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Advancing the treatment of muscle-invasive bladder cancer: Updates on immunotherapy in the perioperative setting

Practice aid for the treatment of muscle-invasive bladder cancer

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Guidelines

Guidelines for neoadjuvant/adjuvant therapy for MIBC

Neoadjuvant therapy

NCCN 2024[1]

- Neoadjuvant cisplatin-based combination ChT
- Cystectomy alone for those not eligible to receive cisplatin-based ChT

EAU 2024[2]

- If eligible for cisplatin-based ChT, offer neoadjuvant cisplatin-based combination ChT (T2-T4a, cN0 M0)
- Do not offer neoadjuvant ChT to patients who are ineligible for cisplatin-based combination ChT
- Only offer neoadjuvant immunotherapy to patients within a clinical trial setting

ESMO 2021[3]

- Three to four cycles of cisplatin-based neoadjuvant ChT

Adjuvant therapy

NCCN 2024[1]

- If no cisplatin neoadjuvant treatment given and pT3, pT4a, or pN+
  - Adjuvant cisplatin-based ChT should be discussed or consider adjuvant nivolumab
- If cisplatin neoadjuvant ChT given and ypT2–ypT4a or ypN+, consider nivolumab
- Consider adjuvant RT in selected patients (pT3–4, positive nodes/margins at time of surgery)

EAU 2024[2]

- If no neoadjuvant ChT has been given offer adjuvant cisplatin-based combination ChT to patients with pT3/4 and/or pN+ disease
- If not eligible for, or declined, adjuvant cisplatin-based ChT, offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease

ESMO 2021[3]

- There is weak evidence to support the use of adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy. Neoadjuvant ChT is preferred

Practical considerations

Insights from key clinical trials

Adjuvant

CheckMate 274[4]

Nivolumab (n=353) vs **placebo (n=356)**

- **Prior NAC*** (ypT2–ypT4a or ypN+)
- **No prior NAC*** (pT3–pT4a or pN+)

3-year median DFS
- **ITT: 22.0** vs **10.9** months
  HR 0.71 (0.58–0.86)

3-year median OS
- **ITT: 69.5** vs **50.1** months
  HR 0.76 (0.61–0.96)

AMBASSADOR[5]

Pembrolizumab (n=354) vs **observation (n=348)**

- **Prior NAC** (≥ypT2, ypN+, microscopic +ve margins†)
- **No prior NAC** (≥pT3, pN+, microscopic +ve margins†)

Median DFS
- **ITT: 29.6** vs **14.2** months
  HR 0.73 (0.59–0.90); p=0.003

3-year OS rate
- **ITT: 60.8%** vs **61.9%** of patients
  HR 0.98 (0.76–1.26)

IMvigor010[6,7]

Atezolizumab (n=406) vs **observation (n=403)**

- **Prior NAC** (ypT2–4a, ypN+, **or** ypT2–4 or ypN+ for UTUC)
- **No prior NAC** (pT3–4a, pN+, **or** pT3–4 or pN+ for UTUC)

Median DFS
- **ITT: 19.4** vs **16.6** months
  HR 0.89 (0.74–1.08); p=0.24

Median OS
- **ITT: 61.4** vs **59.0** months
  HR 0.91 (0.73–1.13)

Perioperative

NIAGARA[8]

NAC‡ + **durvalumab**, then RC + adjuvant **durvalumab (n=533)** vs NAC‡ then RC alone (**comparator; n=530**)

- Histological or cytological MIBC, T2, T3, or T4a, N0 or N1, and M0, and eligible for cisplatin-based chemotherapy

2-year EFS rate
- **ITT: 67.8%** vs **59.8%** of patients
  HR 0.68 (0.56–0.82); p<0.001

2-year OS rate
- **ITT: 82.2%** vs **75.2%** of patients
  HR 0.75 (0.59–0.93); p=0.01

Aspects to consider for perioperative treatment

Eligibility for platinum-based chemotherapy[9]

Surgical considerations include patient preference for cystectomy and fitness to undergo the procedure[10,11]

Cautions for ICI use in certain patients, e.g. those with active autoimmune disease, currently receiving immunosuppressive therapy[12]

95% confidence intervals shown in brackets following HR. *Cisplatin-based NAC. †Presence of individual factors or a combination were allowed.
‡NAC consisted of cisplatin–gemcitabine therapy.

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Safety considerations

Most common AEs with ICIs from key MIBC clinical trials*

Monotherapy

CheckMate 274[13]

Nivolumab (N=351)

Any grade	n (%)
Pruritus	81 (23)
Fatigue	61 (17)
Diarrhoea	59 (17)

Grade ≥3	n (%)
↑ lipase level	18 (5)
↑ amylase level	13 (4)
Diarrhoea	3 (1)

IMvigor010[7]

Atezolizumab (N=390)

Any grade	n (%)
Pruritus	75 (19)
Fatigue	63 (16)
Diarrhoea	37 (9)

Grade ≥3	n (%)
Arthralgia	5 (1)
ALT increased	4 (1)
Colitis	4 (1)

AMBASSADOR[5]

Pembrolizumab (N=330)

Any grade	n (%)
Fatigue	156 (47)
Pruritus	74 (22)
Diarrhoea	68 (21)

Grade 3/4	n (%)
↑ lipase level	15 (5)
Diarrhoea	10 (3)
Fatigue	8 (2)

Combination therapy

NIAGARA[8†]

Durvalumab + ChT (N=530)

Any grade	n (%)
Nausea	284 (54)
Anaemia	205 (39)
Constipation	205 (39)

Grade 3/4	n (%)
Neutropenia	76 (14)
UTI	75 (14)
Anaemia	73 (14)

*Some percentages are the same with different n numbers due to rounding. Three most common AEs presented. †AEs of any cause.

Safety considerations

Identification and management of AEs with immunotherapy

Strategies to support early identification of possible irAEs

Education

- Patient education is an essential element of toxicity management[14,15]
- Enhanced awareness of the expected and possible irAEs improves coping skills and resilience in patients[15]
- Patients must be informed that irAEs can occur at any time and even after treatment cessation[15]

Monitoring

- Routine screening before ICI initiation is advised[15]
- There should be suspicion that new symptoms are treatment related[14]
- Tests to be performed prior to and during ICI therapy include CBC with differential, CMP, TSH, fT4[12]
- Urinalysis should be considered to evaluate for baseline kidney disease[12]

Presentation

- Side effects may involve any system of the body but GI, dermatologic, hepatic, endocrine and pulmonary toxicities predominate[14]
- irAEs to be aware of include rash, diarrhoea, abdominal pain, cough, fatigue, headaches, vision changes[14]

Guidelines for management of immunotherapy toxicities are available e.g. SITC,[12] ASCO[14] and ESMO[15]

Systemic corticosteroids are commonly used as a first-line treatment[12]

Some refractory cases may require other immunosuppressive therapy[14]

Treatment interruption is recommended for grade 2 toxicities[12,14]

Patients should be referred to a specialist when they experience toxicities of grade ≥3[12]

In general, permanent discontinuation of treatment is recommended with grade 4 toxicities[14]

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Abbreviations and references

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; CBC, complete blood count; ChT, chemotherapy; CMP, comprehensive metabolic panel; DFS, disease-free survival; EAU, European Association of Urology; EFS, event-free survival; ESMO, European Society for Medical Oncology; fT4, free thyroxine; GI, gastrointestinal; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related AE; ITT, intention-to-treat; M, metastasis; MIBC, muscle-invasive bladder cancer; N, node; NAC, neoadjuvant chemotherapy; NCCN, National Comprehensive Cancer Network; p, pathologic; OS, overall survival; RC, radical cystectomy: SITC, Society for Immunotherapy of Cancer; T, tumour; TSH, thyroid-stimulating hormone; UTI, urinary tract infection; UTUC, upper tract urothelial carcinoma; yp, pathological after neoadjuvant therapy.

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