadjuvant chemotherapy or pT3 or pT4 or pN+ and M0 for patients receiving adjuvant chemotherapy. Secondary endpoints include overall survival, safety, response rate. The peri-operative chemotherapy schedule was experimental arm dd-MVAC for a total of 6 cycles versus standard arm GC 4 cycles. The toxicity was evaluated according to NCI CTCAE (v 4.0). The progression-free survival rate will be estimated at 3 years by the Kaplan-Meier method. All the patients will be followed for 5 years.

The last patient was randomized in March 2018 and the primary endpoint results are expected for mid-2021. As the dd-MVAC schedule is associated with higher response rates in metastatic disease, the real question today is to confirm such benefit in the peri-operative setting, taking also in consideration the chemotherapy toxicity. Tomorrow, the challenge may be the best chemotherapy and immunotherapy association, the authors hope that final Vesper Trial results will help to determine the gold standard chemotherapy.

## 1. Introduction

Radical cystectomy (RC) remains the standard of care for local treatment of non metastatic muscle invasive bladder cancer (MIBC). However, cancer specific survival is approximately 50% depending on the presence of extravesical extension and/or lymph nodes metastases [1]. In daily practice, more than 50% of patients die of distant metastases within two years after cystectomy, suggesting the presence of

micro-metastases at time of surgery [2]. Therefore, peri-operative chemotherapy (adjuvant or neoadjuvant) has been developed to increase overall survival, with an absolute benefit of 5% reported for neoadjuvant chemotherapy (NAC) and international guidelines recommend NAC based on the available level I evidence [3,4]. The chemotherapy administration time and the optimal chemotherapy regimen to be delivered remain open to discussion. As dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) has been shown to be

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associated with higher response rates in bladder metastatic disease [5], a better efficacy can also be suspected in the peri-operative setting.

Recently, Choueiri et al. and Plimack et al. reported interesting results from two phase II trials using dd-MVAC as neoadjuvant chemotherapy in MIBC. After three to four cycles, the pathologic downstaging (pT1 N0M0) was quite similar (49% and 53%), the pathologic complete response rates (pT0) were 26% and 38%, respectively [6,7]. Our objective was to design a randomized phase III controlled study comparing the efficacy of GC and dd-MVAC in term of progression-free survival in patients for whom chemotherapy has been decided, before or after radical cystectomy.

## 2. Material and methods

### 2.1. - Study design

This randomized phase III study assesses the efficacy of dd-MVAC and GC peri-operative chemotherapy (adjuvant or neoadjuvant) in patients with bladder cancer disease defined by a T2, T3 or T4a N0 ( $\leq 10$  mm on CT scan) M0 staging for patients receiving neoadjuvant chemotherapy or pT3 or pT4 or pN+ and M0 for patients receiving adjuvant chemotherapy. Secondary endpoints include overall survival, safety, response rate in the neoadjuvant setting. From February 2013 to March 2018, a total of 500 patients have been randomized in the French GETUG/AFU V05, controlled phase III trial, including 28 participating centers with referent urologist and oncologist investigators (Fig. 1).

As previously mentioned, the peri-operative chemotherapy schedule proposed was:

### Standard Arm A: GC.

- GEMCITABINE 1250 mg/m<sup>2</sup>: Day 1 and Day 8
  - CISPLATIN 70 mg/m<sup>2</sup>: Day 1
- Every 3 weeks, for a total of 4 cycles**

### Experimental Arm B: dd-MVAC.

- METHOTREXATE 30 mg/m<sup>2</sup>: Day 1
  - VINBLASTINE 3 mg/m<sup>2</sup>: Day 2
  - DOXORUBICIN 30 mg/m<sup>2</sup>: Day 2 - CISPLATIN 70 mg/m<sup>2</sup>: Day 2 - G-CSF: Day 3 to Day 9
- Every 2 weeks, for a total of 6 cycles**

The chemotherapy response was evaluated according to RECIST 1.1 criteria.

The treatment toxicity was evaluated according to NCI CTCAE (v 4.0).

The progression-free survival estimation rate of this trial was determined at 3 years.

In our prospective randomized study all the patients were followed for 5 years.

### 2.2. - Study Procedures

At baseline before screening, a CT with contrast of the chest, abdomen and pelvis was performed for all patients, in association with a systematic bone scan and a complete biological evaluation. Follow up

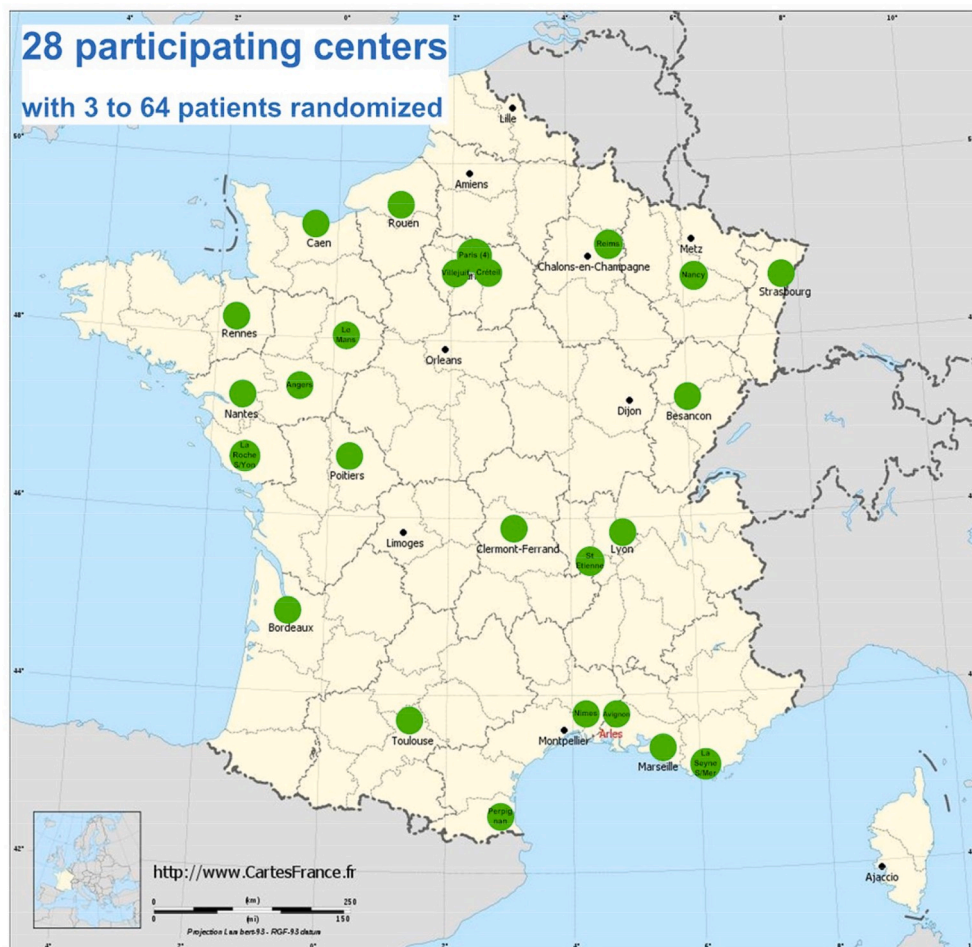


Fig. 1. Participating centers of the GETUG/AFU V05 multicentre, randomised phase III trial.

visits and their schedules and measurements are clearly reported in Fig. 2.

In our clinical trial, a dose reduction of chemotherapy in case of toxicity was allowed. Considering the GC group (standard arm), the cisplatin dose was adapted to renal function (creatinine clearance > 60 ml/mn: 70 mg/m<sup>2</sup>; between 50 and 60 ml: 50 mg/m<sup>2</sup>; between 40 and: 35 ml mg/m<sup>2</sup>; creatinine clearance < 40 ml/mn: end of the chemotherapy). As regards haematologic toxicity (neutropenic fever), a dose reduction of 15% was recommended for the two molecules. Considering the dd-MVAC group (experimental arm), the cisplatin dose was adapted to renal function as previously described. A dose reduction of 15% was also recommended for the four molecules in case of grade 4 toxicity and the chemotherapy stopped in the absence of recovery within 14 days.

The study protocol was approved by the Ethics Committee CPP ROUEN NO on 19 April, 2012 and the competent authority on 27 February, 2012. All patients signed the informed consent form to be enrolled in this randomized phase III study (*Clinical trial registry: clinicaltrials.gov - NCT 018 12369*).

After the exclusion of any analysis of 7 patients who did not meet the inclusion/exclusion criteria, it remained 493 patients for the primary analysis (intent-to-treat population). Baseline characteristics by chemotherapy arm are reported in Table 1, whereas tumour staging at randomization by type of peri-operative chemotherapy are detailed in Table 2.

2.3. - Objectives

The primary objective of our study was the evaluation of efficacy in terms of progression-free survival at three years of the combination of dose dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) versus gemcitabine and cisplatin (GC) as peri-operative chemotherapy for locally advanced -transitional cell carcinoma of the bladder. Final results for primary endpoint will also be available in mid-2021.

Secondary objectives of the trial were to assess toxicity NCI CAE (v 4.0), to assess response rate (RR) in patients treated in the neoadjuvant setting, to assess overall survival (OS), to assess time to progression (TTP) and to study the correlation between response rate, time to progression, overall survival and biological parameters.

Table 1

Baseline characteristics by chemotherapy arm.

Mean (standard deviation) for quantitative data. Frequency (percentage) for qualitative data. Comparisons between GC and dd-MVAC groups are performed with a Student T-test or Chi-2 test. P-value < 0.05 would assume a statistical difference between GC and dd-MVAC groups.

	GC n = 245	dd-MVAC n = 248	p-value	
<b>Demography</b>				
Age	63 (7.6)	62.6 (7.9)	0.62	
Sex	Male	206 (84%)	0.51	
	Female	39 (16%)	46 (19%)	
<b>Physical examination</b>				
Body Mass Index	26.6 (4.7)	26 (4.4)	0.16	
Body Surface Area	1.9 (0.2)	1.9 (0.2)	0.52	
WHO status	0	171 (70%)	0.59	
	1	72 (29%)	82 (33%)	
	Not done	2 (1%)	1 (0%)	
<b>Medical History</b>				
whose	No	10 (4%)	6 (2%)	0.43
	Yes	235 (96%)	242 (98%)	
	neuropathy	3 (1%)	1 (0%)	0.60
	hearing disorder	35 (15%)	46 (19%)	0.28
	high blood pressure	100 (43%)	89 (37%)	0.23
	infarc	9 (4%)	11 (5%)	0.88
	coronary insuff.	5 (2%)	9 (4%)	0.45
	diabetes	14 (6%)	4 (2%)	0.03
	tobacco	198 (84%)	197 (81%)	0.48
	aromatic amines	14 (6%)	7 (3%)	0.16
	<b>Biology and renal function</b>			
	Hemoglobin (g/100 mL)	14.3 (6.8)	13.9 (1.5)	0.33
	Neutrophil polynuclear cells (1000/mm <sup>3</sup> )	7.5 (34.7)	6.9 (22.3)	0.83
Platelets (1000/mm <sup>3</sup> )	272.6 (78.2)	274.3 (85.4)	0.81	
Total bilirubin (mg/L)	5.0 (2.6)	5.2 (2.5)	0.34	
ALT (UI/L)	23.6 (14.6)	22.8 (10.5)	0.49	
AST (UI/L)	20.4 (7.2)	20.6 (7.2)	0.75	
Alkaline phosphatase (UI/L)	77.9 (26.2)	77.9 (31.5)	0.97	
Creatinine (mg/L)	9.6 (3.3)	9.1 (2.1)	0.05	
Clearance of creatinine (mL/min)	89.3 (27.6)	90.2 (25)	0.69	

2.4. - Patients selection

Key inclusion criteria were primary tumour of the bladder; histologically confirmed infiltrating urothelial carcinoma (epidermoid and/

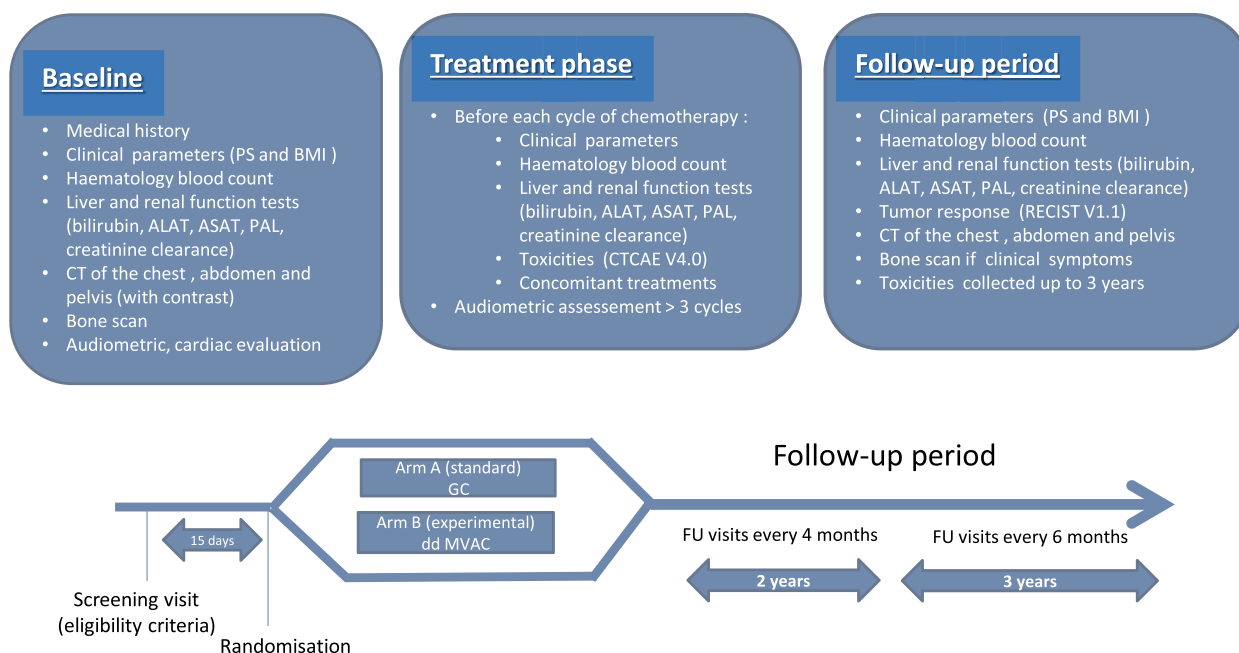


Fig. 2. Study procedures, schedule and parameters of the patients follow-up.

**Table 2**

**Staging at randomization by type of peri-operative chemotherapy and arm** Frequency (percentage). For adjuvant chemotherapy, pTNM staging is performed on cystectomy. For neoadjuvant chemotherapy, TNM staging is performed on TURBT. Staging according to 2009 TNM classification.

		Adjuvant chemotherapy		Neoadjuvant chemotherapy	
		GC	dd-MVAC	GC	dd-MVAC
		n = 26	n = 30	n = 219	n = 218
Tumour	T1	1 (4%)	1 (3%)	0	0
	T2a	0	1 (3%)	141 (64%)	138 (63%)
	T2b	3 (12%)	2 (7%)	66 (30%)	59 (27%)
	T3a	8 (31%)	12 (40%)	4 (2%)	7 (3%)
	T3b	3 (12%)	6 (20%)	4 (2%)	5 (2%)
Nodes	T4a	11 (42%)	8 (27%)	4 (2%)	9 (4%)
	N0	7 (27%)	12 (40%)	219 (100%)	218 (100%)
	N1	12 (46%)	7 (23%)	0	0
	N2	7 (27%)	11 (37%)	0	0
Metastasis	M0	26 (100%)	30 (100%)	219 (100%)	218 (100%)

or glandular variants are accepted if combined with TCC); disease defined by a T2, T3 or T4a N0 (lymph node  $\leq 10$  mm on CT scan) M0 staging for patients receiving neoadjuvant chemotherapy or pT3 or pT4 or pN + whatever pT and M0 for patients receiving adjuvant chemotherapy; 18  $\leq$  age  $\leq$  80 years; general condition 0 or 1 as per the WHO scale; absence of previous chemotherapy for muscle-invasive disease; haematological function: haemoglobin  $>11$  g/dl, neutrophils  $\geq 1500$ /mm<sup>3</sup>, platelets  $\geq 100,000$ /mm<sup>3</sup>; liver function: grade 0 ASAT and ALAT, grade 0 alkaline phosphatases, normal bilirubin; renal function: calculated (or measured) creatinine clearance  $\geq 40$  ml/min; patients covered by a social security scheme and having read the information sheet and signed the informed consent form.

Key exclusion criteria were pure adenocarcinoma or pure epidermoid carcinoma or mixed or pure small-cell neuroendocrine carcinoma; ventricular ejection fraction  $<50\%$ ; history of cancer in the 5 years prior to entry in the trial other than basal cell skin cancer or in situ carcinoma of the cervix; male or female patients not agreeing to use an effective method of contraception throughout the duration of treatment and for 6 months after treatment discontinuation; pregnant women, or female subjects liable to become pregnant or currently breast-feeding; patient already included in another therapeutic trial on an investigational medicinal product; persons deprived of their freedom or under judicial protection (including guardianship); unable to receive medical follow-up during the trial owing to geographical, social or psychological reasons.

## 2.5. - Statistical analyses

The total number of patients expected for this randomized multicenter phase III study was 500, with 250 on each arm. This sample size is sufficient to demonstrate that combination dd-MVAC improves progression-free survival compared to GC with a maximum hazard ratio hypothesis of 0.74 and an alpha risk of 5% and a power of 80%. This sample size allows an interim analysis of the primary endpoint is planned after the occurrence of 174 events. The primary endpoint progression-free survival will be estimated using the Kaplan-Meier method. In order to take into account the mode of administration of the chemotherapy (neo-adjuvant or adjuvant) and the involvement or not of the lymph nodes, the efficacy of the chemotherapy dd-MVAC vs GC will be evaluated by a stratified log-rank test. The adjusted hazard ratio (dd-MVAC/GC) and its 95% confidence interval will be estimated by a proportional hazard Cox model adjusted for the therapeutic option (neoadjuvant vs adjuvant) and the lymph nodes involvement. The hypothesis of proportional hazard of the model will be tested by the Lin method.

## 2.6. - Ancillary study

The identification of predictive biomarkers may help urologists in the selection of patients to benefit most likely from NAC. Different studies have concentrated on the assessment of one genetic marker, nevertheless none of them has allowed the validation of a reliable marker in clinical practice. Therefore, ERCC1, telomere length, BRCA1 mRNA expression and p53 mutation did not demonstrate any correlation with response, toxicity or survival [7,8].

Concomitant ancillary study has started, focusing on DNA repair genes (ERCC2, ATM, FANCC, RB1) and molecular subtypes determined by gene expression profiling to compare and potentially validate these biomarkers previously proposed for muscle invasive bladder tumour sensitivity to neoadjuvant chemotherapy [9-11].

## 3. Discussion

Neoadjuvant chemotherapy is typically validated in patients with cT2-cT4 N0 muscle invasive bladder cancer, with a normal renal function allowing the use of standard doses of cisplatin [3,4]. Patients with locally advanced disease (N1) do require upfront chemotherapy rather than neoadjuvant treatment. Despite the pivotal randomized studies and meta-analyses demonstrating the survival benefit of cisplatin-based combination chemotherapy before cystectomy [12,13], there was a low implementation of this approach in daily practice, even if the use of NAC has been increasing during the 2010s, suggesting that continuous efforts are required to convince more urologists and oncologists to use it [14-16].

The lack of referral to medical oncologist may be an important factor for under-utilization of neoadjuvant schedule [15], nevertheless there is always a need of clarification for optimal chemotherapy regimen. Level I evidence regarding the NAC overall-survival benefit was reported with cisplatin-based regimens that are no longer currently used [12,13], in fact standard MVAC has been supplanted in the metastatic setting by less toxic regimens as gemcitabin-cisplatin (GC) and dose-dense MVAC (dd-MVAC). Zargar et al. have reviewed the clinical data of 319 patients with cT3-4a N0M0 bladder cancer who underwent NAC before cystectomy from 2000 to 2015 in 20 institutions. One hundred patients received dd-MVAC, whereas 219 patients were treated with GC [17]. Baseline characteristics were similar between the two groups except for age (patients who received dd-MVAC were younger) and the proportion of variant histology features (higher in the dd-MVAC group). A significantly lower rate of pathological complete response (ypT0N0) was observed in the GC group (14.6% vs 28.0%,  $p = 0.005$ ). Similarly, the pathological partial response rate (ypT1N0 or less) was 30.1% for GC arm compared to 41.0% for dd-MVAC arm ( $p = 0.07$ ). These results suggest that dd-MVAC could be the optimal regimen for NACT with a translated longer overall survival for patients (7 years vs 4.6 years,  $p = 0.001$ ).

The primary endpoint of the French GETUG/AFU Vesper trial is the disease-free survival at 3 years. As the last patient was randomized in March 2018, the primary endpoint results are attempted for mid-2021. Nevertheless, the authors underline the interest of secondary objectives: chemotherapy safety with side effects analysis, response rate in patients treated in the neoadjuvant setting and time to MIBC progression. The dose-dense MVAC schedule is associated with higher response rates in bladder metastatic disease, the real question today is to confirm such benefit in the peri-operative setting.

A substantial high rate of morbidity (66%) or risk of perioperative mortality (4%) and a negative impact on quality of live have been reported after cystectomy. The subgroup of patients downstaged to pT0 after neoadjuvant chemotherapy usually achieve a survival benefit beyond non complete responders, however the real benefit of radical surgery remains today unclear [18]. Robins et al. reported an interesting series of 48 patients at the Colombia University Irving Medical Center with muscle invasive bladder cancer that were cT0 after neoadjuvant

chemotherapy and also refused radical cystectomy [19]. Five-year cancer specific survival was 87%, disease free survival was 58% and cystectomy-free survival was 79%. A total of 19 patients (46%) relapsed with 5.4 month median recurrence time. Finally, the bladder preservation for patients with complete clinical response after NAC is not recommended currently, but the pathologic downstaging (pT1 N0M0) and the rate of pathologic complete response (pT0) may be significant prognostic factors in NAC response. Vesper Trial results has to confirm the interesting data from two phase II trials using dd-MVAC as neoadjuvant chemotherapy recently reported by Choueiri et al. and Plimack et al. [6,7].

Today, immunotherapy is becoming an interesting option in the second line treatment of metastatic urothelial carcinoma and PD-L1 expression by IHC could be correlated to therapeutic response in metastatic or locally advanced urothelial carcinoma treated with PD-L1 antibody suggesting personalized medicine [20,21]. Powles et al. obtained a 43% (95% CI [26%, 63%]) response rate to atezolimumab in patients with positive PD-L1 tumour (IC or TC or both, at 5% positivity threshold) and a 11% (95% CI [4%, 26%]) response rate in patients with negative PD-L1 tumours [22]. Tomorrow, the oncological challenge will be to determine the best therapeutic option in the peri-operative setting: chemotherapy combined with immunotherapy or immunotherapy in the whole population or personalized treatment with chemotherapy or immunotherapy according to the molecular profiling of tumours. Before the validation of such therapeutic approaches, it is very important to determine the gold standard chemotherapy between gemcitabine and cisplatin (GC) and dose dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC). In conclusion, the authors hope that final Vesper Trial results will be strongly significant to permit guidelines updating.

#### Declaration of competing interest

The authors declare no competing interests with the manuscript.

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#### References

- [1] J.P. Stein, G. Lieskovsky, R. Cote, et al., Radical cystectomy in the treatment of invasive bladder cancer. Long-term results in 1054 patients, *J. Clin. Oncol.* 19 (2001) 666–675.
- [2] S.F. Shariat, P.I. Karakiewicz, G.S. Palapattu, et al., Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder cancer Research Consortium, *J. Urol.* 176 (2006) 2414–2422.
- [3] M.I. Milowsky, R.B. Rumble, C.M. Booth, et al., Guideline on muscle invasive and metastatic bladder cancer. American society of clinical oncology clinical practice guideline endorsement, *J. Clin. Oncol.* 34 (2016) 1945–1952.
- [4] A. Witjes, T. Lebrt, E.M. Comperat, et al., Updated 2016 EAU Guidelines on muscle invasive and metastatic bladder cancer, *Eur. Urol.* 71 (2017) 462–475.
- [5] C.N. Sternberg, P. de Mudler, J.H. Schornagel, 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 tumors, *Eur. J. Canc.* 42 (2006) 50–54.
- [6] T.K. Choueiri, S. Jacobus, J. Bellemut, et al., Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin and cisplatin with pegfilgrastim support in muscle invasive urothelial cancer : pathologic, radiologic and biomarker correlates, *J. Clin. Oncol.* 32 (2014) 1882–1894.
- [7] E.R. Plimack, J.H. Hoffman-Censits, R. Viterbo, et al., Accelerated methotrexate, vinblastine, doxorubicin and cisplatin is safe, effective and efficient neoadjuvant treatment for muscle invasive bladder cancer. Results of a multicenter phase II study with molecular correlates of response and toxicity, *J. Clin. Oncol.* 32 (2014) 1895–1901.
- [8] A. Front, M. Taron, J.L. Gago, et al., BRCA1 mRNA expression and outcome to neoadjuvant cisplatin-based chemotherapy in bladder cancer, *Ann. Oncol.* 22 (2011) 139–144.
- [9] W. Choi, S. Porten, S. Kim, et al., Identification of distinct basal and luminal subtypes of muscle invasive bladder cancer with different sensitivities to front-line chemotherapy, *Canc. Cell* 25 (2014) 152–165.
- [10] E.R. Plimack, R.L. Dunbrack, T.A. Brennan, et al., Defects in DNA repair genes predict response to neoadjuvant cisplatin-based chemotherapy in muscle-invasive bladder cancer, *Eur. Urol.* 68 (2015) 959–967.
- [11] R. Seiler, H.A. Ashab, N. Erho, et al., Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy, *Eur. Urol.* 72 (2017) 544–554.
- [12] International Collaboration of Trialists, Neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle invasive bladder cancer. A randomised controlled trial, *Lancet* 354 (1999) 533–540.
- [13] H.B. Grossman, R.B. Natale, C.M. Tangen, et al., Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer, *N. Engl. J. Med.* 349 (2003) 859–866.
- [14] Z.D. Reardon, S.G. Patel, Zaid, et al., Trends in use of perioperative chemotherapy for localized and locally advanced muscle invasive bladder cancer : a sign of changing tides, *Eur. Urol.* 67 (2015) 165–170.
- [15] C.M. Booth, S. Karim, K. Brennan, et al., Perioperative chemotherapy for bladder cancer in the general population : are practice patterns finally changing ? *Urol. Oncol.* 36 (2018) 89, e13-89.e20.
- [16] S. Culine, Y. Allory, C. Pfister, Refining the use of neoadjuvant chemotherapy in locally advanced bladder cancer : from conviction to optimization, *Transl. Androl. Urol.* 7 (2018) 757–759.
- [17] H. Zargar, J.B. Shah, B.W. van Rhijn, et al., Neoadjuvant dose dense MVAC versus gemcitabine and cisplatin in patients with cT3-4a N0M0 bladder cancer treated with radical cystectomy, *J. Urol.* 199 (2018) 1452–1458.
- [18] F. Petrelli, A. Coiro, M. Cabiddu, et al., Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy : a meta-analysis, *Eur. Urol.* 65 (2014) 350–357.
- [19] D. Robins, J. Matulay, M. Lipsky, et al., Outcomes following complete response to neo-adjuvant chemotherapy for muscle invasive urothelial carcinoma of the bladder in patients refusing radical cystectomy, *Oncology* 11 (2018) 116–121.
- [20] J.E. Rosenberg, J. Hoffman-Censits, T. Powles, et al., Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase II trial, *Lancet* 387 (2016) 1909–1920.
- [21] J. Bellmunt, R. de Wit, D.J. Vaughn, et al., Pembrolizumab as second-line therapy for advanced urothelial carcinoma, *N. Engl. J. Med.* 376 (2017) 1015–1026.
- [22] T. Powles, J.P. Eder, G.D. Fine, et al., MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer, *Nature* 515 (2014) 558–562.