The efficacy and safety of novel immunotherapy agent in high-grade urothelial carcinoma

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Abstract

Intro: Urothelial carcinoma (UC) is the ninth most common cancer globally with high mortality rates in high-grade cases. Treatment options are limited due to the aggressive nature of the cancer and high rates of comorbidities seen in the patient population afflicted with UC. Given the median age of UC patients is 65 years old, many are denied the most effective treatment (platinum-based chemotherapy) due to renal or cardiac impairment, low ECOG (Eastern Cooperative Oncology Group) scores, or hearing loss. The toxic profile of platinum-based chemotherapy also has a high discontinuation rate due to its adverse effects. This paper examines the potential benefits of novel immunotherapies in the treatment of high-grade UC.

Methods: A literature search was completed using PubMed and Google Scholar in November 2019. A total of six articles were selected for evaluation based on publishing date, relevance of the subject matter, and the study type. The articles were then critically appraised for study design and results.

Results: The majority of the studies found a clinically and statistically significant efficacy rate of novel immunotherapies. The studies measured objective response rates (ORR) in which the immunotherapy option was equivalent or higher than chemotherapy controls. Overall survival was also consistently greater than compared to chemotherapy. Additionally, the adverse effects (AE) were substantially lower with the immunotherapy groups compared to the chemotherapy group. Immunotherapy groups had a high-grade AE occurrence rate of 16% or less compared to 47% or higher with the chemotherapy groups. All studies observed the role of PD-1/PD-L1 expression in response rates, which was generally inconclusive.

Discussion: Six studies were analyzed and compared, weighing the study design and elements of each. Collectively, the studies looked to determine the efficacy and safety of PD-1/PD-L1 targeting immunotherapies. Efficacy was determined based on statistical significance of overall survival, objective response rate, progression free survival, and 6 or 12-month survival rates. Safety was determined for each based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. The studies could have been improved by expanding sample sizes and making better efforts in blinding and randomization, but the parameters of the studies were strong enough to support the evidence collected in those studies.

Conclusion: Novel immunotherapy agents should be utilized in the treatment of high-grade UC. Statistical and clinical advantage of increased survival and well as improved safety profiles were demonstrated in the studies analyzed. The main barrier in implementing immunotherapy is the increased cost burden, which can be remediated by insurance with FDA approval. The studies support the benefits of exploring biomarker-targeting treatments in the application of cancers other than UC alone.

Introduction

Globally, urothelial carcinoma (UC) is the ninth most common cancer.[1] There were approximately 430,000 new diagnoses of UC with approximately 165,000 deaths in 2012 alone.[2] In the United States (US), it is the fifth most common cancer accounting for over 70,000 new diagnoses in 2012.[2,3] The majority of the effected population are elderly, with a median age of 65 years old and few cases in individuals under 40 years old.[3,4] UC is over three times more prominent in men than women, but evidence shows women have increased rates of mortality.[1,5] In the US, it is twice as common in white men compared to African-American men.[1] The majority of UC cases are associated with tobacco use; smoking is thought to increase the risk of UC by 2.5 times compared to nonsmoking counterparts.[1] A small portion of UC cases are attributed to occupational chemical exposures or schistosomiasis infections.[1] Both tobacco smoke and occupational hazards such as paints, dyes, and some petroleum products all contain aromatic amines, which are known to be carcinogenic.[5]

Urothelial carcinoma refers mainly to the transitional cells lining the urinary tract.[3] The large majoring of UC originates in the bladder with the remaining small percentage within the renal pelvis, ureters, and the urethra.[3] While less common, it is possible to see mixed histology which is associated with a worse prognosis.[3] Mixed histology includes squamous cell or adenocarcinoma present with the transitional cell pathology.[3] UC is most simply categorized as low-grade or high-grade, where high-grade has an increased recurrence rates or invasive progression.[3] Grade is determined by histology, tumor infiltration depth, and tumor type (papillary or carcinoma).[3] Most cases are detected with tumors still within the mucosa or submucosal layers, which are associated with lower-grade cases.[6] However, recurrence is

extremely common with UC, with recurrence up to 78% in cases confined to the mucosa or submucosal layers.[3]

Current standard of care for urothelial cancer generally consists first of TURBT (transurethral resection of bladder tumor) followed by intravesical BCG.[3] Bacillus Calmette-Guerin (BCG), approved in 1990, is a form of early immunotherapy derived from live, attenuated tuberculosis with a mechanism of action that is not clearly understood.[2] If the UC has extended beyond the mucosa or submucosa, partial or complete cystectomy may be indicated with systemic chemotherapy.[3] Platinum-based chemotherapy has been the standard of care for decades, with cisplatin greatly preferred over carboplatin. Although cisplatin is the first-choice chemotherapy agent for UC, its highly toxic profile leads to exclusion of between 30% and 50% of patients.[4] Carboplatin, the accepted second-line treatment, is a less nephrotoxic analog of cisplatin with decreased efficacy in the application of UC treatment.[4]

Reasons for ineligibility for cisplatin therapy most frequently includes a low ECOG (Eastern Cooperative Oncology Group) performance score, decreased renal function, hearing loss, neuropathy, or Class III heart failure per the New York Heart Association guidelines.[4] Most studies exclude patients with an ECOG score of ≤2, where a score of 2 means a patient can complete all ADLs and lower ECOG scores correlate with increased disability.[7] Inadequate renal function is less than 60 ml/min per the Cockroft-Gault equation.[4] A preexisting hearing deficit of grade 2 per the Common Terminology Criteria for Adverse Events (CTCAE) is disqualifying and defined as a loss of 25 dB at two adjacent frequencies.[4] Disqualifying preexisting neuropathy is grade ≥2 determined by the CTCAE as well.[4] Grade 2 neuropathy limits ADLs as a result of moderate symptoms and more advanced grades correlate with increased disability.[4] With the majority of patients being over 65 years old, the likelihood of not meeting this criteria due to

preexisting comorbidities is high, disqualifying them from the treatment most likely to sustain their lives.

Carboplatin is the treatment of choice for the cisplatin-ineligible, but even carboplatin has a difficult toxicity profile; one study saw 21% of their patients voluntarily discontinue treatment because of the adverse effects.[8] With little UC treatment development since the 1990s and the rise of immunotherapy success with other cancers, researchers started to explore the potential benefits of immunotherapy when applied to UC. Not only could these novel therapies potentially increase survival for all patient with UC, but the improved safety profiles may allow adequate treatment of the large cisplatin-ineligible population.

The majority of immunotherapy treatment options being explored for UC focus on the PD-1/PD-L1 relationship between tumor cells and immune T cells, which is a pathogenic pathway seen in a number of cancers. PD-1 is programmed cell death protein-1 present on T cells and PD-L1 is the ligand on the tumor cells.[2] The binding of the T cell's PD-1 to PD-L1 of the tumor cell downregulates the immune cell function and prevents normal apoptosis.[2] The treatments interrupt this pathway in one of two mechanisms. One mechanism, anti-PD-L1, inhibits PD-L1 of the tumor cells which is utilized by avelumab, atezolizumab, and durvalumab. The second mechanism, anti-PD-1, inhibits the PD-1 receptor of the T cell which is utilized by pembrolizumab. Current studies look at the expression of the tumor cells' PD-L1 with a hypothesis that increased expression would correlate with increased response to treatment. The goals of these treatments are to improve overall survival regardless of PD-L1 expression, as well as have an improved safety profiles to provide treatment to the cisplatin-ineligible or those who have previously failed platinum treatment. Keeping these goals in mind, this paper explores the

question: In high-grade urothelial cancer patients [P], do novel immunotherapies such as monoclonal antibody therapy [I] prolong survival [O] compared to traditional therapies [C]?

Methods

A literature search was performed in November 2019 in PubMed using the terms "urothelial cancer AND high grade AND immunotherapy NOT BCG." Article types were limited to clinical trial and randomized controlled trial yielding 42 articles. Additional parameters were added to only show articles utilizing human studies published within the last 5 years, providing 21 results. The following exclusion criteria was utilized: 1. Articles addressing tumor marker and inflammatory markers for determining disease progression or screening techniques. 2. Articles exploring genes that may contribute to cancer development. 3. Articles discussing cancer other than urothelial. 4. Articles examining immunotherapy complications unrelated to cancer treatment (i.e. organ transplantation).

A secondary literature search was performed in Google Scholar utilizing the same search terms, "urothelial cancer AND high grade AND immunotherapy -bcg." Articles were limited to being published within the last 5 years, yielding 17,500 results. A number of relevant article titles referenced the potential effectiveness of drugs targeting PD-1/PD L-1, so it was incorporated into the search terms to help focus the article subject matter. Search terms were altered to "high grade AND immunotherapy AND pd l1 "urothelial cancer" -bcg." This addition focused subject matter to exclude some extraneous cancer types, yield more treatment-based studies, and narrow the results to 3,180 articles. The same exclusion criteria listed above for PubMed was utilized here, including exclusion of animal-based studies since this filter was not available in this database.

After the aforementioned considerations, 2 articles from PubMed and 10 from Google Scholar were selected. These articles present a variety of study types with varying population sizes. Six articles were excluded from analysis for one of the following reasons: 1. Articles reviewed a collection of studies. 2. Articles explored vastly different treatment approaches which made adequate comparison unlikely. 3. Article was an earlier clinical trial of another article selected. 4. Article utilized an inadequate sample size.

After the application of this final criteria, six articles remained for in-depth analysis. Each article was either a cohort or randomized clinical trial investigating the efficacy of novel immunotherapy agents in the treatment of high-grade urothelial cancer. Some of these studies directly examine the effect of immunotherapy on patients who failed or did not meet criteria for traditional treatment. Following selection and meeting all components of the proposed question, each article was further evaluated for statistical significance.

Results

Powles T, Durán I, Heijden MSVD, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *The Lancet*. 2018;391(10122):748-757. doi:10.1016/s0140-6736(17)33297-x.[9]

In "Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial," Powles et al. explored the efficacy of immunotherapy in the treatment of urothelial cancer that progressed following the use of traditional treatments methods such as platinum-based chemotherapy. Due to the poor prognosis for advanced urothelial carcinoma, the goal of this study was to examine any possible increased survival as well as look at treatment-related adverse effects compared to platinum-based chemotherapy. In the case of

atezolizumab, this agent worked by binding to the programmed death-ligand 1 (PD-L1). It was hypothesized that the atezolizumab would increase median overall survival rates based on stage 1 and 2 clinical trials of anti PD-L1 drugs compared to those treated with chemotherapy. Special attention would be applied to those with high expression of PD-L1, with previous studies suggesting increased expression yields greater treatment response.

The study included 931 patients selected from 198 medical-oncology centers across Europe, North America, and parts of Asia-Pacific. Patients were randomly assigned to either the atezolizumab or chemotherapy groups. Prior to randomization, each patient had one of three possible chemotherapy treatments selected for them in in the event they were assigned to the chemotherapy group. Each patient's expression levels of PD-L1 was determined prior to randomization and masked to all participating members of the study, including sponsors. Regarding inclusion criteria, patients were required to have less than two previous treatments, with at least one being platinum-chemotherapy that did not prevent cancer progression. Major exclusion criteria include one or more of the following: prior immunotherapy treatment, autoimmune conditions, brain metastasis with substantial symptoms, or compromised liver or renal function. Additional exclusion criteria included active tuberculosis, pregnancy or lactation, significant cardiovascular compromise, or patient receiving antibiotics within a 2-week window of randomization. There were also exclusion criteria for each prior treatment. All of the exclusion criteria limited the 1360 initial patient population to the 931 selected for the clinical trial.

Prior clinical trials of immunotherapies focusing on PD-L1 found that the higher the expression of this gene is, the better the response. Because of this finding, additional analysis was done on the response to atezolizumab in patients with high expression: group IC2/3.

Population comparisons were done between IC2/3 and the whole trial population, which found no significant difference in the characteristics of the two groups.

The results of the trial did not support the hypothesis. It was expected based on stage 1 and 2 clinical trials of PD-L1 treatments on urothelial carcinoma and stage 3 trials of PD-L1 treatments in other cancers such as non-small-cell lung cancer that increased gene expression would lead to increased tumor response. Overall median survival rates between the atezolizumab and chemotherapy groups were not significantly different when analyzed using a 95% confidence interval (CI) per the Brookmeyer-Crowley method. Additionally, they did not find that increased expression of PD-L1 played any role in treatment response. However, it was noted that 12-month overall survival rates at the 12-month point was approximately 7% higher in the atezolizumab group compared to the chemo group (under 95% CI). It was also found that the atezolizumab group experienced fewer grade 3 or 4 treatment-related adverse effects (20%) compared to the chemo group (43%). Considering this data, atezolizumab may have a better safety profile compared to the chemotherapies. One factor the authors did not expect was the patient response to chemotherapy agent vinflunine was substantially better than the other chemotherapy agents. Although atezolizumab outperformed the other agents, vinflunine's success mitigated any statistical difference. The authors note separate studies have not been done to compare the selected chemotherapy agents against one another, but probably should given the success of vinflunine compared to the other agents.

The authors of this article received grants from a number of pharmaceutical companies. Additionally, efforts were made to avoid bias by utilizing an independent data monitoring committee and external genetic testing to establish PD-1/PD-L1 burden. With the high number companies involved in the funding of this study, a high number of contributing authors, and

independent data processing, it is fair to assume no substantial bias implicated the results of this study.

Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *The Lancet Oncology*. 2018;19(1):51-64. doi:10.1016/s1470-2045(17)30900-2.[10]

Patel et al. explore the safety profile and efficacy of avelumab, an anti-PD-L1 immunoglobin in the article "Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial." Their study consisted of two cohort studies where the data collected from both of these were pooled for statistical analysis. The first cohort portion of this phase-1 clinical trial was aimed to determine the safety profile and dose-related toxicities of the drug. Within the first portion of the study, they also determined an approximate percentage of urothelial cancer that had high genetic expression of the PD-L1, which other studies concluded play a role in treatment response and disease prognosis. Once this information was obtained, they moved onto the efficacy portion of the cohort. Under the efficacy portion of the study, they wanted to gain an understanding for progression-free survival, overall survival, duration of response to treatment, and additional safety information.

Because the cohort is a combination of two expansion cohort studies, there are two bodies of patients combined to make a total participant population of 249. Unfortunately, this article does not clearly divide the populations from each individual cohort which creates confusion for the reader. What can be ascertained is 44 patients participated in the initial cohort, and the total patient population analyzed in the pooled results cohort was 249. The pooled cohort initially evaluated 329 potential patients for their participation in the study, sourced from 80

clinical location in Europe, the United States, and Asia. 80 patients were excluded for not meeting the following criteria: previous platinum-based chemotherapy, sufficient end-organ function, ECOG of 0 or 1, life expectancy exceeding 3 months, 1 or more lesions suitable for measuring, and no active metastasis to the CNS. It is not very clear if this inclusion criteria were applied to both the initial and efficacy portion of the cohort study. The article discloses some patients who were platinum-naïve were admitted to the initial study. The reason for this is unclear, as it does not agree with the study parameters, but the article does reference a protocol amendment which allows for this exception. Regarding the patient populations, it is also unclear if some or all of the participants in the initial study were participants in the efficacy study.

Although this trial does not have variation in treatment, the authors took extra consideration of patient characteristic which would impact prognosis. This study looked closely at hematologic values such as hemoglobin and albumin, citing them as possible predictors of poor prognosis if their values were low prior to the start of treatment; as well as the presence of liver metastasis and ECOG scores exceeding 0 to a lesser degree. Following analysis, there was a notable difference in the objective patient response in those with elevated ECOG scores, as well as low albumin (<35 g/dL) and low hemoglobin (<100 g/dL) compared to patients with higher values. This information may prove to be helpful in future patient application when considering patient prognosis and response. Although the article mentions liver metastasis as a negative prognosis indicator, data was not produced supporting this notion for this particular study.

The authors determined, based on published chemotherapy trials, an objective patient response to treatment of 10% or greater with a CI of 95% per Clopper-Pearson methods would be deemed significant. The efficacy study patient population had a PD-L1 positive expression of 33%. At 6 months, of the 161 patients who had previously received platinum chemotherapy,

17% has an objective response to avelumab (95% CI) where objective response includes complete or partial tumor reduction response. Even the lower limit of the CI was 11%, exceeding the 10% mark for clinical significance. 40% (95% CI) of the 161 patients at 6 months saw disease control, which included either tumor response or disease stability. A greater percentage of success was seen in those with PD-L1 expression. 96% (95% CI) of those patients who saw disease stability saw at least 24 weeks without disease progression. Regarding the safety profile of the treatment, 67% of patients experience adverse events spanning from Grade 1 to Grade 5 per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0). The greatest proportion (58%) being Grades 1 or 2, most frequently infusion-related reactions, fatigue, or rash. With the objective response rate exceeding the desired 10% for clinical significance and the majority of the adverse reactions being in the lowest grades, the authors determined this cohort study to be successful. Though 17% response rate may seem insignificant, it should be considered the survival rate for advanced UC is extremely low even with platinum chemotherapy. A treatment which may prolong life without causing adverse effects which disrupt quality of life may be a valuable option in patient-centered care.

The authors of this article received support from a number of pharmaceutical companies. However, the main funding for this article is from Merck and Pfizer. Given the project funding and the funding of the individuals, there is potential for bias due to the potential underlying conflicts of interest of the authors. Bias considered, the importance of their findings should not be invalidated as this is a phase-1 trial and more research is required.

Bellmunt J, Wit RD, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. ***New England Journal of Medicine*****. 2017;376(11):1015-1026. doi:10.1056/nejmoa1613683.**[11]

Bellmunt et al. examined the efficacy and safety of pembrolizumab in a phase 3 clinical trial in their article “Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma.” Pembrolizumab is a monoclonal antibody which targets PD-1 of patient T cells. This study looked at pembrolizumab as a second-line treatment following platinum-based chemotherapy as the first-line treatment. The study goals were to determine if pembrolizumab extended the median overall survival rate compared to chemotherapy agents (paclitaxel, docetaxel, vinflunine) as a second-line treatment follow platinum chemotherapy failure as well as compared the safety profiles between the treatment options. The study examined overall population response to treatment, as well as analyzed the response of patients with PD-L1 expression of 10% or greater.

748 patients were evaluated for this study from 120 sites across 29 countries. Patients were required to meet the following inclusion criteria: disease progression or recurrence within 12 months of platinum chemotherapy, received no more than two lines of chemotherapy, at least one lesion was measurable for treatment assessment, ECOG score of 2 or less, and patient could provide tissue sample to determine PD-L1 expression. Patients were excluded if they had ECOG scores of 2 paired with other negative prognosis predictors (low hemoglobin or liver metastasis), received chemotherapy within 3 months of enrolling in the trial, or received PD-1, PD-L1, or CTLA-4 targeting immunotherapy previously. A total of 521 patients commenced treatment and were randomly assigned to treatment groups. The article states the treatment assignment was not blinded – it is unclear if it is referring to which group patients were placed or if this referred to which of the three chemotherapy treatments would be used in the chemotherapy groups.

Using a CI of 95% per the Efron method and $p=0.002$, there was a substantial difference in the overall survival rate between pembrolizumab and chemotherapy treatment, with

pembrolizumab survival rate almost 3 months greater than the chemotherapy group. Additionally, in those who had ≥10% PD-L1 expression, the overall survival rate was approximately 3 months greater in the pembrolizumab group compared to the chemotherapy group as well (CI 95%, p=0.005). Alternatively, the results were comparable between the groups when observing the length of progression-free survival. The results of this study were so substantial, the trial results could be concluded prior to the set deadlines. In regards to safety profile comparison, pembrolizumab was deemed to have notably fewer adverse treatment effects compared to chemotherapy. Overall, pembrolizumab had approximately 61% of the patients report adverse effects whereas 90% chemotherapy patients experienced them. In adverse effects of grade 3 or greater per NCI CTCAE v4.0, pembrolizumab patients had 15.0% compared to the chemotherapy group's 49.4%. These results suggest that not only is pembrolizumab better at extending survival, but the potential for improved quality of life is significant. The article cites the family-wise type I error rate to be 2.5%, and the study has a power of 88%. The overall patient population hazard ration was determined to be 0.781 in favor of the pembrolizumab group.

The opportunity for bias in this study is substantial and should not be ignored. The lack of blinding in treatment assignment presents a large opportunity for bias by the researchers. Additionally, the trial design and data review were in part performed by Merck, the study sponsor. In attempts to mitigate bias, the data was reviewed by a secondary resource, BioClinica, and the imaging used to determine disease progression was evaluated in an independent and blinded manner. All this should be considered when evaluating this article, a phase 3 clinical trial in which Merck has a lot of potential to benefit. However, the statistics were reviewed by a secondary firm and found to be very significant.

Balar AV, Castellano D, Odonnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *The Lancet Oncology*. 2017;18(11):1483-1492. doi:10.1016/s1470-2045(17)30616-2.

In "First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study," Balar et al. determine the efficacy and safety of pembrolizumab as a first-line agent for advanced urothelial cancer in a patient population with limited treatment options. Additionally, researchers note the patient response relative to PD-L1 expression, anticipating greater response with greater expression of the targeted ligand. Pembrolizumab is a monoclonal antibody targeting PD-1, which has shown success in treating advanced urothelial cancer as a second-line agent following chemotherapy failure. However, a large portion of patients are ineligible for cisplatin chemotherapy due to pre-existing comorbidities. This has been problematic as cisplatin therapy is the accepted advanced urothelial cancer first-line treatment. Common disqualifying reasons include kidney and cardiac dysfunction, which is common considering the median age for this study population was 74. Of those with advanced urothelial cancer, approximately 50% are ineligible for these reasons. This study hypothesizes that pembrolizumab will have clinical benefit to those who are not eligible for cisplatin chemotherapy.

Patients in this study were from 91 locations across 20 countries. Of the 541 patients screened, 370 received treatment. To be treated, patients needed to meet the following criteria: locally advanced and unresectable or metastatic urothelial carcinoma, no prior systemic chemotherapy for urothelial cancer, ECOG status of 2 or less, appropriate liver function, and an appropriate hematologic profile. In addition to the aforementioned acceptance criteria, patients needed to be disqualified from cisplatin chemotherapy due to being ECOG status 2, having impaired renal function (CrCl of 30-60 ml/min), Grade 2 or greater audiometric impairment,

Grade 2 or greater peripheral neuropathy or Class III Heart Failure per NYHA. Exclusion criteria included metastasis to the central nervous system, autoimmune diseases, hepatitis, HIV, monoclonal therapy within 4 weeks, and any history of T-cell targeting therapies. Patients were monitored via MRI or CT at a laboratory near them in 6-week intervals initially, and 12-week intervals during the second year of receiving pembrolizumab.

The researchers' hypothesis was supported by the study findings, with 24% of patients having an observed response and 47% saw disease control. Researchers noted that 63 patients were not enrolled in the study long enough prior to the close of data collection to appropriately determine disease response to pembrolizumab. Data adjustment excusing these 63 patients from the population results in a 27% observed response rate. The overall survival rate at 6 months was 67% with 30% of patients seeing no disease progression in 6 months. It was determined that the reason for cisplatin therapy ineligibility played no role in pembrolizumab treatment response. When observing disease response compared to PD-L1 expression, the population with expression >10% saw an objective response of 39%. Comparatively, those with lower expression (<1%) saw only an 11% objective response. Although those with greater PD-L1 expression were more likely to see an objective response, lower expression still saw benefit. However, the population with expression greater than 10% saw more complete responses than groups with less expression. Regarding the safety profile of pembrolizumab, 62% saw adverse effects from treatment, but only 16% of those were a grade 3 or greater per NCI CTCAE v4.0 with fatigue being the most common at just 2%. Treatment discontinuation occurred in 5% with the most common cause of treatment discontinuation being colitis, experienced by 1% of patients. There was only one treatment-related death as a result of myositis. For comparison, carboplatin is the current first-

line option for those who are cisplatin-ineligible, which sees a discontinuation rate of 21% due to its toxicity.

When comparing the success rates of treatment and the enhanced safety profile of pembrolizumab to carboplatin, pembrolizumab is an attractive treatment option. All data presented had a 95% CI featuring binomial distribution. Median data was determined according to Kaplan-Meier methods. Population size was selected for PD-L1 expression to be high in at least 75 patients based on phase 1 statistics and other external study findings.

This well executed and described study does have some points were improvement is possible. Researchers note that there was no control to compare other alternative treatments to pembrolizumab, including supportive care as this is the option a large proportion of cisplatin-ineligible patients typically receive. Additionally, no median overall survival rate was determined given 74 patients were still receiving treatment at the time data collection ended. By extending the follow-up window, this data could have been collected to more effectively compare pembrolizumab to the current standard of care. Funding for this study was primarily sourced from Merck, however, a number of other pharmaceutical companies have funded individual researchers that contributed to this study. The large number of companies participating financially mitigates some potential for bias. Although a control was not present and a median overall survival rate was not determined, the results in this study provide substantial evidence to suggest pembrolizumab may be a sufficient first-line treatment for those who are not eligible for cisplatin treatment.

Powles T, Odonnell PH, Massard C, et al. Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma. *JAMA Oncology*. 2017;3(9). doi:10.1001/jamaoncol.2017.2411.[12]

In “Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma” Powles et al. sought to determine the effectiveness and safety profile of durvalumab, a monoclonal antibody obstructing PD-1 and PD-L1 binding. As other immunotherapy treatments targeting the same proteins that have seen clinical success, researchers anticipated similar effectiveness with durvalumab in the treatment of advanced urothelial cancer. This particular article is an update on data previously submitted and approved by the FDA due to the study success, with additional survival statistics. The narrow data collection window of the initial study parameters prevented analysis of treatment response durability initially observed and reported. The initial hypothesis for the durvalumab phase 1/2 clinical trial predicted a clinical benefit in the treatment of metastatic or locally-advanced urothelial cancer, including that which had progressed following first-line treatments. The patient expression of PD-L1 was also monitored and analyzed to further explore the role of expression levels and disease response to PD-1/PD-L1 immunotherapies.

This study was comprised of 191 patients from 60 sites across 9 countries. Patients were eligible for the study if they had an ECOG score of 0 to 1, appropriate organ function, and appropriate bone marrow function. Patients who had received and failed prior treatment or were seeking treatment for the first time were all eligible for this study. Exclusion from this study would be for the use of any of the following while receiving durvalumab: chemotherapy, additional immunotherapy, biologics, or hormone therapy. Additional exclusion criteria for this study includes investigational anticancer treatments within 4 weeks or monoclonal antibody treatments within 6 weeks prior to study onset. The patient population had a median age of 67, primarily men, and the majority had received one or two previous treatment types for their cancer.

Durvalumab efficacy was determined by the overall response rate, which was a combination of complete and partial responses to treatment. 7 complete responses were recorded, with an overall response rate of 17.8% in those who received treatment. Although complete response was seen in patients with both high and low expression on PD-L1, a larger portion of those who saw an objective response had higher PD-L1 expression. Durability of the responses seen were equivalent regardless of expression level. In terms of progression free survival, at 6 months 22% were still stable and 16% were stable as of 12 months. The overall survival maximum was not determined, but at the last data point collected prior to publishing was 20.0 months. Of patients who experienced a response, those with lymph node metastases greatly outweighed those with organ metastases. 33.6% of patients saw disease control, with a large proportion of this group having high PD-L1 expression. Regarding the safety profile of durvalumab, 60.7% of all patients experienced some degree of adverse effects. However, only 6.8% of those were Grade 3-4 per NCI CTCAE v4.0. 1% of patients experienced adverse effects which attributed to their death; one death was due to autoimmune hepatitis and the other pneumonitis. PD-L1 expression had no significance in the safety profile. The data presented in this study was determined via the Clopper-Pearson method, utilizing a 2-sided 95% CI. Any data incorporating time was determined using the Kaplan-Meier method.

This study was funded solely by MedImmune, however, the authors are associated with a number of other pharmaceutical companies in individual capacities. Although the funding was from one source for this study, the high number of study contributors with support from competing companies mitigates some bias. It can be assumed that the contributors have as much to gain from success of this study as their other pharmaceutical involvements. This article lacks some clarity. There was no disclosure on how the treatment responses were measured, including

diagnostic methods and review of that information collected. Additionally, they mention that this was updated data adding onto a preceding study. There was little clarity on what was new data and what values were derived from the initial study. Although the data presented shows clinical benefit, appropriate safety profile, and the authors report FDA approval of durvalumab, the lack of clarity should be considered when comparing this study to other PD-L1 targeting immunotherapies.

Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *The Lancet*. 2017;389(10064):67-76. doi:10.1016/s0140-6736(16)32455-2.[13]

Balar et al. determine the efficacy and safety profile of atezolizumab in "Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial". This study looks at the functionality of atezolizumab in the treatment of a population with extremely poor prognosis due to limited treatment options. This study cites as much as 2/3 of those faced with metastatic or locally advanced urothelial cancer are ineligible to receive the first-line treatment of cisplatin chemotherapy for a number of reasons. The alternatives to cisplatin have decreased success and often high toxicity leading to treatment discontinuation. Many patients receive only supportive care with late-stage urothelial cancer. Atezolizumab has shown success as a second-line treatment when urothelial carcinoma no longer responding to cisplatin. Balar et al. hypothesized that this success can be utilized in the cisplatin-ineligible population as a first-line treatment, offering increased survival time.

This study looked at 119 patients from 47 locations in 7 countries after initially screening 167 patients. To be eligible for this study, patients needed to be disqualified from cisplatin

chemotherapy due to one or more of the following reasons: ECOG status 2, GFR of 30-60 ml/min, Grade 2 or greater audiometric impairment, or Grade 2 or greater peripheral neuropathy. Additional inclusion and exclusion criteria were not included in this article, however, the full study protocol with detailed criteria was published separately and referenced within the article. Patient responses were monitored every 9 weeks for the first year and then every 12 weeks beyond that year.

The study found an objective response rate of 23%. Of the 119 participants, 11 saw complete response to treatment. After 12 months of atezolizumab, the overall survival rate was 57%. 30% of patients had a clinical benefit to treatment. Patients with an increased expression of PD-L1 saw a greater overall response rate than those with lower expression. Similarly, higher expression correlated with a greater overall survival time. In terms of safety profile, 96% of patients experienced an adverse effect but only 66% of those were treatment-related. 16% of patients experienced a Grade 3 or 4 per event NCI CTCAE v4.0, most commonly related to fatigue or elevated liver function tests. One case of sepsis was recorded, accounting for the only Grade 5 event. PD-L1 expression did not have a significant impact on the safety profile of atezolizumab. Patients greater than 80 years old and those with renal impairment did not see increased incidence of adverse events compared to the rest of the patient population. Researchers consider this an encouraging finding, considering chemotherapy such a carboplatin typically has high incidence of toxicity causing treatment discontinuation sooner in these populations compared to others.

The study population size was selected such that 30% would have high expression of PD-L1 which allows for appropriate analysis. A control response rate of 10% is referenced, seemingly calculated by the statistics associated with typical treatments for the cisplatin-

ineligible population using the information as follows: 75% receive supportive care only, overall response rate of 0%, and 25% receive carboplatin treatment, overall response rate of 36%. The carboplatin overall response rate was sourced from a phase 2/3 clinical trial evaluating treatments for advanced urothelial cancer. Hypothesis tests were calculated using a two-sided α level of 0.05 per IRF-assessed RECIST (Response Evaluation Criteria in Solid Tumors) v1.1. Binomial tests compared the treatment responses to the calculated control response rates to determine statistical significance. The Clopper-Pearson method was used to determine the CI of 95% for the data reported.

This article did not provide the diagnostic method used to determine response rate throughout the study. It does state that the response rates were determined at the sites of treatment, and then reviewed by an external entity, BioClinica. Additionally, this study states that the treatment sites and BioClinica had an agreeance rate of >90% when determining the response rates of treatment. This study broke the population up into numerous subgroups for in-depth statistical analysis. Although this may be done to focus on expression-based responses and certain population aspects, it should be noted that response rates increased with the creation of sub-groups. Careful observation needs to be utilized when evaluating this data to determine values for the whole population, as this was not made clear. Additionally, the extrapolation of a control group was only mentioned in the statistical analysis section of the article with its application to the data was not made clear. There is a clear clinical benefit of atezolizumab to this population, however, this article lacks clarity and the data manipulation has the potential to bias the impression of this study without careful analysis of the results.

Discussion

Immunotherapy is a rapidly expanding branch of medicine, especially in cancer treatment. These treatments are being applied to notoriously challenging cancers such as small-cell lung cancer and urothelial cancer with some success. While being effective, immunotherapy is known for having a safer drug profile which leads to fewer severe adverse reactions, treatment-related toxicity, and treatment discontinuation. This is ideal for the elderly population often suffering comorbidities affected by urothelial carcinoma, demonstrated by the median ages in Appendix A. The combination of efficacy and safety makes it an attractive treatment option for cancer. The results and structure of six studies were analyzed and compared to determine of immunotherapy treatments offer increased survival for those affected by high-grade urothelial cancer.

The articles looked at four different immunotherapy agents: avelumab, atezolizumab, durvalumab, and pembrolizumab. All of these agents focused on the PD-1/PD-L1 relationship. Avelumab, atezolizumab, and durvalumab targeted PD-L1 on the tumor cell and pembrolizumab targeted PD-1 on the patient T cells. Because all of these agents were in early exploration for UC application, four studies were cohort studies and two were randomized clinical trials. Only the clinical trials, Powles T et al. studying atezolizumab and Bellmunt et al. studying pembrolizumab directly compared the variables to chemotherapy controls.[9,11] As seen in Appendix A, all studies had study endpoints of overall survival (OS), objective response rate (ORR), progression free survival (PFS), and either 6-month or 12-month survival rates. Additionally, each study also examined the role of PD-L1 expression on the patient tumors to determine if there was a positive correlation between high PD-L1 expression and response to treatment.

All of the studies also monitored the safety of the treatment in addition to efficacy. Although establishing an appropriate safety profile is crucial for progressing to more advanced

clinical trials, the demonstrated improved safety profile of the immunotherapy agents play a large role in their ability to be used in patients ineligible for chemotherapy. Adverse effects were carefully monitored in all six studies per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0. Each study, regardless of the agent utilized, demonstrated statistically significantly lower incidences of high-grade (Grade 3, 4 or 5) adverse effects compared to the chemotherapy agents well-studied in UC applications. Frequency of adverse effects encountered can be seen in Appendix B.

In addition to safety, Powles T et al. studying atezolizumab measured the comparable quality of life difference in chemotherapy treatment versus the immunotherapy agent via European Organization for research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30).[9] Shown in Appendix A, this study was the most advanced, boasting the largest sample size and being only one of the two studies in phase 3 randomized clinical trials. With the advancement of the other studies to phase 3 or higher, the implementation of EORTC QLQ-C30 would offer increased benefit in comparing chemotherapy and immunotherapy considering overall survival paired with improved quality of life is an ideal in cancer treatment. In the case of atezolizumab, the quality of life per EORTC QLQ-C30 was maintained throughout treatment compared to a decrease in the chemotherapy group.[9] This metric holds substantial value in patient-centered care, especially when a patient has the opportunity to decide the direction they would like to pursue with their care.

The majority of the studies analyzed are weakened by a lack of randomization and blinding, shown in Appendix C. Only the studies examining atezolizumab met adequate standards for randomization and blinding.[9, 13] For example, Balar et al. researching atezolizumab did not have a chemotherapy control, however, PD-L1 expression was a variable being measured

and the researchers, investigators, and sponsors were blinded to the expression levels for each patient. [13] The study demonstrated that a variable treatment or a control is not the only area where blinding and randomization could be employed. Additionally, many of the studies could have bolstered their results by utilizing external resources for data review and interpretation. In a situation where radiographic results are a prime source of data, having blinded external clinicians interpret the images would mitigate bias compared to having the researchers interpret the results themselves. Additionally, a number of the studies had relatively small sample sizes, which is presented in Appendix A. Although each study determined the lowest number of participants required for appropriate statistical analysis, increased sample sizes would be preferred in those with fewer than 200 participants. Subsequent clinical trials at more advanced stages would most likely address this concern.

Each study analyzed provided evidence suggesting a clinical benefit, whether that be longer overall survival or a safer treatment profile compared the platinum-based chemotherapies. All six of the studies represented an appropriate patient population for those impacted by UC globally and featured similar study endpoints. Although there are points of improvement for each of the studies critiqued, there are no confounding elements substantial enough to discredit the clinical benefits determined by these studies. With subsequent clinical trials, researchers may address the flaws noted within this analysis and bolster the promising evidence that effective alternative treatments for UC are in the future.

Conclusion

As it stands, the current standard of care for advanced UC is platinum-based chemotherapy and a large patient population is ineligible. Additionally, the toxicity of this treatment leads to high discontinuation rates in those who are eligible. The superior safety profile

of the immunotherapies explored in the described studies are not only more inclusive of the patient population afflicted by advanced UC, but also saw a statistically significant decrease in high grade adverse effects compared to the platinum chemotherapy controls.

The goals of these studies were to determine the efficacy and safety profile of the immunotherapy treatments. A number of the studies explored saw statistically significant prolonged survived compared to chemotherapy controls. Where statistically significant prolonged survival compared to the controls was not seen, significantly fewer adverse effects were observed in the variable patients versus the chemotherapy controls. All studies analyzed here saw improve quality of life associated with the improve safety profile and the majority saw significant improved survival both clinically and statistically.

The patients represented in these studies are a fair representation of the general patient population of UC. The populations most often affected by UC are men with a median age of 65. These studies all had median ages between 65 and 73. [3, 4] The gender distribution of the study populations were between 70% and 81% men, which is reflective of the UC patient population.

One barrier to care to transitioning from chemotherapy to novel immunotherapies is cost. A study in Sweden looked at the benefits of using pembrolizumab versus carboplatin with gemcitabine, a common treatment for advance UC.[14] Although pembrolizumab saw an improved survival of over 2 years compared to the carboplatin control, there was an increased cost of treatment of over €90,500 or roughly $102,000.[14] This steep cost increase is the most obvious barrier to implementation of making novel immunotherapies the new standard of care. However, if patients are deemed ineligible for platinum-based chemotherapy for any reason, these studies strongly support the implementation of immunotherapies as the first-line treatment option for

these patients. As the first-line option with FDA approval, the immunotherapy treatment should result in insurance covering the treatment.

Implementation of immunotherapy treatment is similar to the current accepted standard of care. The immunotherapy treatments are administered intravenously and most often kept in refrigerated or frozen conditions. Carboplatin similarly is refrigerated and administered intravenously, eliminating the need for additional staff education or substantial modifications to the medical facilities in order to adapt to immunotherapy treatment.

These studies have demonstrated that the PD-1/PD-L1 immunotherapies are viable treatment options for those with advance UC, whether they have failed platinum-based chemotherapy or were initially ineligible for the stand of care. These studies are also supporting the importance of identifying biomarkers, such as PD-1/PD-L1. As cancer research moves forward, the exploration of biomarkers may facilitate progress in a number of other cancers in addition to UC. Prior to these novel immunotherapies, a large patient population had few options at extending their lives when faced with advanced UC. These studies not only demonstrate added overall survival compared to the standard of care, but improved quality of life while receiving treatment due to reduced adverse effects of treatment.

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Appendices

Appendix A: Comparison of Study Designs

Study	Design	Total Population	Median Age	ECOG Score	PD-L1 Expression (%)	Outcome Measures
Powles T et al. (2018) Atezolizumab	RCT	931	67 (31-88)	≤1	≥5%: 230	OS ORR 12MS PFS
Patel et al. (2018) Avelumab	Cohort	249	68 (63-76)	≤1	≥5%: 82	OS ORR 6MS PFS
Bellmunt et al. (2017) Pembrolizumab	RCT	521	Variable: 67 (29-88) Control: 65 (26-84)	≤2	Variable with ≥10%: 74/260 Control with ≥10%: 90/266	OS ORR 12MS PFS
Balar et al. (2017) Pembrolizumab	Cohort	370	74 (34-94)	≤2	≥10%: 80	ORR 6MS PFS
Powles T et al. (2017) Durvalumab	Cohort	191	67 (34-84)	≤1	≥25%: 98	OS ORR 6MS 12MS PFS
Balar et al. (2017) Atezolizumab	Cohort	119	73 (51-92)	≤2	≥5%: 32	OS ORR 12MS PFS

Key: **RCT**- randomized clinical trial; **ECOG**- Eastern Cooperative Oncology Group performance score which determines impact of disease on daily life playing a role in prognosis; **PD-L1**- Gene expression where higher expression is correlated with more aggressive disease and the target for these treatments; **OS**- overall survival; **ORR**- objective response rate (complete or partial responses), **6MS**- 6-month survival rate, **12MS**- 12-month survival rate

Appendix B: Summary of Results

Study	ORR	OS (months)	6 Mon. Survival	12 Mon. Survival	PFS (months)	High Grade AE (3-5)
Powles T et al. (2018) Atezolizumab	**High Exp:** Variable: 23% Control: 22% **Low Exp:** Variable: 13% Control: 13%	Variable: 11.1 Control: 10.6	N/A	Variable: 39.2% Control: 32.4%	Variable: 2.1 Control: 4.0	Variable: <10% Control: 47%
Patel et al. (2018) Avelumab	All: 17% High Exp: 24%	6.5	53%	N/A	1.4	<9%
Bellmunt et al. (2017) Pembrolizumab	Variable: 21.1% Control: 11.4%	Variable: 10.3 Control: 7.4	N/A	Variable: 43.9% Control: 30.7%	Variable: 2.1 Control: 3.3	Variable: 15.0% Control: 49.4%
Balar et al. (2017) Pembrolizumab	24%	N/A	67%	N/A	2.0	<16%
Powles T et al. (2017) Durvalumab	17.8%	All: 18.2 High Exp: 20.0 Low Exp: 8.1	64%	55%	1.5	6.8%
Balar et al. (2017) Atezolizumab	All: 23% High Exp: 28% Low Exp: 21%	15.9	N/A	57%	2.7	16%

Key: **Exp** – Expression of PD-L1; **ORR** – Objective Response Rate (Complete and Partial responses totaled); **OS** – Overall Survival; **PFS** – Progression Free Survival; **High Grade AE** - per National Cancer Institute Common Terminology Criteria for Adverse Events (AE)

Appendix C: Validity assessment of study elements

Study	Blinding and Randomization	Data Review Integrity	Sample Size	Bias	Follow-up Frequency	Imaging Frequency
Powles T et al. (2018) Atezolizumab	A	M	A	A	A	M
Patel et al. (2018) Avelumab	I	A	A	A	A	A
Bellmunt et al. (2017) Pembrolizumab	M	A	A	M	A	A
Balar et al. (2017) Pembrolizumab	I	M	A	A	A	A
Powles T et al. (2017) Durvalumab	M	A	M	M	A	A
Balar et al. (2017) Atezolizumab	A	A	M	M	A	M

Key: The metrics described below were determined by comparing the articles to each other. The study elements described varied for each study. To determine the ranks, the most stringent parameter described in a study was deemed Adequate (**A**), Marginal (**M**) was determined to be close to the adequate standard but there was points of improvement possible, and Inadequate (**I**) was any study element that was greatly below the standards of the other studies being compared.

Blinding and Randomization: **A** – Blinding of both researchers and clinical data reviewers, **M** – Blinding of either researchers or clinical data reviewers, **I** – No blinding or randomization of researchers and clinical data reviewers

Data Review Integrity: **A** – Independent or external review for many elements, **M** – Independent or external review for some elements, **I** – No independent or external review utilized

Sample Size: **A** – $n \geq 200$, **M** – $200 > n \geq 100$, **I** – $n < 100$

Bias: **A** – Strong effort to disclose possible points of bias and monitor data collection, **M** – Moderate effort to disclose and mitigate bias, **I** – Little to no disclosure of possible bias within the study

Follow-Up Frequency: **A** – 3 months or less, **M** – >3 months but ≤6 months, **I** – >6 months

Imaging Frequency: **A** – 8 weeks or less, **M** – 9 weeks to 12 weeks, **I** – Greater than 12 weeks