Management of Advanced Urothelial Carcinoma in Older and Frail Patients: Have Novel Treatment Approaches improved their Care?

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Abstract

Patients with urothelial carcinoma (UC) tend to be older and frailer with a large number of chronic medical conditions. This is particularly pronounced in those with locally advanced or metastatic UC. Prior to 2016, treatment options in advanced urothelial carcinoma (aUC) were limited to chemotherapy, and as a result, a large number of patients were not receiving disease-directed therapy. Over the last six years, multiple alternative modalities including immune checkpoint inhibitors, enfortumab vedotin, sacituzumab govitecan and erdafitinib have been introduced. They are being used clinically in older and frail patients, but their efficacy and safety profiles remain underexplored in these populations. Based upon available evidence, age does not appear to impact the efficacy and tolerance of immune checkpoint inhibitors if patients are fit enough to receive therapy. There is still not enough evidence to draw specific conclusions regarding the use of enfortumab vedotin, sacituzumab govitecan and erdafitinib in older and frail patients. Regardless, in all older patients with aUC, it is critical to evaluate for frailty through geriatric screening tools and comprehensive assessments. Combining these evaluations with consideration of an individual patient's goals should be the foundation upon which therapeutic decisions are made in this population of patients.

Key Points

- Age is not an independent predictor of safety or efficacy in the management of aUC, but instead, should serve as a signal to providers to assess for frailty, which can have a significant impact on outcomes.
- In older and frailer patients with advanced urothelial carcinoma, immune checkpoint inhibitors appear to be a well-tolerated treatment modality in the first and second line settings.
- At present, there is not enough data to comment definitively on the efficacy and safety of enfortumab vedotin, sacituzumab govitecan and erdafitinib in older and frail patients.

1 Introduction

Bladder cancer is a disease that primarily impacts the older population. In the US, 74.8% of newly diagnosed patients are ≥ 65-years-old [1]. The incidence of bladder cancer is actually decreasing [1]; however, as the demographics of the US change and the percent of the population over the age of 65 rises [2], bladder cancer patients will become even older and carry more chronic conditions at diagnosis [3]. Patients with bladder cancer have a median of eight comorbidities [4], and it is likely that this number will grow, particularly amongst those with locally advanced and metastatic urothelial carcinoma (also referred to as advanced urothelial carcinoma, aUC), where patients are already older and have worse performance statuses. Indeed, at least 15% of patients with aUC have an Eastern Clinical Oncology Group (ECOG) performance status (PS) ≥ 2 at diagnosis [5].

In aUC, chemotherapy—specifically platinum-based chemotherapy—remains the backbone of treatment, but the last decade has seen the development of a number of new therapeutic options including immune checkpoint inhibitors (ICIs) and targeted therapies. With an increasingly older and frailer population, the hope is that these non-chemotherapy classes of medications represent a possible panacea. Unfortunately, cancer trials, in general, tend to under-enroll older and frailer patients [6][7][8], a phenomenon which has been replicated in phase I, II and III trials studying immune-checkpoint inhibitors (ICIs) [9], enfortumab vedotin [10],

sacituzumab govitecan [11] and erdafitinib [12]. Thus, the effectiveness and side effect profiles of newer treatment options in these populations remain incompletely understood.

Here, we explore the management of bladder cancer in the elderly and in the frail, focusing on the available data from major trials and real-world assessments of ICIs, enfortumab vedotin, sacituzumab govitecan and erdafitinib in advanced and metastatic bladder cancer. We will also provide recommendations regarding an approach to treating this population.

2 Setting the Stage: The Introduction of ICIs, Enfortumab Vedotin, Sacituzumab Govitecan and Erdafitinib

Since the 1980's, cisplatin has been the primary agent in aUC. It is the foundation upon which multiple combination regimens have been developed including methotrexate, vinblastine, adriamycin and cisplatin (MVAC) as well as gemcitabine plus cisplatin (GC) [13]. Ultimately, a head-to-head phase III trial of GC versus MVAC demonstrated similar overall response rate, progression free survival (PFS) and overall survival (OS), but given less adverse effects associated with GC, it has been the preferred first-line (1L) regimen in cisplatin-eligible patients [14][15]. Prior to 2016, the preferred therapy in cisplatin-ineligible patients was carboplatin and gemcitabine. Carboplatin-based regimens are inferior to cisplatin-based regimens with worse objective and complete responses, but they are better tolerated in frailer patients [16][17]. In those deemed platinum-ineligible, non-platinum-based regimens centered on the use of gemcitabine, but even still, as much as 23.8% – 48.4% of patients were not receiving any cancer-directed treatments, likely due at least in part to their anticipated inability to tolerate chemotherapy [18].

Beginning in May 2016, multiple anti-PD-l (pembrolizumab and nivolumab) and anti-PD-L1 antibodies (atezolizumab, durvalumab, and avelumab) demonstrated benefit in the management of aUC. In the 1L setting, pembrolizumab and atezolizumab received accelerated FDA approval in 2017 for cisplatin-ineligible patients based upon the phase II trials KEYNOTE-052 and IMvigor210, respectively [19][20][21]. However, in 2018, evidence of decreased OS in patients with lower PD-L1 expression in early assessment of the phase III trials IMvigor130 and KEYNOTE-361 led to a limitation of the use of atezolizumab and pembrolizumab to cisplatin-ineligible patients with adequate PD-L1 expression or to those ineligible for any platinum-based chemotherapy regardless of PD-L1 expression [21]. Pembrolizumab has now received full FDA approval, but its use has been further limited to only platinum-ineligible patients regardless of PD-L1 status [22]. Also in the 1L setting, results from the phase III JAVELIN Bladder 100 trial led to approval of avelumab maintenance therapy in patients who do not progress on a platinum-containing regimen [23]. In the at least second line setting (2+L), pembrolizumab, nivolumab, and avelumab are approved in patients with previously treated aUC who have progressed on therapy [24][25][26]. Although atezolizumab and durvalumab were also previously approved in the 2+L setting, these were voluntarily withdrawn in early 2021 based upon results from IMvigor211 and DANUBE, respectively [27].

In addition to ICIs, two antibody-drug conjugates (ADC) have been approved in the management of progressed aUC. Enfortumab vedotin (EV) combines a monoclonal antibody against nectin-4 with monomethyl auristatin E, a microtubule inhibitor [28]. Sacituzumab govitecan is an ADC, which combines an antibody targeting trophoblast cell-surface antigen 2 with SN-38, a metabolite in irinotecan, a topoisomerase inhibitor [11]. EV and sacituzumab govitecan have shown benefit in patients who have progressed on both platinum-based chemotherapy and ICIs, and EV has also been approved in those cisplatin-ineligible patients who

progressed on ICIs or chemotherapy alone [10][29]. For patients with specific FGFR mutations who have progressed on platinum-based chemotherapy, erdafitinib, a tyrosine-kinase inhibitor that targets FGFR1-4, can be considered [12].

3 Defining the Relevant Populations

3.1 Old versus Frail

Before assessing how these non-chemotherapy treatments have impacted the management of older and frailer patients with aUC, we must define and distinguish the old from the frail. Although age is a major risk factor for comorbidity, fragility and mortality at the population level [30][31], this correlation is not as clear on the individual patient level [32]. There is a distinction that can and should be made between chronologic age and functional age because not all older patients are frail and not all frail patients are old [33]. Despite the key differentiation, the old and the frail are relevant because they increasingly reflect the bladder cancer population at large, and yet are excluded from trials, and in the clinical setting, have been shown to receive less disease-directed therapy [34].

Chronologically, old age has historically been identified as ≥ 65-years-old [35]; however, as life expectancy for each successive generation continues to rise, our understanding of who constitutes the elderly has also evolved. As a reflection of this changing landscape, oncologic societies differ as to when providers should begin to screen for age-associated changes more comprehensively. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) recommend a geriatric assessment beginning at age 65 [36][37]. In contrast, the International Society of Geriatric Oncology (SIOG) in 2005 initially recommended starting at age 70, but more recent guidelines from 2014 did not identify a specific age. Instead, they acknowledged that this is an area of controversary, which needs further investigation [38][39].

Characterizing frailty is even more challenging. In fact, there is no clear consensus definition, but generally, frailty refers to a deterioration in functioning and reserve, which places patients at increased risk of adverse outcomes, especially in the setting of metabolic stress [40]. Frailty can derive from changes in physical domains—nutrition, mobility, physical activity, strength and energy level—as well as psychologic [41]. The effect is cumulative; a larger number of domains impacted results in a greater change in function.

The potential influence of frailty on treatment tolerance and outcomes in cancer patients is well-recognized [42]; however, its complexity makes it difficult to quantify when investigating interventions in these populations. As a result, clinical trials and real-world studies will often use proxy measures such as performance status, which is contributing factor of many to the frailty syndrome. In cancer care, the ECOG performance status assessment is commonly utilized. It originated in 1982 and grades patients on a simple scale of 0-5 with lower numbers corresponding to better functional status [43]. The benefit of ECOG is that this is a straight-forward scoring system, which can identify and communicate risk. Although it has been shown to have some prognostic and predictive value—including response to therapy and tolerance [44][45]—its ability to predict efficacy or toxicity is limited [46][47]. Furthermore, the subjective nature of this scoring system results in variability amongst providers. This is most pronounced surrounding ECOG PS 2, a critical cut-off point when making treatment decisions in patients with bladder cancer [48].

Despite the evident limitations, we will also rely upon ECOG PS to investigate the safety and efficacy of newer treatment regimens in frail patients for the purposes of this paper given that this is what is utilized in trials. However, as we make recommendations for clinical care on the individual patient level, we advise evaluating for frailty in a more comprehensive manner. Typically, that is best done through the use of a geriatric assessment [33].

3.1.1 Geriatric Assessments

Geriatric assessments (GAs) refer to an appraisal of age-specific risk factors and geriatric syndromes, which may not be immediately evident on a typical history and physical or performance status assessment [36][49]. There is robust literature demonstrating the importance of systematically identifying frail and at-risk patients in order to optimize their oncologic care. In patients receiving chemotherapy, GAs predict treatment-related toxicity [47][52][53][54], functional decline [53][55], and mortality [52][53][54]. Furthermore, interventions—including dose modifications and geriatrician involvement—based upon results of GAs can reduce adverse effects [56][57].

Given these benefits, multiple oncologic societies, including NCCN, ASCO and SIOG, promote the use of some form of a geriatric assessment in order to help guide management in the older population. In aUC, there are surprisingly no studies specifically investigating the impact of GAs, but it can be extrapolated from other evaluations of patients receiving chemotherapy that those with aUC would also benefit [53][52].

The gold standard, the comprehensive geriatric assessment (CGA), utilizes a combination of tools to investigate functional status, cognitive ability, comorbid conditions, pharmacologic burden, psychosocial risk factors, and nutritional status [56]. While it would be ideal to perform CGAs on all patients, this is not typical in busy clinical practices given time and staffing constraints [58]. Furthermore, the CGA is not standardized and there is no clear consensus on how best to implement and apply findings [59].

Given these limitations, in line with the NCCN and SIOG, it makes sense to start with geriatric screening tools in order to identify patients who would benefit most from more comprehensive evaluation [37][60][61]. There is no consensus on the ideal geriatric screening tool, but table 1 highlights some commonly used in clinical practice. Providers can select their preferred instrument, but we advise the use of the Geriatric-8, a simple eight question assessment that takes under five minutes to perform [62][61][33][63]. It was adopted from the Mini Nutritional Assessment (MNA) and includes a rapid evaluation of multiple domains captured in a CGA including mobility, functional status, psychological risk factors, and pharmacologic burden [63]. The potential score ranges from 0-17. Patients scoring ≥14 points are more likely to be fit and no further assessment is necessary for most. Those who score <14 are more likely to be vulnerable or frail, and thus comprehensive geriatric assessments should be performed [33][63]. Although it hasn't been studied specifically in aUC, it was developed for patients with cancer, has been shown to have a sensitivity of 65-92% when compared to the CGA, and has been successfully implemented in busy oncologic clinical practices [63][62][64]. Furthermore, a SIOG position paper on the management of patients with UC recommended its use in combination with a cognitive evaluation [65].

3.2 Cisplatin and Platinum Eligibility

In addition to the use of geriatric assessments, important branch points in the management of patients with aUC are the determination of cisplatin and platinum eligibility.

Galsky et al defined cisplatin ineligibility as patients with ECOG PS ≥ 2, creatinine clearance (CrCl) <60mL/min, advanced heart failure, and significant hearing loss or neuropathy [66]. While the Galsky criteria has become the gold standard mainly for clinical trials, the strict use of a CrCl <60mL/min is controversial. First, in Galsky's initial survey, 59% of respondents recommended using a less stringent cutoff including 34% in favor of <50mL/min and 19% in favor of <45mL/min [66]. In the older population, this is made more controversial by the fact that the formulas used to calculate CrCl were derived from a younger cohort, and they have been shown to underestimate the true glomerular filtration rate in older patients, potentially unnecessarily excluding patients [67][68]. While Galsky criteria will continue to be utilized, the use of ECOG—and its limitations as noted above—as well as the strict use of a CrCl < 60mL/min should be examined closely in older patients and additional research should be directed towards this.

As novel treatment regimens have emerged, the need to define platinum-eligibility has also arisen. Based upon responses from forty-three genitourinary oncologists, Gupta et al have more recently proposed that platinum-ineligible broadly be defined as ECOG PS ≥ 3, CrCl < 30 mL/min, significant heart failure, significant peripheral neuropathy and ECOG PS 2 with CrCl < 30 mL/min [69]. This criteria has similar limitations as Galsky's, but as will be shown, is useful when making treatment recommendations in these populations.

4 Advanced Urothelial Cancer Management in the Elderly and the Frail: Treatment prior to 2016

With this background, it is important to review prescribing patterns in older and frailer patients prior to 2016. When chemotherapy was the only available treatment option for aUC, a high percentage of older and frailer patients were not receiving 1L or standard of care treatment. One study showed that only 42% of patients ≥ 65-years-old were given 1L chemotherapy [70]. This was replicated in a retrospective analysis of patients with aUC and a median age of 70 which revealed that only 35.9% received cisplatin-based chemotherapy and 23.8% received no chemotherapy [71]. Ultimately, the reasons why patients do not receive treatment are multifactorial and complex, due to a combination of patients' wishes as well as individual oncologists' concerns regarding a given patient's ability to tolerate systemic therapy [72]. However, age clearly has been shown to influence management in older adults despite evidence that cisplatin-based regimens are efficacious and safe in properly selected patients [73].

Appropriately, frailty has an even larger impact on the decision to give chemotherapy. Patients with an ECOG PS ≥ 2 are considered unfit for cisplatin-based chemotherapy. This contributes to the estimated 30-50% of patients with aUC who are deemed cisplatin-ineligible [74]. Given the limited options in older and frailer patients, there was hope that the newest line of medications would improve available therapies for these patients.

5 Treatment of aUC after 2016: Are New Therapies Efficacious and Safe in the Elderly and the Frail?

5.1 ICIs in Older Patients

5.1.1 Overview

Immune checkpoint inhibitors interface with the immune system in order to enact their effect. Thus, the normal physiologic changes that occur with aging are important to consider in

an assessment of efficacy and safety. Immunosenescence is a general term used to capture the alterations in the immune system that develop as individuals age regardless of their comorbidity burden or functional decline [75]. It has been postulated that response to therapy may be impacted by changes in the immune system and in the tumor microenvironment, both of which can occur with aging [76].

Despite these hypotheses, clinical assessments of ICI use in other cancers have demonstrated that they are efficacious and safe regardless of age. In a retrospective analysis of 290 patients with non-small cell lung cancer (NSCLC) who were primarily treated with anti-PD-1 or anti-PD-L1 antibodies, efficacy was assessed in three cohorts of patients: <70 years old (62%), 70-79 years old (32%) and ≥80-years-old (9%). Objective response rate (ORR) was similar between all cohorts (21.5% vs. 22.3% vs. 18.8%, p = 0.95) as was OS (9.1 months vs. 11.3 months vs. 9.6 months, p = 0.52). In this same population, adverse events graded ≥2 were similar across all study groups (35.8% vs. 32.7% vs. 37.5%, p = 0.65) [77]. Comparable results were also seen in a meta-analysis of forty-eight real-world studies investigating ICIs in multiple cancer types, including one study in patients with urothelial carcinoma, where age did not act as a prognostic factor in overall survival (HR 1.04, 95% CI 0.95-1.15). Additionally, rates of adverse outcomes were acceptable [78].

5.1.2 Review of Clinical Trials: Efficacy and Safety

The trials which led to the approval of multiple ICIs in aUC appear to confirm results seen in other cancers: single agent ICIs, specifically anti-PD-1 and anti-PD-L1 antibodies, have comparable efficacy, regardless of age. In cohort 1 of IMvigor210, the phase II trial assessing atezolizumab in the 1L setting for cisplatin-ineligible patients, the average age of participants was 73 and 21% of patients were ≥80-years-old. In patients ≥80-years-old, ORR was 28% (95% CI 12-49) and OS was 14.8 months (95% CI 5.4-not estimable). The entire cohort, regardless of age, had an ORR of 23% (95% CI 16-31) and OS of 15.9 months (95% CI 10.4-not estimable) [19]. Also in the 1L setting, KEYNOTE-052, the phase II trial which studied pembrolizumab for cisplatin-ineligible patients with tumors expressing PD-L1, enrolled patients with an average age in line with IMvigor210 (74-years old). 82% of patients were ≥65-years-old and 49% of patients were ≥75-years-old. ORR was 30% (95% CI 18-43) and 26% (95% CI 21-32) for patients <65-years-old and ≥65-years old, respectively [20]. In post-hoc analysis, ORRs were 27% and 28% for patients ≥75-years-old and ≥85-years-old, respectively. Importantly, older patients also demonstrated sustained response. The median duration of response was 30.1 months and 12.5 months for those ≥65-years-old and ≥75-years-old, respectively. 53% of those ≥65-years-old and 35% for those ≥75-years-old maintained response at two years [79]. Similarly, in KEYNOTE-361, the phase III, three-armed assessment of pembrolizumab with chemotherapy versus pembrolizumab and chemotherapy alone, age did not appear to impact OS significantly [80]. Also in 1L treatment, in subgroup analysis of those ≥65-years-old from JAVELIN Bladder 100, avelumab maintenance therapy showed improved PFS (HR 0.50, 95% CI 0.39-0.62) and OS (HR 0.63, 95% CI 0.47-0.83) [23].

In the 2+L setting, the impact of age has not been investigated as thoroughly, however, data supports findings from the 1L trials. In KEYNOTE-045, a phase III trial comparing pembrolizumab to chemotherapy, survival benefit was similar between those <65-years-old (HR 0.75, 95% CI 0.53-1.05) and those ≥65-years-old (HR 0.76, 95% CI 0.56-1.02), though ORR and PFS were not reported by age [24]. Pooled data from phase I studies, which led to Avelumab approval in the 2+L setting, demonstrated that patients ≥65-years-old actually had numerically

higher ORR (18%, 95% CI 11-26) compared to their younger counterparts (14%, 95% CI 6-27) although head-to-head comparison was not completed [26].

Safety data in the older population is somewhat limited in comparison to efficacy data, but overall, ICIs appear to be equally tolerated in both older and younger patients. In post-hoc analysis of KEYNOTE-052, treatment related adverse events that were grade ≥3 occurred in 22% of patients ≥65-years-old and 20% of patients ≥75-years-old [79]. This appears to be similar to the rate of adverse events that were grade ≥3 in the entire study population, in which 16% experienced grade ≥3 adverse events [20]. Similarly, in updated results from phase 1b of the JAVELIN study, Avelumab had rates of adverse events in older patients that were comparable to the study population at large [81].

Across the KEYNOTE trials, which have studied pembrolizumab in patients with melanoma, head and neck cancers, NSCLC, UC and Hodgkin's lymphoma, the rate of adverse events was similar regardless of age [82]. Of note, multiple pooled studies have showed a trend towards higher rates of treatment related adverse events and immune related adverse events (irAE) in older patients [82]. One analysis of 14 phase I and II trials in multiple caners demonstrated significantly more grade I-II irAEs in patients ≥70-years-old versus <70-years-old ($p < 0.001$); however, grade III-IV adverse events were not significantly higher in the older population ($p = 0.12$) [83]. Although this trend has been seen in other cancers, this has not yet born out in the aUC-specific data.

5.1.3 Real-World Analyses

It is evident based upon current prescribing practices that large percentages of patients receiving ICIs are ≥65-years-old. Using the Flatiron Health database, Morgans et al found that over 80% of patients receiving atezolizumab in the 1L and 2+L setting, and 88% of patients receiving pembrolizumab 1L are ≥65-years-old [84]. Given these use patterns, it is important to review the efficacy and safety of ICI therapy in older adults in the clinical setting.

Overall, real-world analyses are limited, but the available studies suggest that age is not an independent predictor of outcomes. For patients with aUC, given the lack of larger prospective trials, when assessing the impact of ICI use in older patients, PD-L1 and PD-1 inhibitors can be grouped into one class of medications, as they have been shown to have similar efficacy and safety to each other [85]. One prospective trial that comments on their use in the elderly is the SAUL study, a multi-national, single-arm assessment of atezolizumab in 1004 patients in the 2+L setting [86]. In subgroup analysis, patients ≥65-years-old did not have significantly worse ORR, OS, or a significant increase in AEs [87].

Retrospectively, in one study evaluating 79 patients receiving multiple different ICIs in the 1L setting, age did not impact overall survival (HR 1.01, 95% CI 0.99-1.04, $p = 0.34$) or adverse events (CI 0.96-1.07, $p=0.55$) [88]. Multiple additional retrospective studies have shown that age is not a predictor of OS for pembrolizumab as a 2+L agent in univariate or multivariate regression analyses [89][90][91][92].

Although outcomes are limited, safety assessments generally align with data from other cancers where ICI therapy has been approved for longer periods of time. They demonstrate that adverse events are similar regardless of age [93][78]. Of note, there is some data that age may actually decrease the rate of adverse events, but overall that has not been seen in aUC yet, and instead safety outcomes seem to be independent of age [94].

5.1.4 Summary

As a result of available trial data, age alone does not appear to increase the incidence of adverse events or significantly impact efficacy. When considering the use of ICI, age should not necessarily be a primary driving factor, but instead, it should prompt providers to investigate frailty.

5.2 ICIs in Frail Patients

5.2.1 Review of Clinical Trials: Efficacy and Safety

While trials assessing ICI use in aUC enrolled patients with age distributions that are reflective of the clinical setting, frail patients remain underrepresented. Still, it is important to review this data because this population is the one that genitourinary oncologists had hoped would particularly benefit from non-chemotherapy treatment options. Prescribing patterns reflect this hope as a large percentage of those receiving ICIs for aUC have poor performance statuses. Data from the Flatiron Health database demonstrate that >30% of patients receiving atezolizumab or pembrolizumab 1L have an ECOG PS ≥2 and as many as 20% of patients receiving pembrolizumab in the 2+L setting have an ECOG PS ≥2 [84].

Unfortunately, it is challenging to comment on the efficacy and safety of ICIs in frail patients based upon clinical trials in a comprehensive manner given that the majority of enrolled patients had ECOG PS <2. The studies that included the most patients with ECOG PS 2 were in the 1L, cisplatin-ineligible setting. KEYNOTE-052 enrolled 156 patients with an ECOG PS of 2 and 1 patient with an ECOG PS of 3. Patients with ECOG PS 2 had ORR 27% (95% CI 19-35) and ECOG of 0 or 1 had ORR 27% (95% CI 21-35). Safety profile was not reported by ECOG status in the initial trial [20]. In post-hoc analysis, they did assess safety data in patients with ECOG PS 2, but did not make direct comparisons to patients with ECOG PS 0-1 [79]. KEYNOTE-361 enrolled 70 patients with ECOG PS 2. When stratified by ECOG PS, there was no significant difference in OS between pembrolizumab and chemotherapy versus chemotherapy or in pembrolizumab versus chemotherapy alone in patients with PD-L1 combined positive score (CPS) ≥10 [80]. IMvigor210 enrolled 24 (20%) patients with ECOG PS 2 in the 1L cisplatin-ineligible setting. In this study, the ORR was 25% (95% CI 10-47) in patients with ECOG PS 2 versus the entire population, which had an ORR 23% (95% CI 16-31). The median OS in patients with ECOG PS 2 was 8.1 months (95% CI 2.9-not estimable) and across all patients was 15.9 months (95% CI 10.4-not estimable), but comparative analysis was not performed. Safety was also not assessed by ECOG status [19].

In the 2+L setting, of the trials supporting the use of pembrolizumab, nivolumab and avelumab, only KEYNOTE-045 included patients with ECOG PS 2. KEYNOTE-045 enrolled 6 patients with an ECOG PS 2 and only two patients were in the pembrolizumab group [24] so it is challenging to draw any specific conclusions. CheckMate-275 and JAVELIN limited enrollment to patients with PS 0-1 [25][26].

5.2.2 Real-World Analyses

Given the limitations of trials for patients with poor performance statuses, it becomes even more important to investigate their use in clinical setting. Figure 1 summerizes these findings. Khaki, et al. assessed 499 patients retrospectively who received any ICI for aUC. 52% of patients received ICI 1L and 48% received it 2+L [95]. 31% of patients treated 1L had an ECOG PS ≥2 and 21% in the 2+L group had an ECOG ≥2. ORR was actually similar for ECOG PS 0-1 versus ECOG PS ≥2 in the 1L setting (31% vs. 33%, p = 0.75) as well as 2+L (27% vs.

23%, p = 0.56) setting. OS, on the other hand was worse for patients with ECOG ≥2 versus ECOG 0-1 in 1L (7.2 months vs. 15.2 months, p = 0.01), but interestingly, was similar in 2+L setting (HR 0.78, 95% CI 0.51-1.21, p = 0.27).

In studies focusing exclusively on 2+L treatment, contrary to findings from Khaki et al, frail patients have been found to have worse outcomes, but frailty does not appear to increase the risk of adverse events. In a meta-analysis of thirteen studies assessing pembrolizumab use in the 2+L setting, ten examined the impact of ECOG PS. Pooled results from these ten studies demonstrated that ECOG-PS ≥2 was associated with a worse OS (HR 3.34, 95% CI 2.57-4.09) [96]. The prospective SAUL study, which also assessed the impact of age, included 102 patients with an ECOG PS 2. In subgroup analysis, patients with ECOG PS 2 had worse ORR and worse OS. Median OS for patients with ECOG PS 2 was 2.3 months (95% CI 1.6-2.6 months) versus 10.0 months (95% CI 8.9-11.2 months) in those with ECOG PS 1. Overall safety, the primary endpoint, was actually similar when assessed in the first 45 days of therapy; however, the number of grade ≥ 3 adverse events was higher in patients with ECOG PS 2 [87]. Ito et al. retrospectively assessed patients receiving pembrolizumab in 2+L therapy. Unlike in other studies, they also included patients with ECOG PS 3-4, which made up 7.3% of the 755 patients. Here, they found similar results; patients with higher ECOG performance statuses had similar safety profiles, but worse ORR and worse ORR [9].

5.2.3 ICIs and Trial Endpoints in Frail Patients

Although it is important that ICIs have been demonstrated to be safe in frailer populations, safety is certainly not the only indicator. At present, more patients are receiving ICI therapy at the end of life, and in aUC, the group where ICI use has increased most dramatically at the end of life is in patients with poor performance statuses [97]. In Khaki et al, 32% of patients started ICI therapy in the last 90 days of life [95] and Ito et al showed that 20% of patients with a ECOG PS 3-4 who started therapy died within 30 days [9]. End of life ICI use has been associated with higher rates of in-hospital deaths and lower likelihood of transitioning to hospice [98]. Although there may be more acceptable adverse effects for ICIs in general, the downstream consequences of potential increased in-hospital death and lower hospice enrollments are significant and should be taken into consideration.

This, along with the mixed efficacy data, only serves to underscore the fact that traditional outcome markers such as ORR, PFS, and OS may not be adequate in assessing efficacy in the frailest patients. As has been highlighted in the past, studies integrating quality-of-life metrics, functional improvements and end-of-life considerations should be developed [99][100]. This is particularly true in ICIs since they are being prescribed when oncologists would otherwise have not pursued more toxic treatments.

5.2.4 Summary

Based upon available studies, ICIs appear to be well tolerated regardless of performance status. In regards to efficacy, patients with poor performance status who receive ICIs in the first line setting demonstrate more comparable ORR and OS to those without functional impairments. In the 2+L setting, there is clearly some discrepant data, which primarily surrounds the outcomes from Khaki et al [95], but in general patients with worse PS tend to have worse outcomes. It is challenging to know if ECOG PS, particularly in the 2+L setting is actually a proxy for worse disease, which may be driving their impaired response, but this remains unclear. This discrepant

data only undergoes the need to expand the conception of positive and negative outcomes in this population.

5.3 ICIs: Prognostic and Predictive Markers

Given the challenges surrounding borderline performance statuses when making treatment decisions on the individual patient level, there must be better measures of predicting response. This is particularly true given that at best, only approximately 30% of patients demonstrate any objective response to ICIs in the first line setting and even less in the 2+L setting. In addition to integrating more comprehensive assessments of performance status, other clinical and molecular markers beyond PD-L1 expression need to be explored.

Multiple clinical prognostic models have been developed for patients receiving first-line [101] as well as 2+L chemotherapy [44][102]. More recently, factors have been investigated for patients being treated with ICIs. Sonpavde et al identified five factors – ECOG PS 1 versus 0, liver metastases, platelet count, neutrophil-to-lymphocyte ratio (NLR) and LDH – that predict survival in patients receiving ICIs in the 2+L setting; however, this was from clinical trial data, and thus, did not enroll patients with poor performance status. A separate study of patients receiving ICIs as 1L and 2+L treatment demonstrated that five factors – ECOG PS ≥2, liver metastases, peritoneal metastases, albumin <3.5g/dL and PPI use – could predict overall survival [103]. Although these are useful prognostic models, they do not solve the challenge of predicting those with poor performance statuses who would most benefit and respond to treatment, an area that needs more research.

In addition to clinical factors, multiple molecular markers are being investigated to predict ICI response. This is particularly relevant given the questions surrounding the use of PD-L1 expression. Prognostically, PD-L1 expression has been reliably associated with worse mortality, but it's use as a predictive marker has proven inconsistent [104]. As a result, multiple other markers including tumor mutational burden (TMB), microsatellite instability-high (MSI-H), tumor infiltration lymphocytes (TILs), and others are being investigated [105]. In the end, ICI use appears safe in frail patients with poor performance status, but better predictive factors must be identified in order to determine those who are most likely to respond.

5.4 ICIs versus Carboplatin-based regimens in Older and Frail Patients

Based upon results from the trials referenced above, the choice of carboplatin and gemcitabine or atezolizumab in patients with adequate PD-L1 expression is an important decision that has emerged in the current guidelines for 1L management of aUC [15]. Carboplatin and gemcitabine have been studied in cisplatin-ineligible patients. The impact of age was not specifically investigated; however, carboplatin-based regimens appear to be well-tolerated in frail patients, as 95.2% with a PS ≥ 2 did not experience severe toxicity [17]. At present, no head-to-head trial of carboplatin and gemcitabine versus atezolizumab has been pursued. Carboplatin-based regimens followed by avelumab are preferred, but ultimately, decisions should be made based upon fitness for platinum-based chemotherapy, PD-L1 expression and patient preference.

5.5 Enfortumab Vedotin: Initial Clinical Trials and Real-World Analyses

Given that the only current approved indication of enfortumab vedotin (EV) is in aUC, the amount of data investigating its impact on the old and the frail is limited. EV-201 and EV-301 are the primary trials which were instrumental in the conditional approval of enfortumab

vedotin for aUC [106]. EV-201 was a single-arm phase II trial of 89 cisplatin-ineligible patients who had progressed on ICI therapy [107] and EV-301 was a phase III trial comparing enfortumab vedotin to chemotherapy in 608 patients who had received both platinum-based chemotherapy and PD-1 or PD-L1 inhibitors [108].

Based upon trial data, EV appears to be effective in the older population. In EV-201, 52% of enrolled patients were ≥75-years old. Patients <75-years old had ORRs (58%, 95% confidence interval 42.1-73.0) that were similar to those ≥75-years-old (46%, 95% CI 30.9-61.0). In EV-301, in comparison to chemotherapy, ORR favored EV in those <65-years-old (Absolute difference 26.1%, 95% CI 12.4-38.5) and those ≥65-years-old (Absolute difference 20.9%, 95% CI 10.8-30.6). Additionally, patients ≥ 65-years-old tended to have better survival when compared to chemotherapy although this was not statistically significant (HR 0.75, 95% CI 0.56-1.00).

In terms of safety, neither trial performed subgroup analysis on adverse events by age. As a cohort, patients in EV-201 were older, with a median age of 75. 55% of patients in the trial had grade ≥3 adverse events. As stated, they did not stratify by age, but of note, there were four treatment-related deaths and they all occurred in patients at least 75-years-old. EV-301 had similar rates of grade ≥3 adverse events at 51.4% in the EV group. When compared to the chemotherapy group, in which 49.8% of patients had grade ≥3 adverse events, the outcomes were similar.

Both trials produced limited data on the impact of performance status on efficacy and safety. Given the small number of patients with ECOG 2 in EV-201, no specific analysis was pursued, and EV-301 did not enroll patients with an ECOG PS ≥2. Overall, there is an indication that EV may be equally efficacious regardless of age, but due to inadequate numbers, we cannot draw any specific conclusion regarding the efficacy or safety of EV in older and frailer patients.

5.5 Sacituzumab Govitecan: Initial Clinical Trials and Real-World Analyses

The initial trial that resulted in accelerated approval of sacituzumab govitecan (SG) was TROPHY-U-01, a phase II assessment of SG in patients who had progressed after treatment with both a platinum-containing chemotherapy regimen as well as an ICI. Clinical trial data supporting SG aligns with EV in that it appears to be efficacious in older patients. In this study, 53% of patients were ≥65-years-old and 26% of patients were ≥75-years-old. In subgroup analysis of patients ≥65-years-old, ORR was 23.3% (95% CI 13.38-36.04), which was similar to those aged 50-64 (ORR 33.3, 95% CI 20.00-48.95) and <50-years-old (ORR 25.0, 95% CI 3.19-65.09). In regards to safety, adverse effects were relatively high overall with 94.7% of patients experiencing an adverse event and 39% of patients requiring dose reduction due to an adverse event; however, they did not stratify these AEs by age. This trial did not include patients with ECOG PS ≥2 so its efficacy and safety in frail patients with aUC has not been explored [11].

Ultimately, there are not any real-world analyses of SG use in aUC given its recent approval. The current phase III clinical trial TROPiC S-04 should provide further information on efficacy and safety in older patients, but given the exclusion of patients with ECOG PS ≥2, we must await more real-world assessments to better understand its use in frail patients [109].

5.6 Erdafitinib: Initial Clinical Trials and Real-World Analyses

Erdafitinib exerts its effect by inhibiting FGF-receptors, which can drive proliferation when they become constitutively activated in UC. Similar to EV, the data supporting erdafitinib is limited to initial clinical trials. The primary trial is a phase II, single-arm investigation of

patients with an FGFR3 mutation or FGFR2/3 fusion who had progressed on at least one course of chemotherapy or immunotherapy [12].

The median age of patients enrolled was 68-years-old. ORR appeared to be independent of age as those <65-years-old and ≥65-years-old had an ORR of 37% (95% CI 22-52) and 42% (95% CI 30-55), respectively. In regards to safety, 67% experienced grade ≥3 adverse effects, but subgroup analysis was not performed by age. Like EV and SG, it is challenging to draw conclusions of tolerance and efficacy in frail patients as the trial only enrolled 7 patients with an ECOG of 2 [12].

Erdafitinib is another second line agent that can be used after progression of chemotherapy, and there has been debate if this should be the preferred agent over ICIs, particularly in patients with FGFR3 mutations [110]. Ultimately, there is very limited data on older and frailer patients with erdafitinib, and further prospective research must be performed to understand its effects in these populations.

6 Expert Opinion: Management of aUC in the Old and the Frail

Despite numerous new treatment options, age still does not appear to be a reliable marker of efficacy or tolerance. Instead, it should serve as a signal to providers to begin to assess for frailty, which plays a critical role in treatment decisions and tolerance. There is no specific age at which this should begin, but as shown in figure 1, providers should generally start at ages 65-70 or earlier if they have any concerns. While performance status assessments including ECOG can be used, they should not be the lone instrument, particularly if patients have an ECOG PS ≥ 1. We recommend starting with a screening tool such as Geriatric-8 in order to categorize patients as either fit or vulnerable/frail. In patients who score <14, this is a red flag for potential vulnerability to treatment. More comprehensive geriatric assessments (CGA) should then be pursued with the goal of characterizing deficiencies and ultimately instituting interventions to optimize patients prior to initiating therapy [33][37][63].

In the 1L setting, utilizing the Galsky criteria and geriatric assessments as above, if a patient is fit for cisplatin-based chemotherapy, gemcitabine plus cisplatin is the optimal first line therapy followed by avelumab maintenance. For those patients, deemed unfit for cisplatin, more careful assessment should be performed. In those who are platinum-eligible, gemcitabine and carboplatin followed by avelumab maintenance is the optimal approach [15].

Fortunately, in unfit patients, ICIs appear to be well tolerated in 1L treatment. Atezolizumab can be considered in those patients who express ≥5% PD-L1 in cisplatin-ineligible patients and both pembrolizumab and atezolizumab are recommended for those who cannot tolerate any platinum-containing chemotherapy independent of the PD-L1 status [22][111]. Even still, given that only approximately 30% demonstrate response to ICI treatment, more accurate molecular and clinical markers need to be developed.

In the 2+L setting, ICIs still appear to be a safe option, but they may not be as efficacious in unfit patients, potentially attributable to a patient's overall frailty. Although enfortumab vedotin, sacituzumab govitecan and erdafitinib in FGFR-mutated cancers are potential choices as further lines of therapy, there is limited data to comment on their safety and efficacy in frail patients.

Ultimately, it is exciting that there are a number of new treatment options for this population, which has historically been excluded from clinical trials, but is such a large part of clinical care. More resources should be dedicated to investigating the use of these therapies,

particularly in the frail population, in order to develop a comprehensive understanding of their safety and efficacy profiles.

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	Time to Completion	Sensitivity	Score Necessitating Comprehensive Evaluation	Initial Study
Geriatric-8 (G8)	5 minutes	65-92%	<14	Bellera et al. *J Eur Soc Med Oncol*, 2012.
Vulnerable Eldeers Survey (VES-13)	5 minutes	39-88%	≧3	Saliba et al. *J Am Geriatric Soc*, 2001.
Flemish version of the Triage Risk Screening Tool (fTRST)	2 minutes	64-67%	≧2	Kenis et al. *Crit Rev Oncol Hematol*, 2006.
Groningen Frailty Indicator	5 Minutes	39-66%	≧4	Stevernik et al. *The Gerontologist*, 2001.
Abbreviated CGA	5 minutes	51%	Variable	Overcash et al. *Crit Rev Oncol Hematol*, 2006.

Table 1 Short list of geriatric assessments, which have been utilized as screening tools to evaluate patients who would benefit from more comprehensive evaluation.
Adapted from Decoster et al, *Ann Oncol*, 2015 and the NCCN Guidelines on Older Adult Oncology.
Citations: [37][61][63][112-116]

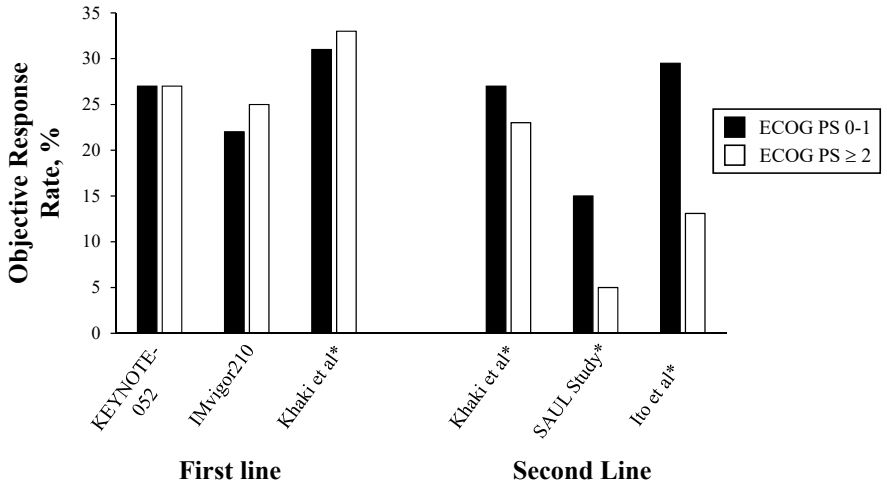

Fig. 1 Objective response rate to immune checkpoint inhibitors in the first and second line setting for patients with ECOG PS 0-1 versus ECOG PS ≥ 2
*Real-world analysis
Citations: [9][19][20][87][95]

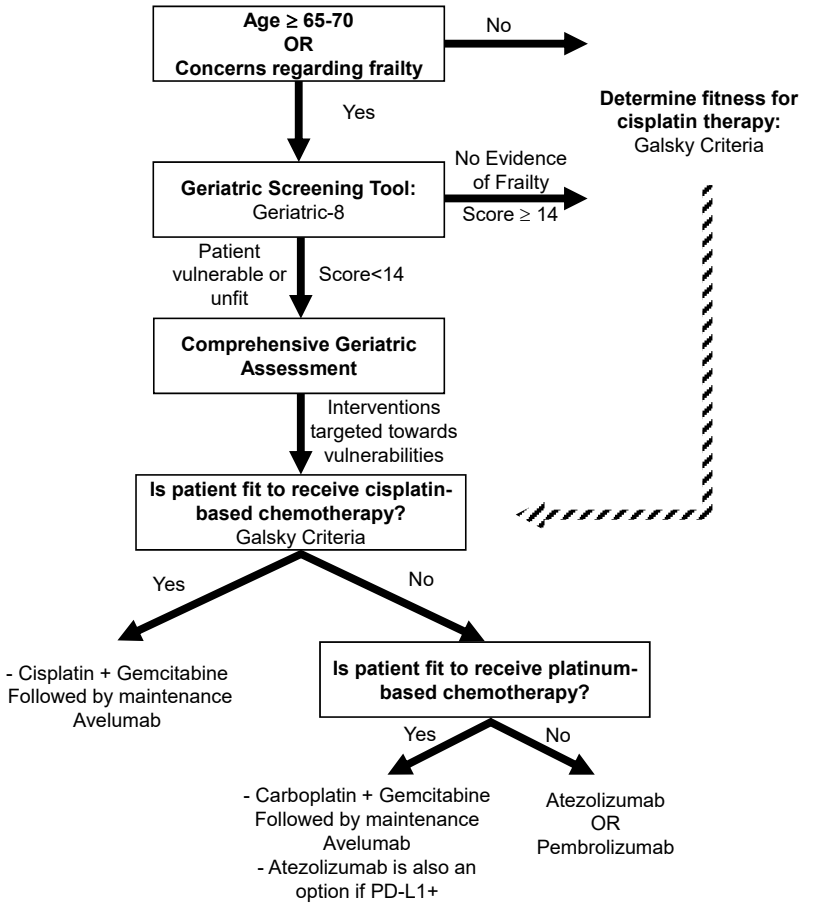

Fig. 2 Algorithm for first-line management of aUC in older/frail patients
Citations: [15][16][33][37][63]