Advances in immunotherapies and targeted treatments for patients with bladder cancer: An update from ESMO 2022

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Overview

- Part 1: Latest efficacy and safety data for emerging immunotherapies and targeted treatments for patients with bladder cancer
- Part 2: Future directions in the use of immunotherapy and targeted therapies for the treatment of bladder cancer
- Part 3: Recent data on biomarkers and prognostic factors for immunotherapy and targeted treatment outcomes in patients with bladder cancer

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Latest efficacy and safety data for emerging immunotherapies and targeted treatments for patients with bladder cancer

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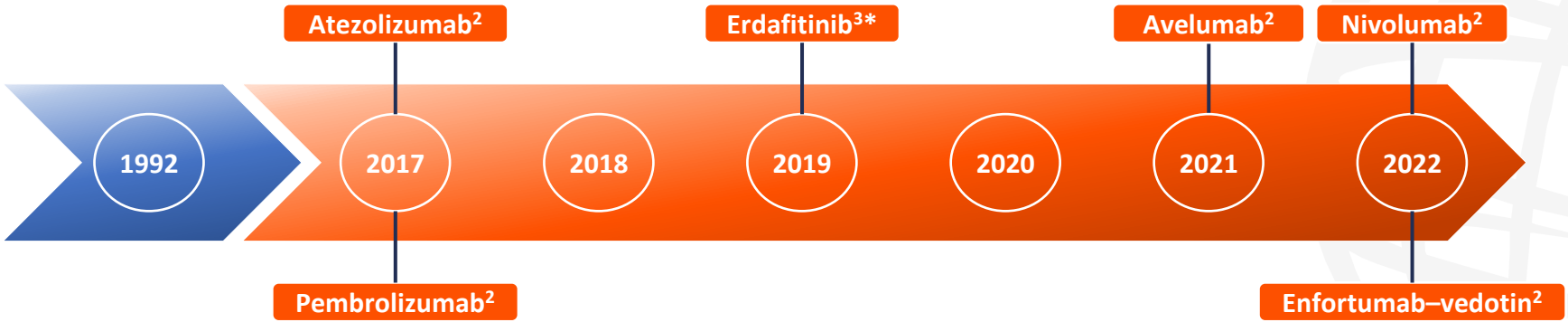
Overview of approvals for bladder cancer treatment

Platinum-based chemotherapy[1]

Immunotherapies and targeted treatments



Although mortality rates have declined recently, at least in part as a consequence of therapeutic improvements, patients with metastatic urothelial carcinoma have a very poor prognosis[4]

*FDA approval date. All others are EMA approval dates.
EMA, European Medicines Agency; FDA, Food and Drug Administration.
1. Lavoie JM, et al. *Oncologist*. 2021;26:e1381–94; 2. EMA. History of approval for all drugs. Available at www.ema.europa.eu (accessed 8 July 2022);
3. FDA. History of approval for erdafitinib. Available at: www.fda.gov/drugs (accessed 8 July 2022); 4. Rizzo M, et al. *Biologics*. 2021;15:441–50.

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Avelumab for first-line maintenance: Clinical trial data

Aragon-Ching JB, et al.

- JAVELIN Bladder 100: Phase III randomized open label trial[1,2]
- Avelumab in patients who had not progressed after first-line platinum-based chemotherapy[1,2]

N=700[2]

- Unresectable laUC or mUC[1,2]
- No prior immunotherapy or adjuvant systemic therapy[2]

Randomized 1:1 to:[2]
- Avelumab IV Q2W + BSC
- BSC alone

Primary endpoint:[2]
- OS

Secondary endpoints:[2]
- PFS
- ORR
- Safety

Prior first-line chemotherapy:
- Between four and six cycles of gemcitabine + cisplatin, or gemcitabine + carboplatin[2]

BSC, best supportive care; DOR, duration of response; IV, intravenous; laUC, locally advanced UC; mUC, metastatic UC; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; TTR, time to tumour response; UC, urothelial carcinoma.

1. Aragon-Ching JB, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1760P; 2. Clinicaltrials.gov. NCT02603432. Available at: www.clinicaltrials.gov/ct2/show/NCT02603432 (accessed 6 September 2022).

Avelumab for first-line maintenance: Clinical trial data

Aragon-Ching JB, et al.

Efficacy

Patients treated with avelumab ≥12 months:

- mOS was not reached
  (95% CI 50.9 months to not estimable)
- mPFS was 26.7 months
  (95% CI 19.4–32.2 months)

Safety

All avelumab-treated patients (n=344):

- Grade ≥3 TRAEs: 19.5%
- Grade ≥3 irAEs: 7.6%

Patients treated with avelumab ≥12 months (n=118):

- Grade ≥3 TRAEs: 11.9%
- Grade ≥3 irAEs: 4.2%

First-line avelumab maintenance until progression or unacceptable toxicity is further supported by the results of this study

AE, adverse event; CI, confidence interval; irAE, immune-related AE; m, median; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related AE.

Aragon-Ching JB, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1760P.

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Avelumab for first-line maintenance: RWD

Barthelemy P, et al.

- AVENANCE: Non-interventional real-world, ambispective study[1,2]
- Patients who had not progressed with first-line platinum-based chemotherapy[1,2]

N=267[1]

- laUC or mUC[1]
- Not progressed after first-line platinum-based chemotherapy[1]

- Avelumab as provided in real-world practice[2]

Primary endpoint:[1,2]

- OS from start of avelumab

Secondary endpoints:[1,2]

- OS from start of first-line chemotherapy
- PFS
- DOR
- Safety

- Preliminary analysis of patients who started avelumab ≥6 months prior to data cut-off

DOR, duration of response; laUC, locally advanced UC; mUC, metastatic UC; OS, overall survival; PFS, progression-free survival; RWD, real-world data; UC, urothelial carcinoma.

1. Barthelemy P, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1757P; 2. Clinicaltrials.gov. NCT04822350. Available at: www.clinicaltrials.gov/ct2/show/NCT04822350 (accessed 6 September 2022).

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Avelumab for first-line maintenance: RWD

Barthelemy P, et al.

Endpoint	Result
12-month OS rate (avelumab)	66.9%
12-month OS rate (1L chemo)	79.1%
mDOT	5.6 months
12-month PFS rate (avelumab)	36.9%
mPFS	5.7 months

Safety

- TEAEs experienced by 63.7% of patients
- 28.1% of patients experienced serious AEs
- Temporary/permanent discontinuation was seen in 27.0% of patients with TEAEs

In the real-world setting, maintenance avelumab after first-line chemotherapy demonstrated clinical benefit and did not raise new safety concerns compared with clinical trials

1L, first-line; AE, adverse event; BSC, best supportive care; DOT, duration of treatment; m, median; OS, overall survival; PFS, progression-free survival; RWD, real-world data; TRAE, treatment-emergent adverse event.

Barthelemy P, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1757P.

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Enfortumab-vedotin after chemotherapy: RWD

Darr C, et al.

- Retrospective, multicentre cohort
- Enrolled patients who have received prior platinum-based chemotherapy

N=56

- aUC or mUC
- Previously treated with platinum-based chemotherapy and/or ICI

- Treatments given according to routine care

Primary endpoint:
- ORR

Secondary endpoints:
- PFS
- Safety

- Data were collected from 11 tertiary treatment centres from November 2019 to April 2022

aUC, advanced UC; ICI, immune checkpoint inhibitor; mUC, metastatic UC; ORR, objective response rate; PFS, progression free survival; RWD, real-world data; UC, urothelial carcinoma.

Darr C, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1759P.

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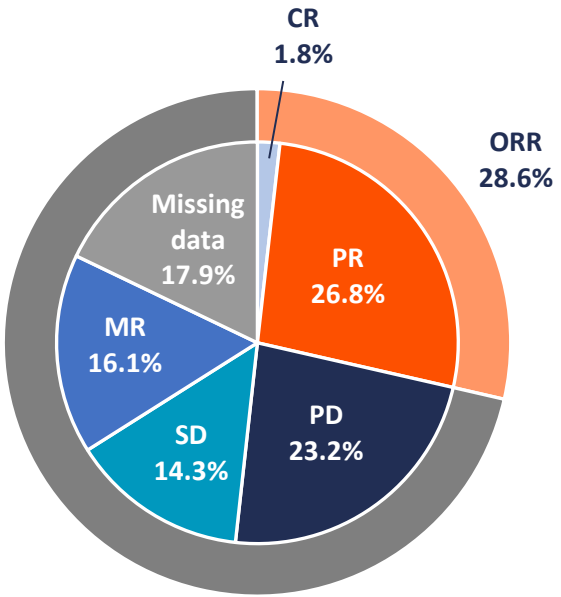
Enfortumab-vedotin after chemotherapy: RWD

Darr C, et al.



- mPFS = 3 months

Safety

- Discontinuation was due to progressive disease in 44.6% and toxicity in 10.2% of patients
- AEs of all grades were observed in 78.6% of patients
- AEs of grade ≥3 were observed in 42.9% of patients

In real-world clinical practice, enfortumab-vedotin demonstrated efficacy after platinum chemotherapy without raising new safety concerns

AE, adverse event; CR, complete response; mPFS, median progression-free survival; MR, mixed response; ORR, objective response rate; PD, partial disease; PR, partial response; SD, stable disease.

Darr C, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1759P.

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Adjuvant nivolumab: Biomarkers for DFS

Necchi A, et al.

- Exploratory biomarker analysis of CheckMate 274 (phase III randomized triple blind trial)[1,2]
- Nivolumab vs placebo after radical resection[1,2]

N=709[1]

- High-risk invasive UC[2]
- Prior radical resection[2]
- No secondary treatment after resection[2]
- Nivolumab 240 mg Q2W vs placebo[1]

- Pre-treatment tumour tissue for biomarker analysis[1]

Biomarkers:[1]

- TMB (whole-exome sequencing)
- CD8+ immune cell infiltration (digital IHC)
- IFN-γ gene signature scores (RNA-seq)

DFS, disease-free survival; IFN-γ, interferon gamma; IHC, immunohistochemistry; Q2W, every 2 weeks; TMB, tumour mutation burden; UC, urothelial carcinoma.

1. Necchi A, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1737MO; 2. Clinicaltrials.gov. NCT02632409. Available at: www.clinicaltrials.gov/ct2/show/NCT02632409 (accessed 6 September 2022).

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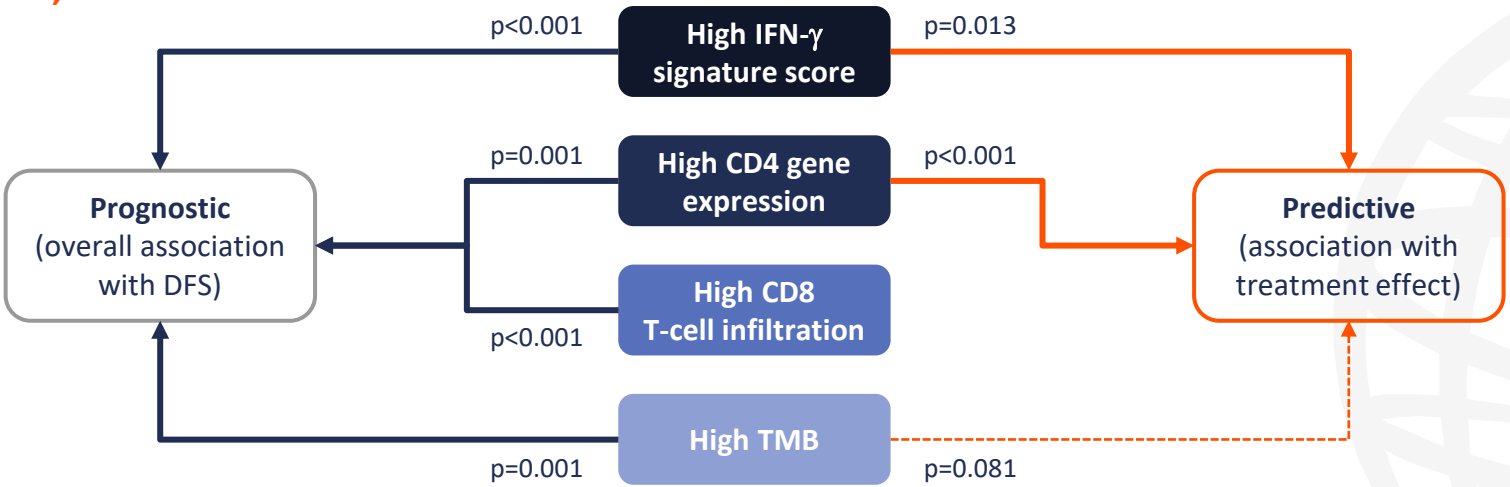
Adjuvant nivolumab: Biomarkers for DFS

Necchi A, et al.



- The IFN-γ gene signature and CD4 gene expression were predictive of nivolumab clinical benefit
- The associations appeared more pronounced in patients with PD-L1 ≥1%
- A positive prognostic association between CD8 infiltration and DFS was observed
- There was a positive association between TMB and DFS that may be predictive of nivolumab efficacy

DFS, disease-free survival; IFN-γ, interferon gamma; PD-L1, programmed death-ligand 1; TMB, tumour mutation burden.

1. Necchi A, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1737MO.

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Conclusions

- First-line avelumab maintenance until progression or unacceptable toxicity was confirmed in patients treated for 12 months or more in the JAVELIN Bladder 100 trial
- In the real-world setting, maintenance avelumab after first-line chemotherapy demonstrated clinical benefit compared with best supportive care and did not raise additional safety concerns compared with clinical trial data
- Enfortumab-vedotin demonstrated efficacy after platinum chemotherapy in real-world clinical practice without new safety concerns
- Exploratory biomarker analysis of CheckMate 274 showed that the DFS benefit provided by neoadjuvant nivolumab is associated with the biomarkers of antitumour activity

DFS, disease-free survival.

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Future directions in the use of immunotherapy and targeted therapies for the treatment of bladder cancer

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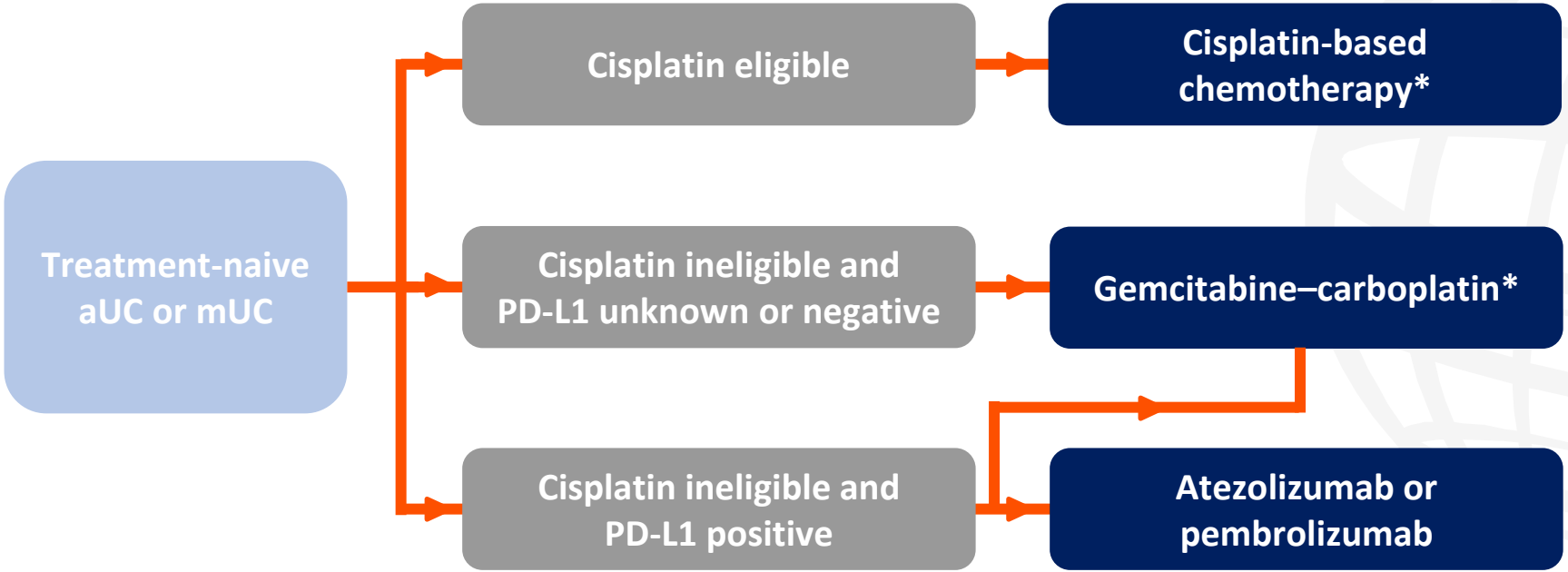
ESMO clinical practice guidelines for advanced or metastatic bladder cancer: First-line treatment



*Followed by maintenance avelumab in those tumours not progressing on chemotherapy.
aUC; advanced UC; mUC, metastatic UC; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.
Powles T, et al. *Ann Oncol*. 2022;33:244–58.

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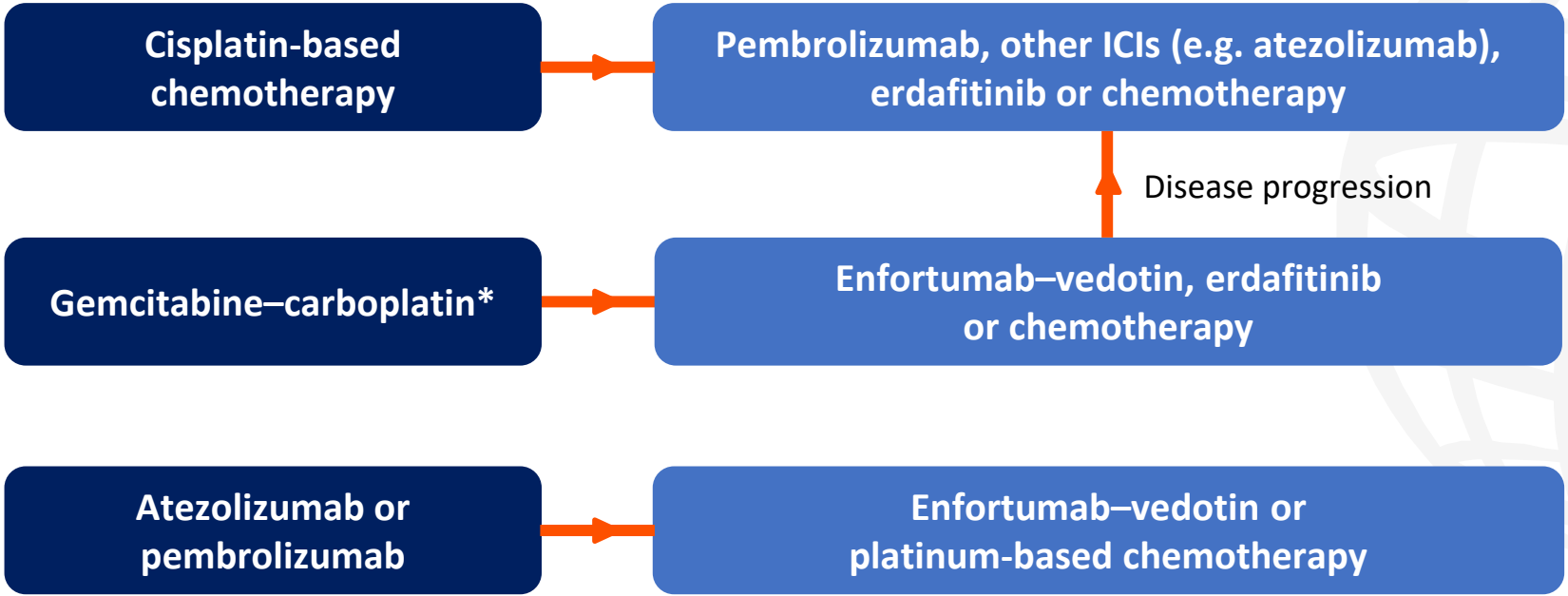
ESMO clinical practice guidelines for advanced or metastatic bladder cancer: After disease progression



*Followed by maintenance avelumab in those tumours not progressing on chemotherapy.
ICI, immune checkpoint inhibitor.
Powles T, et al. *Ann Oncol*. 2022;33:244–58.

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Neoadjuvant pembrolizumab: 3-year follow-up

Padua TC, et al.

- PURE-01: Phase II open label trial[1,2]
- Pembrolizumab and radical cystectomy[1,2]

N=155[1]

- Patients with MIBC receiving radical cystectomy
- No prior IV chemotherapy, anti-PD-1 or anti-PD-L1 antibody therapy[2]
- No metastatic disease[2]

- Pembrolizumab 200 mg IV Q3W[2]

Primary endpoints:[1,2]
- EFS
- pCR

Secondary endpoints:[2]
- RFS
- OS
- Safety

EFS, event-free survival; IV, intravenous; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; RFS, recurrence-free survival.

1. Padua TC, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1738P; 2. Clinicaltrials.gov. NCT02736266. Available at: www.clinicaltrials.gov/ct2/show/NCT02736266 (accessed 6 September 2022).

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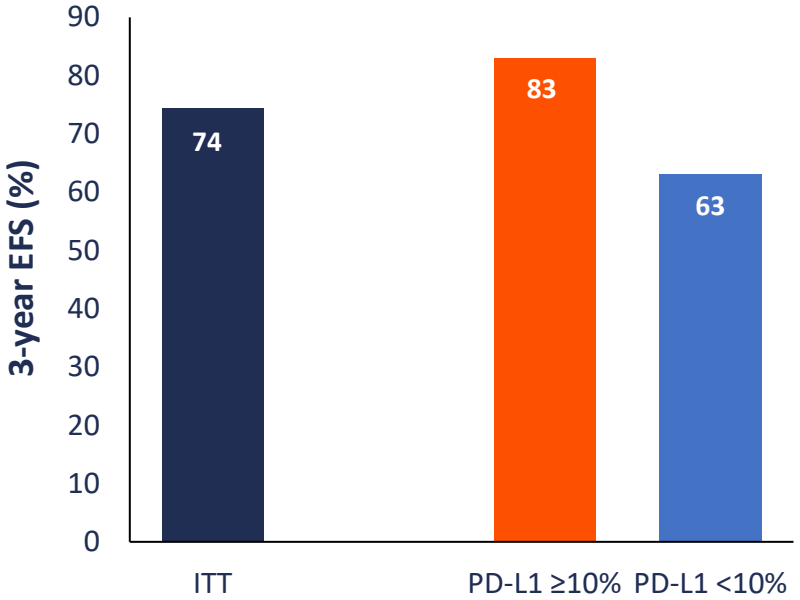
Neoadjuvant pembrolizumab: 3-year follow-up

Padua TC, et al.



- ITT 36-month OS = 83.8%

3-year follow-up data confirm the benefit of neoadjuvant pembrolizumab monotherapy in patients with MIBC with PD-L1 expression ≥10%

EFS, event-free survival; ITT, intention-to-treat; MIBC, muscle-invasive bladder cancer; OS, overall survival; PD-L1, programmed death-ligand 1.
Padua TC, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1738P.

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Neoadjuvant radio-immunotherapy

Schmid SC, et al.

- RACE-IT: Phase II, prospective, single arm, multicentre, open label trial[1,2]
- Preoperative radiation therapy prior to radical cystectomy combined with immunotherapy[2]

N=33[1]

- laUC[1,2]
- Eligible for radical cystectomy[2]
- Unfit for, or refusing, neoadjuvant chemotherapy[2]

- Nivolumab 240 mg IV Q2W (four cycles starting 1 week before radiotherapy)
- Neoadjuvant radiotherapy for 6 weeks
- Radical cystectomy between weeks 11 and 15[2]

Primary endpoint:[1,2]

- Patients with completed treatment (week 15)

Secondary endpoints:[2]

- OS
- ORR
- DFS
- Safety

DFS, disease-free survival; laUC, locally advanced urothelial carcinoma; IV, intravenous; ORR, objective response rate; OS, overall survival; Q2W, every 2 weeks.

1. Schmid SC, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr LBA75; 2. Clinicaltrials.gov. NCT03529890. Available at: www.clinicaltrials.gov/ct2/show/NCT03529890 (accessed 8 September 2022)

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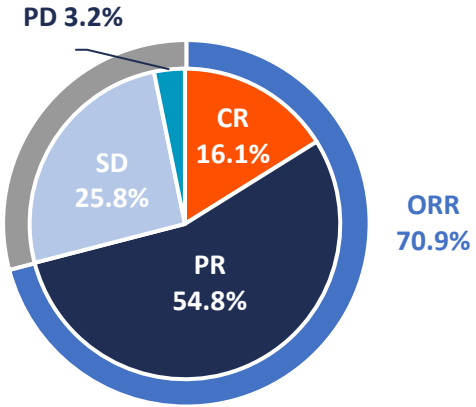
Neoadjuvant radio-immunotherapy

Schmid SC, et al.

n=31 patients eligible for primary endpoint and efficacy analysis



- Completed treatment (week 15): 87.1%
- 12-month DFS rate: 90.6%

Safety

- TRAE: 54.5% (mostly grades 1–2)
- Most common TRAEs:
  - Thyroid (15.2%)
  - Gastrointestinal (15.2%)
  - Skin reactions (33.3%)
- Nivolumab discontinuation: 25.8%

Neoadjuvant radio-immunotherapy followed by radical cystectomy demonstrates tolerable safety profile and clinical efficacy

DFS, disease-free survival; CR, complete response; ORR, objective response rate; PD, partial disease; PR, partial response; SD, stable disease; TRAE, treatment related adverse event.

Schmid SC, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr LBA75.

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First-line enfortumab–vedotin ± pembrolizumab

Rosenberg JE, et al.

- EV-103: Phase I/II randomized open label trial[1,2]
- Enfortumab–vedotin as a monotherapy or in combination with pembrolizumab[1]

N=149[1]

- laUC or mUC[1]
- Previously untreated[1]
- Cisplatin-ineligible[1]
- No prior systemic treatment[2]

- EV (1.25 mg/kg) on days 1 and 8 every 21 days[1,2]
- EV (1.25 mg/kg) on days 1 and 8 every 21 days + P (200 mg) on day 1 every 21 days[1,2]

Primary endpoints:[2]
- Safety (AEs)
- ORR
- pCR

Secondary endpoints:[2]
- DLT
- DCR
- DOR
- PFS
- EFS
- OS
- PK
- DFS

AE, adverse event; DCR, disease control rate; DFS; disease-free survival; DLT, dose-limiting toxicity; DOR, duration of response; EFS, event-free on study therapy; EV, enfortumab–vedotin; la, urothelial carcinoma; mUC, locally advanced or metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; P, pembrolizumab; pCR, pathological complete response; PFS, progression-free survival PK, pharmacokinetics.

1. Rosenberg JE, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr LBA73; 2. Clinicaltrials.gov. NCT03288545. Available at: www.clinicaltrials.gov/ct2/show/NCT03288545 (accessed 6 September 2022).

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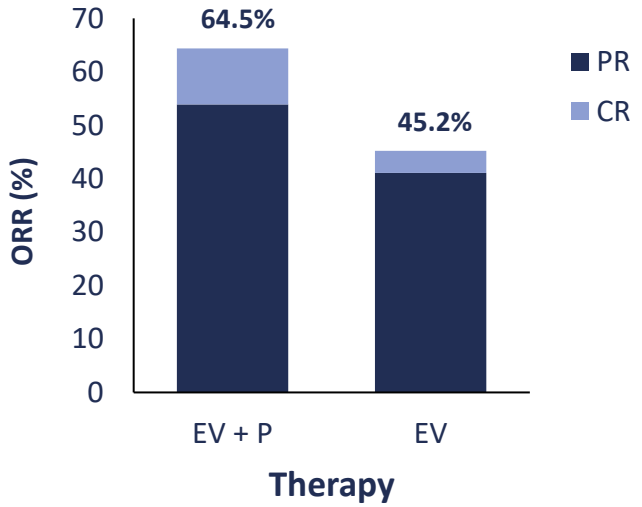
First-line enfortumab–vedotin ± pembrolizumab

Rosenberg JE, et al.



Safety

- Most common TRAEs of special interest:
  - Skin reactions (EV + P: 67.1%; EV: 45.2%
  - Peripheral neuropathy (EV + P: 60.5%; EV: 54.8%)
  - Ocular disorders (EV + P: 26.3%; EV: 28.8%)
  - Hyperglycaemia (EV + P: 14.5%; EV:11.0%)
- Most were grade ≤2

mDOR

- Not reached in patients receiving EV + P
- 13.2 months in patients receiving EV alone

ORR and DOR results support ongoing investigations of first-line EV+P in patients with laUC or mUC ineligible for platinum-based chemotherapy

CR, complete response; DOR, duration of response; EV, enfortumab–vedotin; la, locally advanced urothelial carcinoma; m, median; mUC, metastatic urothelial carcinoma; ORR, overall response rate; P, pembrolizumab; PR, partial response; TRAE, treatment-related adverse event.

Rosenberg JE, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr LBA73.

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Conclusions

- 3-year follow-up data from the PURE-01 study confirmed the benefit of neoadjuvant pembrolizumab monotherapy in patients with muscle invasive bladder cancer with PD-L1 expression ≥10%
- Neoadjuvant radio-immunotherapy followed by radical cystectomy demonstrated a tolerable safety profile and clinical efficacy in the RACE-IT trial
- Early ORR data from the cohort K of the EV-103 trial support ongoing investigation of first-line enfortumab vedotin in combination with pembrolizumab in patients with laUC or mUC ineligible for platinum-based chemotherapy

PD-L1, programmed death-ligand 1; ORR, overall response rate; la, locally advanced urothelial carcinoma; mUC, metastatic urothelial carcinoma.

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Recent data on biomarkers and prognostic factors for immunotherapy and targeted treatment outcomes in patients with bladder cancer

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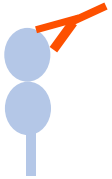
Biomarkers for response to immunotherapy

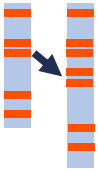


PD-L1

- Meta-analyses of prospective trials show that, overall, PD-L1 expression is associated with radiographic response to ICIs in patients with mUC
- However, even among PD-L1 positive patients, single-agent ICI response rates are low and variable across randomized trials, ranging from 20% to 40%

Mutation burden

- Exploratory analyses of prospective trials in mUC suggest that the combination of TMB and PD-L1 may more effectively distinguish ICI responders and non-responders than either biomarker alone



Somatic mutation

- *TRAF2* loss is a predictor of ICI response and *CCND1* amplification is as a marker of ICI resistance
- Somatic mutations in DDR or cycle regulator genes are associated with both TMB and response

DDR, DNA damage repair; ICI, immune checkpoint inhibitor; mUC, metastatic urothelial carcinoma; PD-L1, programmed death-ligand 1; TMB, tumour mutation burden.

Jun T, et al. *J Cancer Metastasis Treat*. 2022;8:1.

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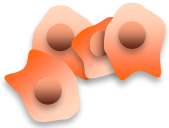
Biomarkers for response to immunotherapy

Gene expression

- IMvigor210 trial found *TGFB1* and *TGFBR2* were associated with non-response and reduced OS
- A 25-gene interferon gamma signature was associated with response in the CheckMate-275 trial
- An 8-gene subset of that signature focused on CD8+ T-cell effector activity was positively associated with response in the IMvigor210 trial
- *CXCL9* and *CXCL10* expression were individually associated with ICI response in both the IMvigor210 and CheckMate-275 trials



Molecular subtypes

- IMvigor210 trial found the highest response rates among the luminal II subtype
- CheckMate-275 trial found the highest response among the basal I subtype
- The JAVELIN Bladder 100 trial found no association between subtypes and OS

ICI, immune checkpoint inhibitor; OS, overall survival.

Jun T, et al. *J Cancer Metastasis Treat*. 2022;8:1.

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Biomarkers for response to targeted therapy

FGFR

- Erdafitinib is approved for use in previously treated mUC with susceptible *FGF2/3* alterations
- Ongoing trials include
  - Phase III PROOF302 trial of infigratinib (BGJ398) as adjuvant therapy for cisplatin-ineligible bladder cancer or upper tract UC
  - Phase Ib/II FIERCE-21 trial of vofatamab in *FGFR3*-altered mUC in the post-chemotherapy setting
  - Phase Ib/II FIDES-02 trial of derazantinib as a monotherapy or in combination with atezolizumab for cisplatin-ineligible aUC with *FGFR1–3* mutations and fusions

Nectin-4

- Enfortumab–vedotin is an antibody–drug conjugate targeting Nectin-4
- Nectin-4 is not currently utilized as a biomarker in patient selection
- Phase III EV-301 trial demonstrated an OS benefit for enfortumab–vedotin in a biomarker-unselected population

aUC, advanced UC; FGFR, fibroblast growth factor receptor; mUC, metastatic UC; OS, overall survival; UC, urothelial carcinoma.

Jun et al. *J Cancer Metastasis Treat*. 2022;8:1.

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Pre-treatment tumour PD-L1 expression

Grivas P, et al.

- PREVAIL: Prospective cohort study assessing the prevalence of high PD-L1 expression in patients with laUC or mUC[1]

N=129[1] → laUC or mUC[1] → Tissue samples collected prior to treatment[2]

Primary endpoint:[1]
- Proportion of pre-treatment tumours with high expression of PD-L1

Secondary endpoints:[2]
- Pre-treatment tumour tissue PD-L1 expression
- ORR
- PFS
- OS

PD-L1 high expression was defined as any of:[1]
- ≥25% of tumour cells exhibiting membranous staining
- Immune cells present >1% and immune cells with staining ≥25%
- Immune cells present=1% and immune cells with staining=100%

laUC, locally advanced urothelial carcinoma; mUC, metastatic urothelial carcinoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; UC, urothelial carcinoma.

1. Grivas P, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1775P; 2. Clinicaltrials.gov. NCT03788746. Available at: www.clinicaltrials.gov/ct2/show/NCT03788746 (accessed 8 September 2022).

Pre-treatment tumour PD-L1 expression

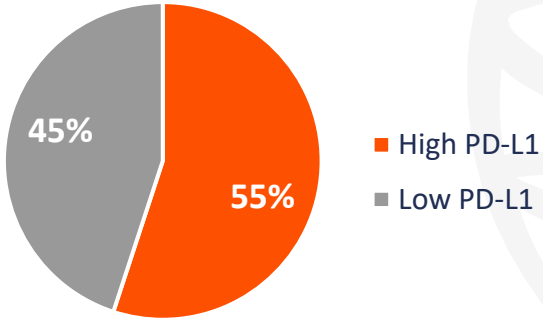
Grivas P, et al.

Patient characteristics

- Mean age: 72.4 years
- Gender: 65.9% male
- Race: 86.0% white
- Location: 24.1% upper tract tumour, 34.9% visceral metastases
- ECOG PS score: 76% 0–1
- Smoking status: 24.8% never smoked

Results

n=129 evaluable patients



PD-L1 high expression in the real-world community setting in patients who started first-line therapy for laUC or mUC was consistent with clinical trial data

laUC, locally advanced urothelial carcinoma; mUC, metastatic urothelial carcinoma; ECOG PS, European cooperative oncology group performance status; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

Grivas P, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1775P.

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PD-L1 expression on immune cells association with OS

Grande E, et al.

- Post-hoc analysis of IMvigor130 arms B and C[1]
- Associations between two PD-L1 IHC tests (SP142 and 22C3) and OS[1]

n=627[1]

- laUC or mUC[2]
- No prior lines of therapy[2]
- Eligible for first-line platinum-based chemotherapy[1]

- Arm B: Atezolizumab monotherapy[1]
- Arm C: Placebo + platinum + gemcitabine[1]

- Archival tumour samples were assessed for PD-L1 expression using two assays
- Assays cut-offs for high PD-L1 staining:[1]
  - SP142, IC ≥5% vs IC <5%
  - 22C3, CPS ≥10 vs CPS <10
- Samples were also stained for IC subtypes[1]

CPS, combined positive score; IC, immune cells; IHC, immunohistochemistry; laUC, locally advanced urothelial carcinoma; mUC, metastatic urothelial carcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

1. Grande E, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1735O.; 2. Clinicaltrials.gov. NCT02807636. Available at: www.clinicaltrials.gov/ct2/show/NCT02807636 (accessed 14 September 2022).

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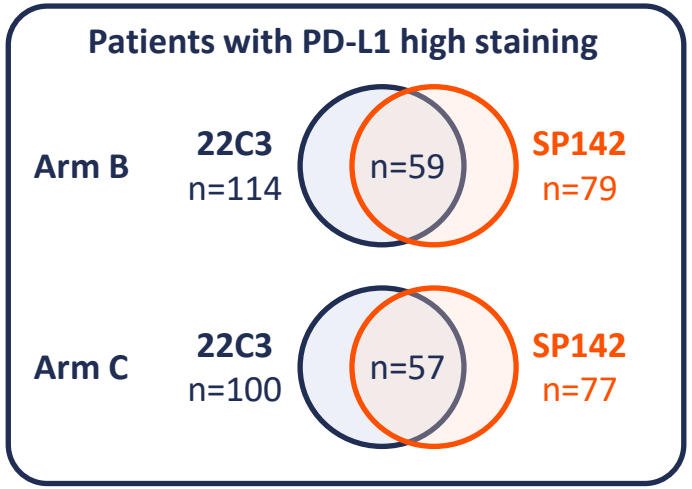

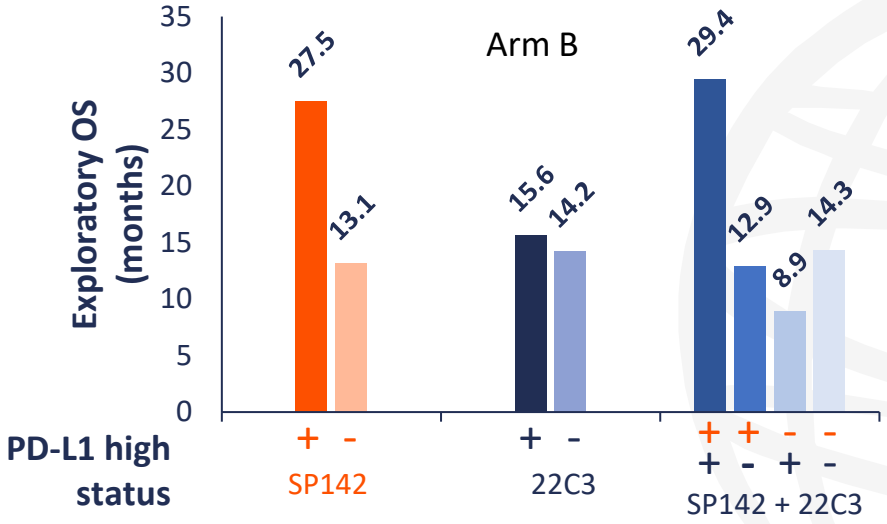

- SP142 PD-L1 staining preferentially co-localized with dendritic cells
- The SP142 assay was associated with OS and was both prognostic and predictive
- Combined analysis showed longer OS in patients whose tumour tested positive for high PD-L1 expression with both assays

OS, overall survival; PD-L1, programmed death-ligand 1.

Grande E, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1735O.

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Genomic biomarkers in avelumab-treated patients

Powles TP, et al.

- Sub-analysis of the JAVELIN Bladder 100 trial investigating genomic biomarkers in the peripheral blood of patients[1]

N=496

- laUC or mUC with no progression after first-line chemotherapy
- First-line avelumab maintenance therapy ± BSC

- Tertiary lymphoid structures (ectopic lymphoid tissues that arise in inflamed tissue, including cancer) may correlate with outcome to ICI therapy[1,2]
- Analysis of chromatin conformation signatures has the potential to identify host immune factors associated with anti-tumour immune activity in circulating white blood cells[1]
- In this analysis, tumour immune activity was scored using a gene expression signature (JAVELIN Renal 101 Immune [JR101I])[1]
- Chromatin conformation signature association with tumour JR101I scores was then determined[1]

BSC, best supportive care; ICI, immune checkpoint inhibitor; laUC, locally advanced urothelial carcinoma; mUC, metastatic urothelial carcinoma; UC, urothelial carcinoma.

1. Powles TP, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr LBA74; 2. Van Dijk N, et al. *Nat Med*. 2020;26:1839–44.

Genomic biomarkers in avelumab-treated patients

Powles TP, et al.

- Tertiary lymphoid structure gene expression scores were positively associated with lymphoid aggregates and maintenance avelumab survival benefit
- Chromatin conformation loops in white blood cells were associated with the JR101I immunosignature
  - The strongest association was with *POU2F2*, a transcription factor regulating B-cell responses to T cells
  - The presence of the *POU2F2* chromatin loop was associated with reduced *POU2F2* expression and function, as well as tertiary lymphoid structure biomarkers, suggesting a negative regulatory role

Further statistical analysis is required as these analyses were exploratory in nature and not corrected for multiple testing

JR101I, JAVELIN Renal 101 Immune; WBC, white blood cells.

Powles TP, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr LBA74 .

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DFS and DMFS as surrogate markers for OS

Sternberg C, et al.

- Two-level metanalytic approach investigation of surrogate outcomes beyond OS that can enable earlier evaluation of trial efficacy

N=1075 • MIBC • Adjuvant chemotherapy

Primary endpoints:
- DFS association with OS
- DMFS association with OS

- Individual patient data from nine randomized control trials (median follow-up 3.5–14.6 years) comparing cisplatin-based combination chemotherapy vs observation ± deferred chemotherapy at relapse
- Strength of patient-level associations between DFS/DMFS and OS was measured

DFS, disease-free survival; DMFS, distant metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival.

Sternberg C, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1746P.

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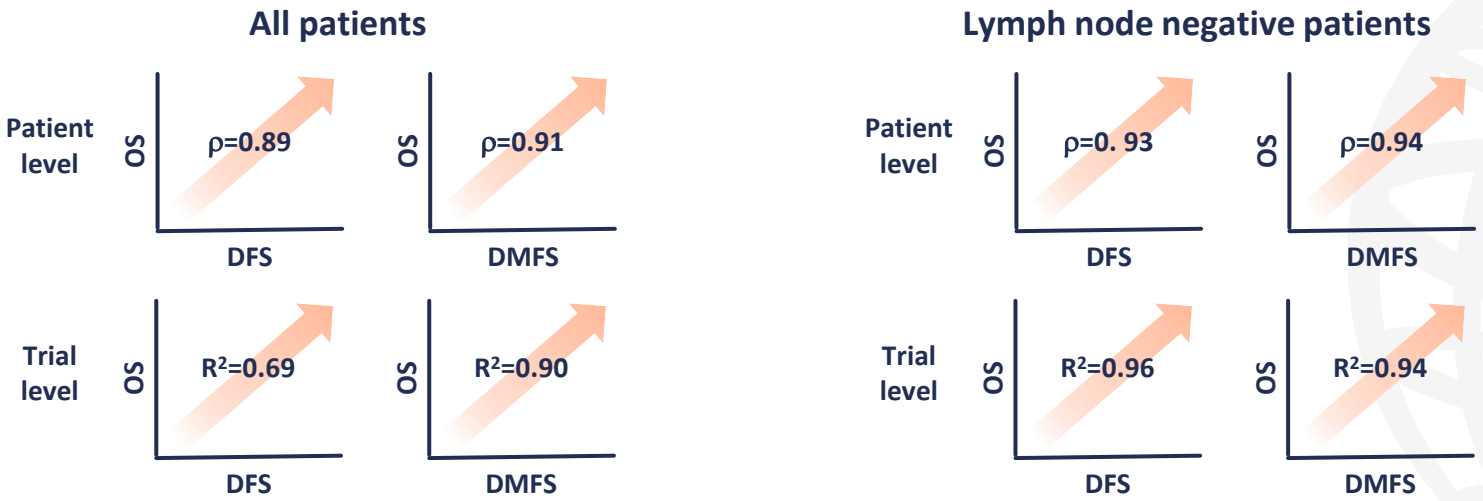
DFS and DMFS as surrogate markers for OS

Sternberg C, et al.

Estimated correlation measures*



DFS and DMFS are potentially surrogates for OS for patients with MIBC treated with adjuvant cisplatin-based chemotherapy

*Strength of patient-level associations between DFS/DMFS and OS was measured by Spearman's (ρ) rank correlation. Strength of trial-level associations between treatment effects on the surrogates and OS was measured by coefficient of determination (R^2)

DFS, disease-free survival; DMFS, distant metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival.

Sternberg C, et al. Presented at: ESMO 2022, Paris, France. 9–12 September 2022. Abstr 1746P.

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Conclusions

- PD-L1 high expression in patients who started first-line therapy for laUC or mUC in the real-world community setting is consistent with clinical trial data
- PD-L1 expression on dendritic cells assessed with the SP142 IHC assay is associated with OS and has both prognostic and predictive value
- An exploratory sub-analysis of the JAVELIN Bladder 100 trial investigating genomic biomarkers in the peripheral blood of patients indicates that specific chromatin conformation signatures are associated with the ability to form tertiary lymphoid structures and may influence response to avelumab treatment
- In a two-level metanalytic study of nine clinical trials, DFS and DMFS were found to be potential surrogates for OS for patients with MIBC treated with adjuvant cisplatin-based chemotherapy

DFS, disease-free survival; DMFS, distant metastasis-free survival; IHC, immunohistochemistry; laUC, locally advanced urothelial carcinoma; MIBC, muscle invasive bladder carcinoma; mUC, metastatic urothelial carcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

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