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Evaluating the efficacy and safety of bladder-sparing regimen with Disitamab Vedotin combined with Toripalimab and pelvic lymph node dissection in muscle-invasive bladder cancer patients: study protocol of a multicenter single-arm phase II trial

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Abstract

Background Muscle invasive bladder cancer (MIBC) is a malignancy with high recurrence and metastasis rate. Radical cystectomy and lymph node dissection are the current standard cares for MIBC. The demand for bladder preservation in MIBC patients is growing daily; however, the recognized trimodal bladder-sparing regimen has been shown to have substantial radiation damage and inconsistent efficacy in numerous investigations. In order to address these issues, a secure and efficient bladder preservation program is desperately needed. Therefore, a novel bladder-sparing modality that employing antibody-drug conjugates and immune checkpoint inhibitors combined with pelvic lymph node dissection is worth investigating further in this setting.

Methods In this multicenter, single-arm clinical trial, subjects who were diagnosed with muscle-invasive bladder cancer with human epidermal growth factor receptor-2 expression ≥ 2 + will be enrolled. Eligible subjects will receive 12 cycles Disitamab Vedotin combined with Toripalimab treatment and pelvic lymph node dissection after completed transurethral bladder tumor resection, efficacy evaluation would be performed in all of them, patients who achieved clinical complete response will receive 1-year bladder-sparing therapy with Toripalimab immune maintenance treatment. The primary endpoint is 2-year Bladder-intact disease-free survival, and the secondary endpoints include clinical complete response rate, over survival, quality of life, safety and exploratory objectives that biomarkers will be evaluated.

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Discussion Disitamab Vedotin combined with Toripalimab therapy and pelvic lymph node dissection is a promising bladder-sparing treatment option that has the potential to improve the rate of bladder-intact disease-free survival and may become a novel modality of bladder-sparing regimen if the study endpoints are met.

Trial registration This study was registered at Chinese Clinical Trial Registry (Identifer: ChiCTR2400081555) on March 5, 2024.

Keywords Muscle-invasive bladder cancer (MIBC), Bladder-sparing treatment, Disitamab Vedotin, Toripalimab, Transurethral bladder tumor resection (TURBT), Pelvic lymph node dissection (PLND)

Introduction

Bladder cancer, the 10th most frequent malignancy globally, is categorized into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) [1, 2]. Currently, the standard management for MIBC is radical cystectomy (RC) coupled with Pelvic lymph node dissection (PLND) [3–5]. However, RC has a high rate of postoperative complications that the early complications rate is around 20%, and the late complications rate can reach up to 45–66% [6, 7]. As a supplementary treatment to RC or an alternative therapeutic option in select cases, the efficacy of the established trimodal therapy (TMT) for bladder preservation has shown inconsistent outcomes, with clinical response (CR) rates ranging from 66 to 88% [8]. Furthermore, the radiation component of this approach is associated with significant toxicity profiles that may substantially compromise patients' quality of life [9]. Therefore, there remains an urgent clinical need to develop novel bladder-preserving strategies characterized by enhanced therapeutic efficacy and reduced toxicity.

Over the past decade, it has been demonstrated that the blockade of the programmed cell death protein 1 (PD-1) or programmed cell death 1 ligand 1 (PD-L1) pathway is an effective approach in inducing durable anti-tumor responses [10–12]. Immune checkpoint inhibitors (ICIs) have been incorporated into several bladder preservation studies with promising initial results. There were 76 patients with MIBC accepted 4 cycles of gemcitabine and cisplatin in combination with Nivolumab treatment in the HCRN16-257 study, those who achieved clinical complete response (cCR) were performed a minimum of 8 cycles of immune maintenance therapy. According to the study, there are 33 (43%) subjects achieved cCR and the 2-year bladder-intact metastasis free survival in the cCR population was approximately 65% [13]. In another study, 54 subjects with cT2N0M0 staging underwent one cycle of pembrolizumab followed by complete transurethral bladder tumor resection (cTURBT) and radiotherapy, and then accepted 3 cycles of pembrolizumab. This research revealed that 80% of patients in intention-to-treat (ITT) population reported CR after 12 weeks and 71% of patients had bladder-intact disease-free survival after two years [14].

Disitamab Vedotin (RC48 or DV) as an antibody-drug conjugate (ADC) was approved for the first-line therapy of advanced urothelial carcinoma in January 2022. In the RC48-C005 study, DV was applied to treat human epidermal growth factor receptor-2 (HER-2) overexpressing inoperable locally progressive or metastatic urothelial carcinoma. The study demonstrated that 59.1% of patients experienced progression-free survival and 51.2% encountered objective response [15]. The 2022 American Society of Clinical Oncology updated the latest data of RC48-C005 and RC48-C009 study that an objective response rate (ORR) of 50.5%, with a median progression-free survival and over survival of 5.9 and 14.2 months, respectively. Moreover, 54.2% of grade ≥ 3 treatment-related adverse events (TRAEs) were reported [16]. In the RC48-C014 study, DV combined with Toripalimab resulted in an ORR of 75% in ITT population, with a 100% ORR in patients with HER2 expression (3+) and a 77.8% ORR in patients with HER2 expression (2+) [17]. And there was no grade 4 or 5 TRAEs in either study (C005 and C014).

Collectively, DV and Toripalimab have demonstrated promising therapeutic efficacy in the management of MIBC. Their synergistic combination therapy may potentially enhance the success rate of bladder-preserving strategies. Furthermore, the presence of lymph node metastases is a significant predictor of poor prognosis MIBC patients [18]. PLND and complete transurethral bladder tumor resection (cTURBT), as effective local treatments, can effectively remove tumor lesions and are worth considering as part of bladder conserving therapy. Therefore, we are supposed to construct a novel bladder-preserving regimen that evaluating the efficacy and safety of bladder-sparing regimen with Disitamab Vedotin combined with Toripalimab and PLND in MIBC patients after cTURBT.

Methods

Objectives

The study aims to investigate the safety and effectiveness of cTURBT in patients with cT2-4aN0M0 staging bladder urothelial carcinoma with HER-2 expression ≥ 2+, followed by DV in combination with Toripalimab and PLND.

Participants

63 MIBC subjects will be diagnosed by imaging examination, transurethral bladder tumor resection (TURBT) or cystoscopy at Sun Yat-sen Memorial Hospital and other research centers. And the principal inclusion and exclusion criteria is showed in Table 1.

NOTE HER-2 Immunohistochemistry (IHC) Classification System HER-2 IHC Classification System is relying on a clinical pathological expert consensus, which a slight modification from Breast Cancer HER-2 IHC Classification [19]. HER-2 positive is considered as IHC score ≥ 2+. The scoring system is as follows:

- Score 0: No staining or incomplete, faint membrane staining in < 10% of invasive tumor cells.
- Score 1+: Incomplete, faint membrane staining in ≥ 10% of invasive tumor cells.
- Score 2+: Weak to moderate complete membrane staining in ≥ 10% of invasive tumor cells or Complete, intense circumferential membrane staining in < 10% of invasive tumor cells.
- Score 3+: Complete, intense circumferential membrane staining in ≥ 10% of invasive tumor cells.

Primary endpoint

2-year Bladder-intact disease-free survival (2-yr BI-DFS) rate

Defined as the proportion of subjects who had no muscle-invasive recurrence, regional lymph node recurrence or distant metastasis, bladder cancer related death and retained intact bladder at the 2-year follow-up assessed by imaging, urinary cytology, and cystoscopy.

Table 1 Principal inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Subjects voluntarily participate in this trial and sign an informed consent form.	1. Prior treatment with therapies targeting PD-1, PD-L1, PD-L2, CTLA4, or HER2, or other antibodies/pharmaceuticals specifically directed against T-cell co-stimulatory or checkpoint pathways.
2. Age ≥ 18 years, male and female.	2. Administration of approved systemic anticancer therapies or immunomodulatory agents within 28 days prior to enrollment.
3. Imaging or pathologically confirmed staging of cT2-T4aN0M0 urothelial carcinoma of the bladder.	3. Previous radiotherapy for bladder cancer.
4. Patients who refuse to undergo radical cystectomy.	4. Prior antitumor pharmacotherapy, except intravesical chemotherapy or immunotherapy completed ≥ 2 weeks before study initiation.
5. Immunohistochemistry status of HER-2 was 3 + or 2 + [a].	5. Severe infections that require systemic antibacterial, antifungal, or antiviral treatment.
6. ECOG Performance Status: 0 or 1point [b].	6. Subjects having undergone major surgery or experienced significant trauma within 28 days prior to enrollment (excluding implantable vascular access device placement and TURBT) [c].
7. Sufficient reserves of organ function, such as the heart, liver, kidneys, hematopoiesis and so on.	7. Administration of live vaccines (excluding seasonal influenza vaccine) within 28 days prior to enrollment.
8. Patients with fertility are willing to rigorously adhere to contraception during the study period (male and female).	8. Have received any Chinese herbal medicine or traditional Chinese patent medicines within 14 days before enrollment.
9. Expected lifespan exceeding 12 months.	9. Patients with active autoimmune diseases that require systemic treatment.
10. Willing and able to follow our research and follow-up procedures.	10. Patients who require utilize hormones or other immunosuppressive medicines for an extended period of time.
	11. Other disease such as heart disease, pneumonia, tuberculosis, neuropathy, psychosis, or a history of uncontrolled systemic disease that the experts believe could have an impact on the course of treatment.
	12. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
	13. History of immunodeficiency, allogeneic stem cell transplantation, or organ transplantation.
	14. Patients who are allergic to any investigational drug ingredient.
	15. Pregnant or lactating women.
	16. Patients are concurrently enrolled in other therapeutic clinical studies.
	17. Merge with other malignant tumors.
	18. Patients deemed ineligible for participation in this study by researchers.

[a] HER-2, human epidermal growth factor receptor-2; [b] EOCG, eastern cooperative oncology group

[c] TURBT, transurethral bladder tumor resection

HER-2 IHC Classification System

Score 0: No staining or incomplete, faint membrane staining in < 10% of invasive tumor cells

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Score 2+: Weak to moderate complete membrane staining in ≥ 10% of invasive tumor cells or Complete, intense circumferential membrane staining in < 10% of invasive tumor cells

Score 3+: Complete, intense circumferential membrane staining in ≥ 10% of invasive tumor cells

Second endpoints

Clinical complete remission (cCR) rate

Defined as the proportion of subjects with no evidence of malignant tumors in imaging, cystoscopy or TURBT biopsy, and negative urine cytology after treatment (if the subjects underwent PLND, no evidence of lymph node metastasis is required), with evaluation nodes at 12 weeks, 24 weeks, and 1 year.

Over survival (OS)

Defined as the survival of subjects from screening enrollment to death for any reason stage.

5-year over survival (5-yr OS)

Proportion of patients who did not die from any cause from screening enrollment at 5-year survival follow-up.

Quality of life (QoL)

The European Organization for Research and Treatment of Cancer QoL thirty item score questionnaires will be used for health-related QoL.

Safety

Including evaluation of adverse events (AEs), Serious adverse events (SAEs), vital signs, physical examinations, laboratory tests, imaging examinations, and some special examinations.

Ethics statements and approvals

The study was approved by Medical Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Ethical approval number: SYSKY-2024-134-03). Written informed consent will be obtained from all objects prior to enrollment. This study adheres to all relevant ethical guidelines.

Study design

After cTURBT, the subjects are about to receive treatment with DV in combination with Toripalimab for 6-cycle (12 weeks), followed by the first assessment after undergoing TURBT and PLND. Patients who achieved cCR and partial response (PR) would be accepted treatment with DV combination with Toripalimab for another 6-cycles (12 weeks); Comprehensive treatment (not limited to chemotherapy, radiotherapy, immunotherapy, targeted treatment, surgical treatment, etc.) or salvage cystectomy for patients with progressive disease (PD).

Re-assessment at 24 weeks post-treatment, if cCR is achieved, the patients are going to be conducted Toripalimab immune maintenance for 1 year or until the tumor recurrence. However, if cCR is not achieved, the endpoint event will be reached. Follow-up diagnosis and treatment will be carried out based on clinical practice, and only survival follow-up will be performed. The process chart of the trial is exhibited in Fig. 1.

Intervention scheme

Medicine

Combination therapy period Subjects will be received 6 cycles of treatment with DV combination with Toripalimab after completed cTURBT at the first combination therapy period; For patients with initial efficacy evaluation of cCR or PR, DV combination with Toripalimab will be administered for another 6 cycles at the second combination therapy period. Among them, the dosage of Toripalimab is 3 mg/kg, once every two weeks (Q2W), intravenous infusion. And the dosage of DV is 2 mg/kg, Q2W, intravenous infusion.

Immune maintenance period Patients who achieved cCR after re-evaluation will be received maintenance treatment with Toripalimab for one year or until the tumor recurrence. In addition, the dosage of Toripalimab is 240 mg, once every three weeks (Q3W), intravenous infusion.

Surgery

cTURBT should be performed two weeks before the beginning of the first combination therapy period. And the first assessment should be conducted with TURBT and PLND, which should be occurred after the first combination therapy period, before the period of immune maintenance therapy, or before starting another new anti-cancer treatment, whichever occurs first.

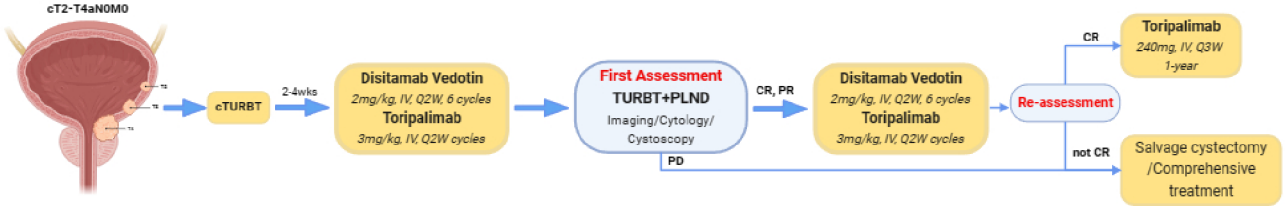

Fig. 1 The research process chart. cTURBT, complete transurethral bladder tumor resection; IV, intravenous injection; Q2W, once every 2 weeks; TURBT, transurethral bladder tumor resection; PLND, pelvic lymph node dissection; CR, complete response; PR, partial response; PD, progressive disease; Q3W, once every 3 weeks

Table 2 Follow-up schedule of five years

Assessment items	Screening	cTURBT	FCTP	TURBT and PLND	SCTP	Immune maintenance period	Post-therapy
	within 4 wks, prior to enrollment	1 wk after enrollment	Every 2 wks, 3 m in total	2–4 wks after FCTP	Every 2 wks, 3 m in total	Every 3 wks, 24 m in total	Every 3 m (up to 60 m)
Informed consent	X						
Characteristics	X						
Medical history	X						
physical examination	X	X	X	X	X	X	X
ECOG status	X	X	X	X	X	X	X
Blood examination [a]	X	X	X	X	X	X	X
Urine examination [b]	X	X	X	X	X	X	X
Imaging tests [c]	X		X	X	X	X	X
Special tests [d]	X		X	X	X	X	X
Cystoscopy [e]	X		X		X	X	X
Disitamab Vedotin			X		X		
Toripalimab			X		X	X	
Quality of life	X	X	X	X	X	X	X
Adverse event	X	X	X	X	X	X	X
Pathology [f]	X	X		X			
Survival assessment	X	X	X	X	X	X	X

cTURBT, complete transurethral bladder tumor resection; **TURBT**, transurethral bladder tumor resection; **PLND**, pelvic lymph node dissection; **FCTP**, the first combination therapy period; **SCTP**, the second combination therapy period; **ECOG**, Eastern Cooperative Oncology Group; **wk/wks**: week/weeks; **m**: moth

(a) Including blood routine, blood biochemistry, liver and kidney function, coagulation function, infectious disease indicators, thyroid function, ctDNA, etc. **(b)** Including urine routine, urine cytology, urine DNA methylation, urine FISH, urinary pregnancy test, etc. **(c)** Including chest CT, abdominal CT, pelvic CT or bladder MR, etc. Follow-up frequency: Q3m for 18 months, Q6m for 18 months, Q12m for 24 months. **(d)** Including electrocardiograms, echocardiography, and other necessary examinations based on research needs. **(e)** Follow-up frequency: Q3m for 12 months, Q4m for 12 months, Q6m for 3 years. **(f)** Pathological tissues are used to analyze relevant biomarkers

Follow-up

Based on the study protocol, subjects are supposed to accept regular examination at the baseline and the whole period of treatment, including the treatment stage of medication and surgery, and each follow-up visit. Vital signs, physical examinations and laboratory examinations should be performed before every therapy of medication or surgery. Detailed follow-up is displayed in Table 2.

Sample size considerations

Sample size consideration for this study is based on the primary outcome of 2-year BI-DFS rate. Based on previous results, the 2-year BI-DFS rate of patients with TMT was of approximately 62% [20]. Given that longer treatment cycles and application of DV and Toripalimab in our study, we hypothesize that 2-year BI-DFS rate can be improved from 62 to 75% in this trial. Using a one-sided alpha of 2.5% and a study power of 80%. In total, 63 subjects will be enrolled to test the null hypothesis with a power of 80% at a one-sided significance level of 0.25 (one-sample log-rank test).

Statistical analysis

Regularly, standard descriptive methods will be performed in the ITT set. Distribution parameters will be used to describe continuous variables according to the data distribution and counts and percentages for categorical data. Multivariate analyses may be performed using appropriate regression models. For tests and confidence intervals, a two-sided significance level $\alpha = 5\%$ will be used except for the primary endpoint and unless otherwise specified.

Efficacy and safety analyses will be conducted in all-treated population, defined as the population of subjects treated with at least one dose of any investigational drug. For the primary analysis, Kaplan Meier method will be used to estimate the 2-year BI-DFS rate and its 95% confidence interval.

For the secondary outcomes, the proportion of patients with the outcome and two-sided 95% confidence intervals will be calculated using two-sided Clopper-Pearson method. Kaplan-Meier analysis will also be applied to the other time-to-event data. The safety analysis contains type, incidence of AEs, vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) status, and laboratory test values. AEs and SAEs will be evaluated based on NCI-CTCAE v5.0 [21], and surgical related adverse events will be evaluated based on Clavien-Dindo grading [22].

Discussion

Current clinical guidelines recommend cisplatin-based neoadjuvant chemotherapy followed by RC and PLND as the standard management for MIBC. However, both in the process of clinical practice and in the demands of patients, the need for bladder-sparing treatment is increasing. Patients with bladder cancer frequently forfeit the opportunity to undergo surgery of orthotopic neobladder with retained urinary control function if bladder-sparing therapy fails, this is mainly because the addition of radiotherapy to current bladder preservation treatments, which is able to cause abdominal adhesions, bowel damage, and other radiotherapy-related complications. As a result, we designed a novel bladder-sparing treatment model that utilizes surgical approach rather than localized radiotherapy, allowing patients maintain their own urine control function even when bladder preservation treatment fails. It is worth noting that the absence of radiation may result in the efficacy of bladder preserving treatment. Therefore, systemic medication with significant therapeutic effects is also required.

A meta-analysis study demonstrated that HER-2 positive with a pooled positive rate of 41.2% in bladder cancer patients [23], while HER-2 overexpression has been found to be associated with tumor progression and poor prognosis [24, 25], and patients with HER-2 overexpressing exhibit therapeutic resistance to conventional chemoradiotherapy compared to HER-2 negative MIBC patients [26]. During the past few years, ADCs have been gaining much attention as potential solutions to figure out the bottleneck, which consist of monoclonal antibody, linkers, and chemotherapeutic agents. The monoclonal antibody recognizes the antigen on the surface of the cancer cells, and the chemotherapeutic drugs are connected to the antibody through the linkers, allowing for precise targeting treatment of the tumor [27]. Currently, ADCs have been illustrated to be effective in the treatment of advanced bladder cancer. For example, in the DESTINY-PanTumor02 study, Trastuzumab deruxtecan (T-DXd) demonstrated significant efficacy in patients with previously treated HER2-expressing advanced solid tumors, including biliary tract cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and other tumor types. In the overall study population of 267 patients, the confirmed ORR assessed by the investigators was 37.1% (95% CI: 31.3–43.2). The highest response rates were observed in patients with HER-2 IHC 3 + tumors, with an ORR of 61.3% (95% CI: 49.4–72.4). Notably, in the cohort of bladder cancer patients, patients with HER-2 IHC 3 + bladder cancer ($n = 16$), the ORR reached 56.3% (95% CI: 29.9–80.2) [28]. This study provides brand new treatment options for patients with HER-2 positive bladder cancer, especially in the subgroup of patients with IHC 3 + expression, where the increase in ORR is more pronounced. DV as another ADC has also been proven safe and effective in studies C005, C009, and C014 as mentioned in the background part earlier. Several current bladder-preserving studies have included DV in their treatment regimens [29, 30]. Taking the Hope-03 study as an example, all four enrolled patients achieved cCR. In terms of safety, DV related-toxicity included transaminase, erythema, sensory abnormalities, which occurred in 3 subjects [29]. ICIs will also be considered as part of bladder-sparing therapy, not only because of its satisfactory anti-tumor effects and generally tolerability, but also owing to the synergistic effect of immunotherapy with ADC drugs [31]. Toripalimab is a specific ICI for human PD-1, it has been proven to have good efficacy and safety in the treatment of bladder urothelial carcinoma [12, 32, 33].

Patients with cT2-T4aN0M0 staging identified by imaging and pathology will be enrolled in this prospective, multicenter, open-label, single-arm study, which is designed to evaluate the efficacy and safety of DV combination with Toripalimab therapy in patients with HER-2 expressing ≥ 2 + bladder cancer. Enrollment is expected to be completed within 2 years with a target enrollment of 63 patients. The trial is intended to identify an optimal bladder-sparing regimen, which is supposed to be further validated in large randomized controlled Phase III clinical trials in the future.

Abbreviations

NMIBC	Non-muscle invasive bladder cancer
MIBC	Muscle invasive bladder cancer
RC	Radical cystectomy
cTURBT	Complete transurethral bladder tumor resection
TURBT	Transurethral bladder tumor resection
PLND	Pelvic lymph node dissection
TMT	Trimodal therapy
CR	Clinical response
cCR	Clinical complete response
PR	Partial response
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death 1 ligand 1
ICIs	Immune checkpoint inhibitors
BI-DFS	Bladder-intact disease-free survival
ITT	Intention-to-treatment
AEs	Adverse events
SAEs	Serious adverse events
TRAEs	Treatment-related adverse events
irAEs	Immune related adverse events
RC-48 or DV	Disitamab Vedotin
ADC	Antibody-drug conjugate
HER-2	Human epidermal growth factor receptor-2
ORR	Objective response rate
OS	Over survival
QoL	Quality of life
Q2W	Once every two weeks
Q3W	Once every three weeks
ECOG	Eastern Cooperative Oncology Group

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Author contributions
W.H. and J.H. are the general supervisor and responsible for the project. T.H.L., W.H, J.H., W.L.Z., T.X.L., Q.H.T. were responsible for in the design of this study. Y.Y.Z. provided proposal of clinical research design and statistical guidance for this study. All authors participated in the initial protocol writing and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by Medical Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University. Written informed consent will be obtained from all objects prior to enrollment. Participants will be made aware that participation is strictly voluntary. Participants may withdraw from the study at any time.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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