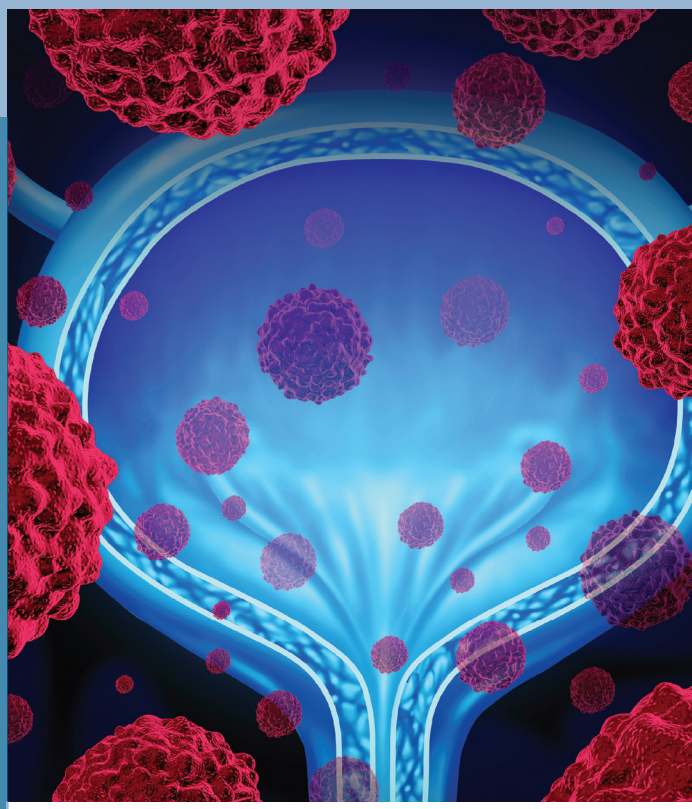
From Sledgehammer to Selective: Transforming Cytotoxic Potency Through Targeted Treatments for Advanced or Metastatic Urothelial Cancer



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INTEGRITY CONTINUING EDUCATION

From Sledgehammer to Selective: Transforming Cytotoxic Potency Through Targeted Treatments for Advanced or Metastatic Urothelial Cancer

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INTRODUCTION

This monograph recounts recent successes and failures, hope and investment, in the decades-long medical crusade against advanced and metastatic urothelial cancer (mUC). Advances in first- and second-line approaches are selectively captured, and the role played by immunotherapy and targeted treatments is explored.

Fortunately, >80% of the almost 82,000 cases of urothelial cancer (UC) that occur in the United States each year are diagnosed at early or localized stages, when it is highly curable.[1] But approximately 12% of cases are detected at regionally advanced or metastatic stages. These patients typically have poor outcomes with low 5-year survival rates.

In recent years, however, survival rates have been gradually climbing as newer targeted agents work in tandem with systemic chemotherapy.

Novel Therapies After a Long Treatment Drought

A 30-year-long drought of new treatment options for advanced and mUC ended in 2017. The following years saw the floodgates open to release a torrent of agents that work on an immunotherapeutic or molecularly targeted basis. This has transformed the sledgehammer-like cytotoxic approach of chemotherapy in years past to a more controlled therapeutic intervention that emphasizes quality of life as well as disease and symptom regulation. New treatments have now been approved by the Food and Drug Administration (FDA) for first-line, second-line, and maintenance indications.

Updated results from pivotal clinical trials of new treatments for advanced and mUC (**Tables 1 and 2**) were released during the 2019 and 2020 meetings of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO).

TABLE 1

Phase 3 Trials of ICIs Being Studied for First-Line or Maintenance Treatment

Agent(s)	Target	Trial Name/ID	Description	# Pts.
Atezolizumab	PD-L1	IMvigor130 NCT02807636	Atezolizumab as monotherapy or in combination w/ chemotherapy	1,213
Avelumab	PD-L1	JAVELIN Bladder 100 NCT02603432	Avelumab as switch maintenance	700
Durvalumab Tremelimumab	PD-L1 CTLA-4	DANUBE NCT02516241	Durvalumab +/- tremelimumab vs SOC chemotherapy	1,032
Pembrolizumab	PD-1	KEYNOTE-361 NCT02853305	Long-term follow-up of first-line pembrolizumab	1,010

CTLA-4, cytotoxic T-lymphocyte antigen 4; ICIs, immune checkpoint inhibitors; PD-1, programmed death cell protein 1; PD-L1, programmed death cell protein ligand 1; SOC, standard of care.

TABLE 2

Phase 2 Trials of Targeted Treatments Being Studied for Second-Line Therapy

Agent	Target	Trial Name/ID	Description	# Pts.
Enfortumab vedotin	Nectin-4	EV-201 NCT03219333	Enfortumab vedotin in patients who previously received ICIs	125
Erdafitinib	FGFR2/3	BCL2001 NCT02365597	Erdafitinib in patients with prior chemotherapy & ICI who have FGFR genomic alterations	99

FGFR2/3, fibroblast growth factor receptor 2 and 3.

1st-Line Treatment: Chemotherapy

Chemotherapies, particularly platinum-based treatments with cisplatin or carboplatin, are an important part of mUC treatment in the first-line setting. Cisplatin-based chemotherapy remains the initial combination of choice. In a recently published study of long-term survival with chemotherapy in advanced or mUC in the real-world setting, cisplatin was found to yield a 31.5% probability of 3-year survival.[2] Unfortunately, approximately half of patients with advanced or mUC are ineligible for cisplatin-based treatment.[3]

Cisplatin ineligibility occurs for a wide variety of reasons in this typically older patient population for which the median age at diagnosis is 73.[1] Because of cisplatin's potential for neuro-, nephro-, and ototoxicity, consensus criteria to determine cisplatin ineligibility is largely based on the presence of certain comorbidities as well as poor performance status (**Table 3**).[4]

With so many patients unable to take cisplatin, treatment alternatives are needed, but there is no agreed-upon first-line SOC aside from cisplatin. First-line combinations of carboplatin plus gemcitabine or other chemotherapeutic options generally yield lower response rates and inferior overall survival (OS) rates compared with cisplatin.[3]

TABLE 3

Definition of Cisplatin Ineligibility

Presence of ≥1 of the following:
• ECOG or WHO PS of 2 (or Karnofsky PS of 60%–70%)
• Creatinine clearance <60 mL/min
• CTCAE v4 Grade ≥2 audiometric hearing loss
• CTCAE v4 Grade ≥2 peripheral neuropathy
• NYHA Class III heart failure

CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status; WHO, World Health Organization.[4]

1st-Line Treatment: Immunotherapies

Nonchemotherapeutic agents are often used as first-line treatment for cisplatin-ineligible patients. In a 2019 survey of 301 US-based oncologists, only 19% said they usually use carboplatin-based chemotherapy for such patients while 75% indicated they preferred to use ICIs.[5]

MOA

The revolutionary mechanism of action (MOA) of ICIs show that these drugs work by inhibiting PD-1/PD-L1 or CTLA-4. These are the three most extensively researched regulatory checkpoints that control immune system activity. By expressing PD-L1, cancer cells often use these checkpoints to their advantage to evade adaptive immune system cells that could otherwise destroy them. By blocking the immune suppression activity of these checkpoints, lethal T-cells, natural killer cells, and other cytotoxic lymphocytes are released to detect, neutralize, and destroy cancer cells more efficiently.[6]

While 5 of the currently available PD-1/PD-L1 inhibitors have been approved for the second-line treatment of mUC after disease progression, two—atezolizumab and pembrolizumab—were approved by the FDA in 2017 as single-agent, first-line treatments for cisplatin-ineligible patients (**Figure 1**). Approvals were granted based on findings from the single-arm, phase 2 trials IMvigor210 (atezolizumab) and KEYNOTE-052 (pembrolizumab), which showed objective response rates (ORRs) of 23.5% and 28.6%, respectively.[7] However, in 2018, the FDA limited the use of these drugs in the first-line setting by requiring that cisplatin-ineligible patients must have tumors that demonstrate certain levels of PD-L1 tumor expression.[8]

Figure 1

Agent(s)	Target	Schedule	Approved in 2nd Line? (Post-Platinum)	Approved in 1st Line? (Cisplatin Ineligible)
Atezolizumab	PD-L1	Q3W	Yes, in 2016	Yes, in 2017
Avelumab	PD-L1	Q2W	Yes, in 2017	No
Durvalumab	PD-L1	Q2W	Yes, in 2017	No
Nivolumab	PD-1	Q4W	Yes, in 2017	No
Pembrolizumab	PD-1	Q3W	Yes, in 2017	Yes, in 2017

June 2018: Use of atezo and pembro restricted to PD-L1 positive patients only

Figure 1. ICIs approved for advanced or mUC indication. Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

First-line indication labeling for PD-L1 expression requirements for patients unable to receive cisplatin was changed accordingly:

- Atezolizumab[9]
  - PD-L1 with stained tumor infiltrating immune cells that cover ≥5% of the tumor area
- Pembrolizumab[10]
  - PD-L1 ≥ 10 with Combined Positive Score

Atezolizumab and Pembrolizumab

Both atezolizumab and pembrolizumab are now being evaluated more robustly for first-line use in the phase 3 IMvigor130 and KEYNOTE-361 clinical trials, respectively.[11,12]

These trials, which carry dual primary endpoints of OS and progression-free survival, have a similar study design with 3 trial arms[13,14]:

1. PD-1/PD-L1 + chemotherapy (cisplatin OR carboplatin + gemcitabine)
2. PD-1/PD-L1 as monotherapy
3. Chemotherapy alone (investigator's choice of cisplatin OR carboplatin + gemcitabine)

Preliminary analysis results with ORRs can be seen in **Table 4**. Both immunotherapies showed some improved response in the trial arms that combined the ICI with chemotherapy (55% for pembrolizumab in KEYNOTE-361[13] and 47% for atezolizumab in IMvigor130[14]). Data across both trials showed less response in trial arms with PD-1/PD-L1 used as monotherapy and with chemotherapy alone. This appears to suggest a synergistic but slight response when PD-1/PD-L1 inhibitors are added to chemotherapy.[13,14]

TABLE 4

Response Rates Across Trial Arms in IMvigor130 and KEYNOTE-361

Trial	ICI + Chemotherapy	ICI Alone	Chemotherapy Alone
IMvigor130 (pembrolizumab, PD-1)	47%	23%	44%
KEYNOTE-361* (atezolizumab, PD-L1)	55%	30%	45%

*Figures are rounded.[13,14]

Unfortunately, neither study showed a benefit in OS in any of the trial arms. It is also interesting that neither the IMvigor130 nor the KEYNOTE-361 trials have thus far showed an improvement in OS for patients with high tumor expression of PD-L1.[13,14] This may have implications going forward for the 2018 FDA mandate to use these immunotherapies only for cisplatin ineligible patients with PD-L1 expression. But currently, chemotherapy in combination with immunotherapy is not recommended in UC.

Durvalumab

Another trial that was summarized at ESMO 2020 was the phase 3 DANUBE trial, which compared the PD-L1 inhibitor durvalumab alone or in combination with the CTLA-4 inhibitor tremelimumab (thus far not approved for any indication) vs SOC chemotherapy.[15] This trial was considered a "negative" study in that it did not meet its primary endpoint of OS. Surprisingly, patients whose tumors have high expression of PD-L1—who were expected to have a better response, particularly to the PD-L1 + CTLA-4 trial arm—did not show any significant improvement with durvalumab vs chemotherapy alone.[15]

Maintenance Therapy

With the ICIs, the biggest breakthrough news of 2020 was the approval of avelumab as maintenance therapy after response to first-line SOC chemotherapy. In June, the FDA granted accelerated approval to avelumab for this indication based on the strength of interim analysis findings from the phase 3 JAVELIN Bladder 100 trial that was presented at 2020 ASCO Virtual Scientific Program.[16-18] This marks the first approval of a maintenance treatment for this form of cancer.

Of the 700 patients involved in this trial, 72% had a complete or partial response to platinum-based chemotherapy while the remainder showed stable disease.[17] Patients were randomized to avelumab plus best supportive care (BSC) or BSC alone (**Figure 2**).

Figure 2

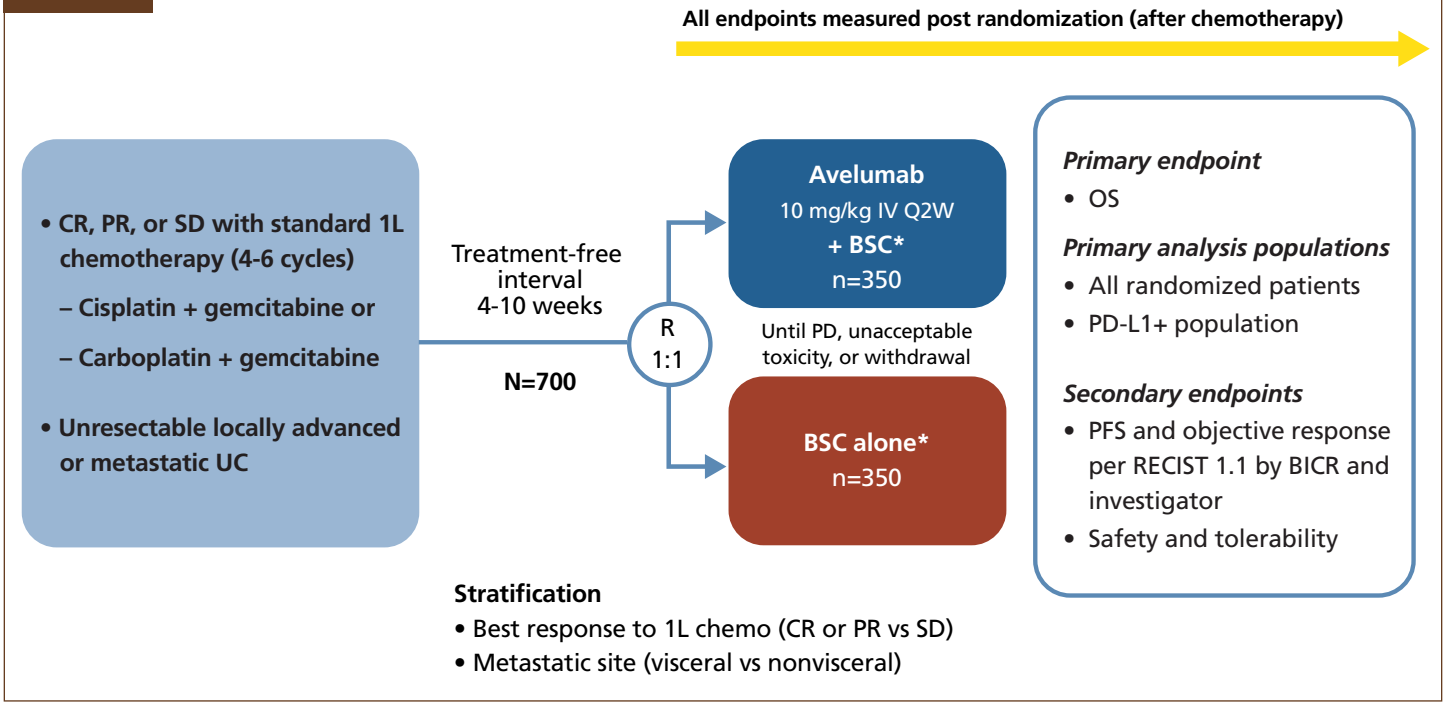

Figure 2. Study design for JAVELIN Bladder 100. 1L, first-line; BICR, blinded independent central review; CR, complete response; IV, intravenous; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 3 shows OS curves in the entire patient population, which includes the 50% of patients whose tumors expressed PD-L1. At year 1, OS was 71.3% for patients in the avelumab + BSC cohort vs 58.4% in the cohort receiving only BSC. Median OS was 21.4 months for avelumab vs 14.3 months for BSC.[17] The JAVELIN Bladder 100 trial showed the longest OS ever documented for any line of therapy in a phase 3 trial of mUC and showed that avelumab is clearly superior to BSC alone.

Adverse events (AEs) were observed in 98% of patients in the avelumab + BSC cohort compared with 77.7% in the control group. Grade ≥3 AEs were experienced by 47.4% of patients in the investigative trial arm vs 25.2% of those randomized to BSC alone.[17]

Based on these findings, switch maintenance therapy with avelumab for patients who show a response to platinum-based chemotherapy is likely to become the new SOC.

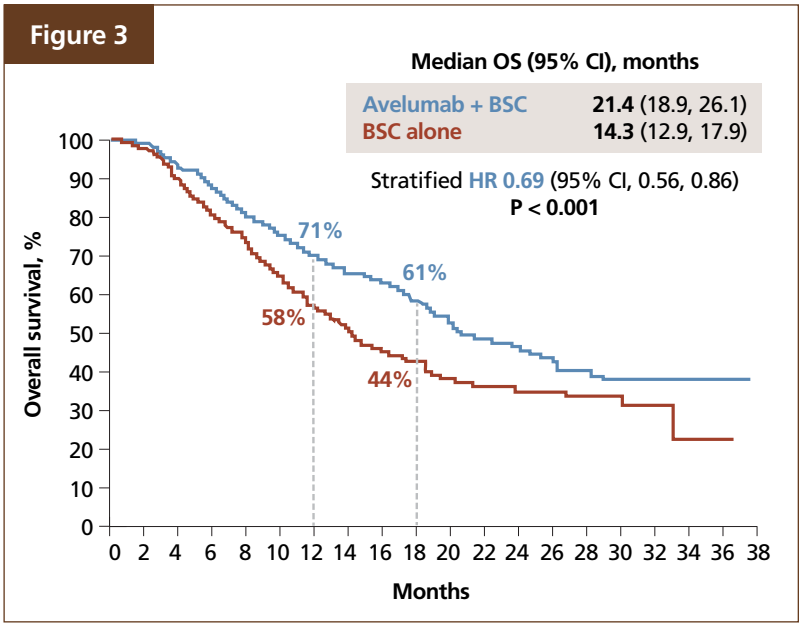

Figure 3. Overall survival in entire JAVELIN Bladder 100 trial population.[17]

2nd-Line Treatment: Novel Targets

The approvals in 2019 of two highly selective, targeted agents gave patients and their clinicians new hope in the form of second-line treatments. Enfortumab vedotin and erdafitinib are both first-in-class therapies approved based on findings from phase 2 clinical trials.[19,20]

MOAs

With unique MOAs and highly selective targets,[21,22] enfortumab vedotin and erdafitinib were approved in 2019 for patients with advanced or mUC who had previously been treated with platinum-based chemotherapy ***and*** PD-1/PD-L1 inhibitors.[23,24]

- Enfortumab vedotin[23]
  - Class: monoclonal antibody (mAb), antibody-drug conjugate (ADC)
  - Delivery: intravenous
  - MOA: targets nectin-4, an adhesion protein highly expressed in UC
- Erdafitinib[24]
  - Class: FGFR antagonist
  - Delivery: oral, tablets
  - Target: FGFR2 or FGFR3 genetic alterations

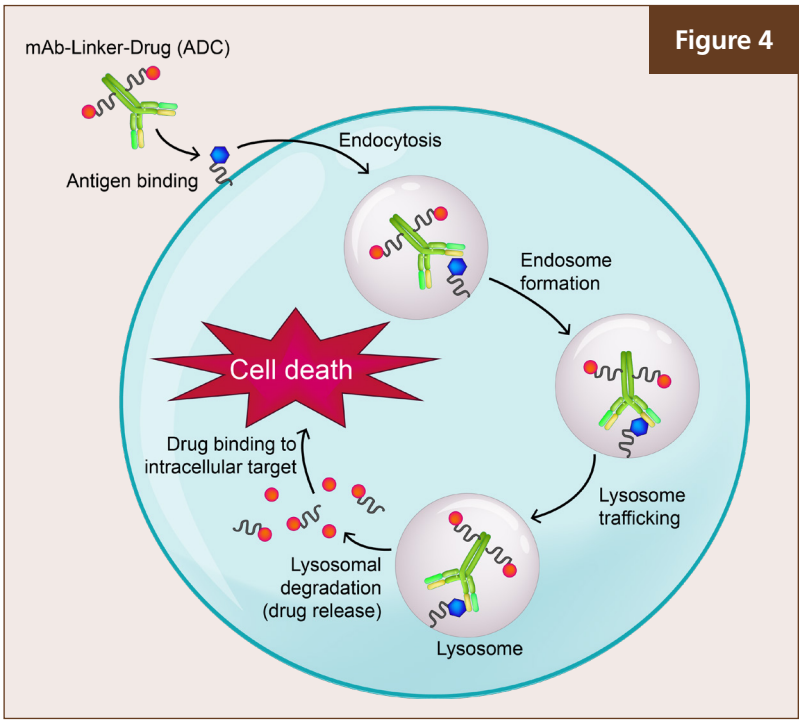

Figure 4. MOA of the antibody-drug conjugates (ADC) enfortumab vedotin.[25]

Enfortumab Vedotin

Approved based on findings from the EV-201 trial, enfortumab vedotin is a fully immunized mAb that uses a protease cleavable linker to conjugate with the microtubule-disrupting agent monomethyl auristatin E (MMAE) (**Figure 4**).[25] MMAE targets nectin-4, which is ubiquitously expressed by mUC tumor cells.[20]

Long-term efficacy results from the phase 2 EV-201 trial of 125 patients were presented at ESMO 2020, reporting an ORR of 44%. OS rates after 12 and 18 months can be seen in the survival curve in **Figure 5**. Median duration of response (DOR) was 4.6 months with maximum DOR of 27.3 months and ongoing at the time of data cutoff.[19]

The most common treatment-related adverse events (TRAEs) in the long-term EV-201 follow-up report were rash (51.2%), peripheral neuropathy (50.4%), alopecia (49.6%), fatigue (49.6%), and decreased appetite (44%).[19] Hyperglycemia, dry eye, reduced hemoglobin, and lowered phosphate levels were also noted in the original presentation of EV-201 data.[20] These can be managed by dose reduction as outlined in the package insert.[23]

Careful consideration must be given to effective management of baseline comorbidities such as diabetes mellitus, because neuropathies resulting from it (or from prior mUC treatments), can increase the potential for this side effect with enfortumab vedotin. Performing weekly complete blood counts and blood chemistries can improve early recognition and amelioration of enfortumab vedotin TRAEs. Infusion nurses also need to be taught to do careful, detailed investigation of the following TRAEs to determine if they are severe enough to require dose reduction or dose withholding:

- Rash
- Skin infections
- Neuropathies

Erdafitinib

An oral tyrosine kinase inhibitor (TKI), erdafitinib targets FGFR2/3 alterations, which affect 15%–20% of patients with mUC. This TKI was shown in the phase 2 BCL2001 trial to yield a 40% response rate in FGFR-positive patients who had ≥1 previous course(s) of treatment. **Figure 6** shows results in the primary endpoints of OS and progression-free survival.[26]

Longer-term follow-up information reported at ASCO 2020 confirmed the earlier-reported BCL2001 ORR of 40% and showed that 31% of patients had a DOR of ≥1 year with the median DOR being 5.98 months.[27]

Figure 5

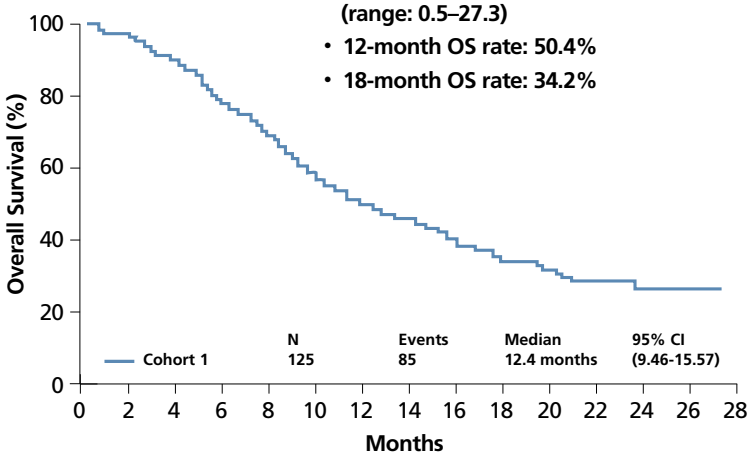

Figure 5. OS curve for enfortumab vedotin.[19]

Figure 6

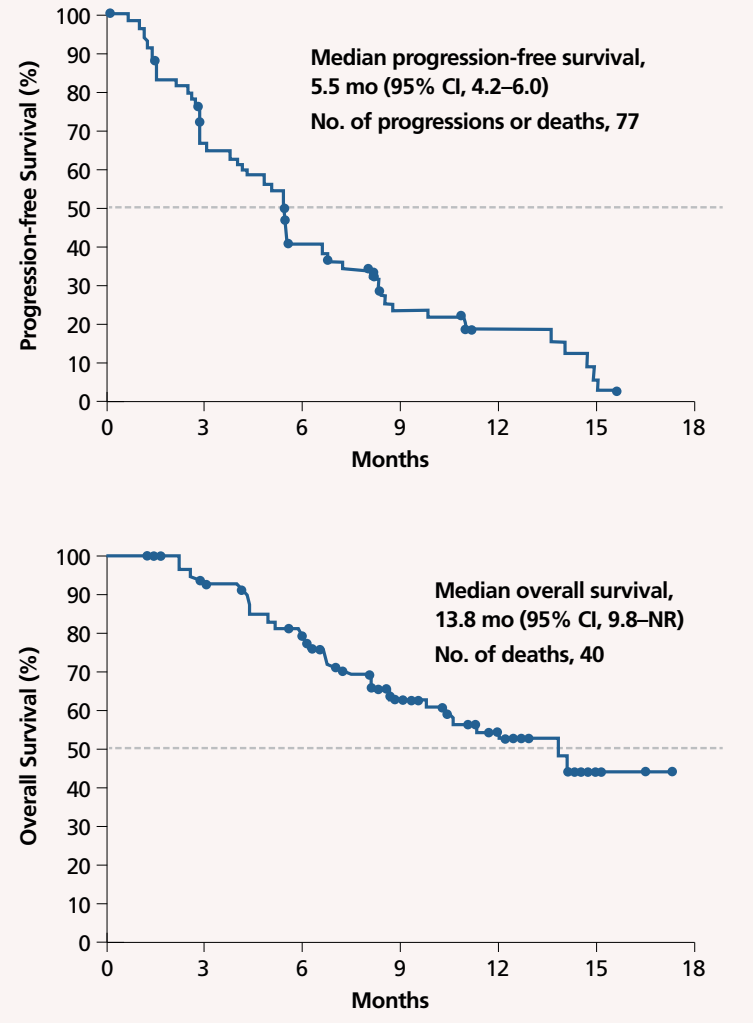

Figure 6. OS and PFS Kaplan-Meier curves for erdafitinib.[26]

AEs that are common to this TKI include stomatitis, dry mouth, diarrhea, fatigue, and nail/skin changes. This drug can also increase phosphate levels and ocular disorders. The most noteworthy TRAE, which occurred in 27% of patients in the BCL2001 trial, was central serous retinopathy.[27] Because of this, monthly eye examinations are recommended for the first 4 months and every 3 months thereafter.

AEs caused by erdafitinib can be managed by a series of 4 or 5 dosage reductions (depending on starting dose) as outlined in the package insert[24] and by these supportive measures:

- Medicated or saliva-stimulating mouthwashes for stomatitis/dry mouth
- Emollients for nail and skin changes
- Antidiarrheal agents
- Artificial tears and lubricants for dry eye

Managing irAEs

Adverse events caused by PD-1/PD-L1 inhibitors are unlike those clinicians who treat advanced or mUC have been used to encountering with platinum-based chemotherapy. The same can be said for UC patients who had been treated only with chemotherapy prior to starting ICI therapy. For this reason, clinicians and patients alike must be carefully educated about the difference in potential AEs.

Because the ICIs achieve their oncocidal efficacy through amplification of the immune system, healthy tissues can be negatively affected by immune system dysregulation. This can result in toxicities associated with checkpoint blockade that alter recognition of self cells. Known as immune-related adverse events (irAEs), these toxicities can closely resemble autoimmune disease and can affect any organ system (**Figure 7**).[28]

Most irAEs appear within the first 32 weeks after initiating treatment—usually within 16 weeks—but it's important to note that they can occur at ***any*** time, including just days after starting treatment or even within months after stopping treatment. It's also important to know that irAEs can:

- Vary widely in incidence and severity
- Affect one organ or many
- Occur simultaneously or sequentially
- **Be life-threatening!**

The principles for diagnosing and managing irAEs depends on patient education and awareness as well as a multidisciplinary approach.

- Primary care providers are typically the "first responders" to irAEs, but specialists are often needed to diagnose and manage site-specific toxicities
- When an irAE is suspected, first rule out other causes, but do not delay potentially life-saving immunosuppressive treatment while tests are being processed

Red flags for patients and clinicians to watch for:

- Any new signs or symptoms
  - Most important: cough, diarrhea, rash, extreme fatigue, headache, chest pain
- New-onset signs or symptoms that impact daily living
- Sudden changes in lab values, particularly:
  - Creatinine >1.5x over baseline
  - Liver function tests >3x upper limit of normal
  - Glucose >200 mg/dL

Figure 7

Dermatologic
- Rash
- Vitiligo

Digestive
- Dry mouth
- Enterocolitis

Endocrine
- Adrenal insufficiency
- Autoimmune diabetes
- Hypothyroidism
- Hypophysitis

Liver
- Hepatitis

Lung
- Pneumonitis

Musculoskeletal
- Arthralgia

Ophthalmic
- Orbital inflammation
- Uveitis

Pancreatic
- Pancreatitis

Managing strategies for irAEs largely depends on grade, with corticosteroids or other interventions being required for Grade ≥3 (**Table 5**).

TABLE 5

Management/Interventions for irAEs by Grade

Grade	Interventions	Notations
1	• Continue ICI but monitor & manage supportively	• Consider holding ICI for cardiac, neurologic, ocular, or respiratory symptoms
2	• Hold ICI, treat supportively & restart when Grade ≤1 • Consider steroids 0.5–1.0 mg/kg	• Don't hold ICI for hypothyroid/hyperthyroid; instead, treat w/ replacement hormones
3	• Hold ICI and start steroids 1–2 mg/kg	• Consider in-patient admission • Taper over 4–6 weeks after symptoms improve
3–4	• IV steroids if irAE is severe or if there are worries about absorption	• Taper over 4–8 weeks after symptoms improve • Add secondary drug if no improvement in 48–72 hours
4	• In-patient hospitalization • Permanently discontinue ICI	• Don't discontinue ICI if only irAE is hypothyroid/hyperthyroid; instead treat with replacement hormones
Progressive/Refractory irAEs		
Anti-TNFα (eg, infliximab)	• Check TB and HBV status before starting due to risk for reactivation; however, don't wait in life-threatening cases • Dose at 5 mg/kg and repeat 2 weeks later • Do NOT use in immune hepatitis; instead consider MMF or α4β7 integrin inhibitor (eg, vedolizumab)	
Other agents, depending on organ system	• ATG, IVIG, azathioprine, cyclosporine, MTX, plasmapheresis, other DMARDs	

α4β7, alpha4, beta7; ATG, anti-thymocyte globulin; DMARDs, disease-modifying antirheumatic drugs; HBV, hepatitis B virus; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; TB, tuberculosis; TNFα, tumor necrosis alpha.

SUMMARY

In first-line treatment of advanced or metastatic mUC, chemotherapy with cisplatin is still regarded as the most effective treatment choice. However, in the ~50% of patients who are ineligible for cisplatin, treatment with atezolizumab or pembrolizumab is approved for first-line treatment. Interim analyses of the phase 3 IMvigor130 and KEYNOTE-361 trials showed best ORR when these ICIs were combined with chemotherapy, although no benefit has thus far been shown in OS. For patients who do respond to SOC chemotherapy, maintenance therapy with avelumab was shown by the phase 3 JAVELIN Bladder 100 trial to extend OS over BSC alone. For patients whose disease has progressed, two new agents—enfortumab vedotin (an infusional ADC) and erdafitinib (an oral TKI targeting FGFR2/3) can extend OS.

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