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# Safety and efficacy of immune checkpoint inhibitors in advanced urological cancers with pre-existing autoimmune disorders: a retrospective international multicenter study

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## ABSTRACT

**Background** There is limited experience regarding the safety and efficacy of checkpoint inhibitors (CPI) in patients with autoimmune disorders (AD) and advanced urological cancers as they are generally excluded from clinical trials due to risk of exacerbations.

**Methods** This multicenter retrospective cohort analysis of patients with advanced renal cell cancer (RCC) and urothelial cancer (UC) with pre-existing AD treated with CPI catalogued the incidence of AD exacerbations, new immune-related adverse events (irAEs) and clinical outcomes. Competing risk models estimated cumulative incidences of exacerbations and new irAEs at 3 and 6 months.

**Results** Of 106 patients with AD (58 RCC, 48 UC) from 10 centers, 35 (33%) had grade 1/2 clinically active AD of whom 10 (9%) required corticosteroids or immunomodulators at baseline. Exacerbations of pre-existing AD occurred in 38 (36%) patients with 17 (45%) requiring corticosteroids and 6 (16%) discontinuing CPI. New onset irAEs occurred in 40 (38%) patients with 22 (55%) requiring corticosteroids and 8 (20%) discontinuing CPI. Grade 3/4 events occurred in 6 (16%) of exacerbations and 13 (33%) of new irAEs. No treatment-related deaths occurred. Median follow-up was 15 months. For RCC, objective response rate (ORR) was 31% (95% CI 20% to 45%), median time to treatment failure (TTF) was 7 months (95% CI 4 to 10) and 12-month overall survival (OS) was 78% (95% CI 63% to 87%). For UC, ORR was 40% (95% CI 26% to 55%), median TTF was 5.0 months (95% CI 2.3 to 9.0) and 12-month OS was 63% (95% CI 47% to 76%).

**Conclusions** Patients with RCC and UC with well-controlled AD can benefit from CPI with manageable toxicities that are consistent with what is expected of a non-AD population. Prospective study is warranted to comprehensively evaluate the benefits and safety of CPI in patients with AD.

## BACKGROUND

Checkpoint inhibitors (CPI) are routinely used across a wide spectrum of cancers types including advanced renal cell cancer (RCC) and urothelial carcinoma (UC).[1 2] A distinctive class of side effects, collectively termed immune-related adverse events (irAEs) akin to physiological autoimmune diseases (AD), has been recognized and are inherent to the mechanism of action potentiating T-cell driven immune responses via the programmed death-1 (PD-1) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4) pathways. While the majority of irAEs are manageable and reversible, some episodes can be severe with rare permanent or fatal outcomes.[2–4] Generally, patients with pre-existing AD have been excluded from clinical trials evaluating CPI given concerns of exacerbating the underlying AD and obfuscating the toxicity profile of the drug.

AD encompass a broad spectrum of diseases resulting from a misdirected immune system attack on self.[3 4] Their prevalence is rising and varies significantly depending on disorder type and geoepidemiological factors; it is estimated that up to 24–50 million North Americans have an AD.[5] Associations between AD and cancer have been described[6] with upwards of 30% of patients with RCC harboring a comorbid AD in one series.[7]

No prospective studies have defined strategies for effectively managing CPI in patients with documented AD, and clinical practice is variable. Given the rarity of CPI use in patients with pre-existing AD and safety

concerns, clinical experience is relatively limited and the literature consists mostly of retrospective series and case reports.[8–15] Recognizing the scarcity of data, we sought to investigate the safety and antitumor activity of CPI in patients with advanced RCC and UC with pre-existing AD across multiple centers to capture real-world evidence.

## METHODS

### Study population

We undertook a multicenter, international retrospective cohort analysis of patients with advanced RCC and UC who had a documented pre-existing AD, received at least one dose of CPI monotherapy or in combination, and who had adequate baseline and on-therapy clinical and imaging data. Each participating center obtained institutional review board approval.

Investigators collected baseline clinicodemographic, pathological, systemic therapy, response and toxicity data via chart review using a uniform database template. AD definitions were based on the American Autoimmune Related Diseases Association; full listing available in online supplementary table 1.[5] All AD symptoms and irAEs were investigator assessed using Common Terminology Criteria for Adverse Events version 5 and recorded from the date of first CPI dose to 90 days after last dose. Baseline AD severity was characterized as historical or clinically active and whether on concurrent immunomodulators. Exacerbations were considered flares of symptoms consistent with underlying AD. New irAEs were defined as development of irAEs not related to the underlying AD. Toxicities leading to treatment discontinuation or necessitating therapeutic intervention were captured. Clinical and radiological assessments were not standardized and were performed according to each center's standard of care. Response was investigator assessed using general Response Evaluation Criteria in Solid Tumors principles.[16] Multidisciplinary care and involvement of the AD specialist during CPI treatment were performed per local practice.

### Statistical analysis

Patient and disease characteristics were described using frequencies (percentages) and medians (ranges). Overall response rate (ORR) was defined as the proportion of patients with complete responses or partial responses and calculated as percentage of patients who achieved ORR along with 95% Clopper-Pearson exact CI. Patients not evaluable for response were conservatively included as non-responders. Time-to-treatment failure (TTF) was determined from CPI initiation until therapy discontinuation for any reason, including progression of disease (PD), toxicity or death. Overall survival (OS) was calculated from CPI initiation until death or last follow-up. Distributions of TTF and OS rates were estimated using the Kaplan-Meier methodology for the overall cohort and by subgroups. No formal comparisons were made for subgroup analyses given the small sample size. Competing risk models estimated cumulative incidences of AD exacerbations and/or new irAEs at 3 months and 6 months, whereas treatment discontinuation due to progression or other reasons without irAE was considered a competing risk. Statistical analyses were performed using SAS V.9.4 (SAS Institute).

## RESULTS

### Baseline characteristics

Across 10 centers in the USA and Europe, 106 patients with documented pre-existing AD and advanced RCC (n=58) or UC (n=48) were identified who were treated with CPI between 2015 and 2018. Most patients received CPI as the first line or second line (n=92; 87%) and as PD(L)-1 inhibitor monotherapy (n=85; 80%) (table 1).[17–19] Dual CPI (anti-PD(L)-1+anti-CTLA-4) were administered in 16% (n=9) of patients with RCC and 2% (n=1) of patients with UC. Eleven (19%) patients with RCC received CPI+vascular endothelial growth factor (VEGF) inhibitor.

A broad spectrum of baseline AD was captured (figure 1). Psoriasis (n=24, 23%), thyroiditis (n=14, 13%), rheumatoid arthritis (n=12, 11%) and polymyalgia rheumatica (n=8, 8%) were most common. Other clinically relevant disorders were identified such as inflammatory bowel diseases (IBD, n=6, 6%), systemic lupus erythematosus (n=4, 4%), multiple sclerosis (n=3, 3%), sarcoidosis (n=2, 2%) and vasculitis (n=2, 2%) including one case[15] of granulomatosis with polyangiitis.

At CPI initiation, 35 (33%) had baseline grade 1/2 AD symptoms including rheumatological (n=15, 14%), dermatological (n=13, 12%), thyroiditis (n=2, 2%), ulcerative colitis (n=2, 2%), multiple sclerosis (n=2, 2%) and IgG4-related sclerosing kidney disease (n=1, 1%) (table 2, online supplementary figure 1). Ten patients required baseline immunosuppression with systemic corticosteroids (n=5) or other immune-modulating agents (one each: hydroxychloroquine, mesalamine, sulfasalazine, teriflunomide and methotrexate).

### AD exacerbations

Globally, 38 (36%) patients experienced an exacerbation of their underlying AD. Median time to exacerbation was 76 days (range: 25–315) for RCC (n=18, 31%) and 33 days (range: 1–368) for UC (n=20, 42%) (figure 2, table 3). The cumulative incidence at 3 and 6 months in the overall cohort was 29% (95% CI 20% to 38%) and 32% (95% CI 23% to 41%), respectively.

Exacerbations occurred most frequently among patients with rheumatological disorders (n=18/36, 50%), followed by dermatological (n=14/32, 44%), neurological (n=1/4, 25%), endocrine (n=5/25, 20%) and gastrointestinal (n=1/6, 17%; online supplementary tables 2–3) and were generally low grade (grade 1/2: n=27, 71%). Six patients (16%) experienced grade 3 exacerbations including arthralgias (n=4), neurological events (neuromuscular weakness, loss of sensation) (n=2),

**Table 1** Clinicodemographic characteristics at baseline

| Baseline characteristics | RCC (n=58) N (%) | UC (n=48) N (%) | Overall (n=106) N (%) |
|---|---|---|---|
| Age | | | |
| Median, years (range) | 66 (25–82) | 72 (47–87) | 68(25-87) |
| Gender | | | |
| Male | 40 (69) | 35 (73) | 75 (71) |
| Female | 18 (31) | 13 (27) | 31 (29) |
| Histology | | | |
| ccRCC | 46 (79) | NA | NA |
| nccRCC | 12 (21) | NA | NA |
| UC* | NA | 47 (98) | NA |
| Non-UC† | NA | 1 (2) | NA |
| ECOG performance status | | | |
| 0 | 21 (36) | 12 (25) | 33 (31) |
| 1 | 29 (50) | 28 (58) | 57 (54) |
| 2–3 | 8 (14) | 8 (17) | 16 (15) |
| RCC IMDC risk group[17] | | | |
| Favorable | 10 (17) | NA | NA |
| Intermediate | 39 (67) | NA | NA |
| Poor | 9 (16) | NA | NA |
| **UC risk group** | | | |
| Platinum-sensitive group: Bajorin criteria[19] | | n=21 | |
| 0 | NA | 5 (24) | NA |
| 1 | NA | 13 (62) | NA |
| 2 | NA | 3 (14) | NA |
| **UC risk group** | | | |
| Platinum-refractory group: Bellmunt criteria[18] | | n=33 | |
| 0 | NA | 2 (6) | NA |
| 1 | NA | 8 (24) | NA |
| 2 | NA | 19 (58) | NA |
| 3 | NA | 4 (12) | NA |
| Number of prior systemic therapies | | | |
| 0 | 20 (34) | 22 (46) | 42 (40) |
| 1 | 26 (45) | 24 (50) | 50 (47) |
| 2 | 4 (7) | 2 (4) | 6 (6) |
| ≥3 | 8 (14) | 0 (0) | 8 (8) |
| Type of CPI regimen | | | |
| PD-1/PD-L1 inhibitor monotherapy | 38 (66) | 47 (98) | 85 (80) |
| PD-1/PD-L1 +CTLA-4 inhibitor | 9 (16) | 1 (2) | 10 (9) |
| PD-1/PD-L1 +VEGF inhibitor | 11 (19) | 0 (0) | 11 (10) |
| Sites of metastases‡ | | | |
| Lymph nodes | 46 (79) | 43 (90) | 89 (84) |
| Lung | 42 (72) | 24 (50) | 66 (62) |
| Bone | 16 (28) | 8 (17) | 24 (23) |
| Liver | 12 (21) | 14 (29) | 26 (25) |
| Brain | 5 (9) | 0 (0) | 5 (5) |

*Includes pure urothelial histology and mixed histology with predominant urothelial component.
†Includes one patient with a small cell bladder tumor.
‡Patients may have had more than one metastatic site.
ccRCC, clear cell renal cell carcinoma; CPI, checkpoint inhibitors; CTLA-4, cytotoxic T lymphocyte associated protein-4; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NA, not applicable; nccRCC, non-clear cell renal cell carcinoma; PD-1, programmed death-1; PD-L1, programmed death ligand-1; RCC, renal cell carcinoma; UC, urothelial carcinoma; VEGF, vascular endothelial growth factor.

myalgia (n=1), and colitis (n=1); 33% had more than one symptom. No grade 4/5 events were observed.

Regarding the impact of baseline symptom status, 40% (n=14/35) of symptomatic and 34% (n=24/71) of asymptomatic patients experienced AD exacerbations. There was a higher cumulative incidence at 3 months among symptomatic patients compared with non-symptomatic patients at baseline: 30% (95% CI 16% to 46%) and 24% (95% CI 14% to 34%), respectively (online supplementary figure 2). A lower exacerbation rate was described among patients treated with single agent CPI: 32% (n=27/85) compared with 52% (n=11/21) treated with combinations. Similar frequencies were observed between dual CPI (n=5/10, 50%) and CPI+VEGF inhibitors (n=6/11, 55%). Of 11 patients who flared on combination therapy, only one patient treated with CPI+VEGF discontinued treatment (both agents). More exacerbations were described among patients receiving baseline immunomodulators (n=5/10, 50%) compared with patients who were not (n=33/96, 35%). Details of the 13 patients with AD of clinical interest such as IBD, neurological and renal disorders, of whom five were symptomatic and three required baseline chronic immunomodulators, are described (online supplementary table 4). Of these, only two patients with ulcerative colitis and Guillain-Barre syndrome experienced exacerbations and both discontinued CPI.

Among the 38 AD exacerbations, immunotherapy was continued in 24 patients (63%) and discontinued in 14 patients (37%): eight (21%) temporarily, six (16%) permanently. AE types leading to discontinuation were arthralgia (n=3), myalgia (n=1), diarrhoea (n=1) and neuropathy (n=1); all were grade 3 except for neuropathy

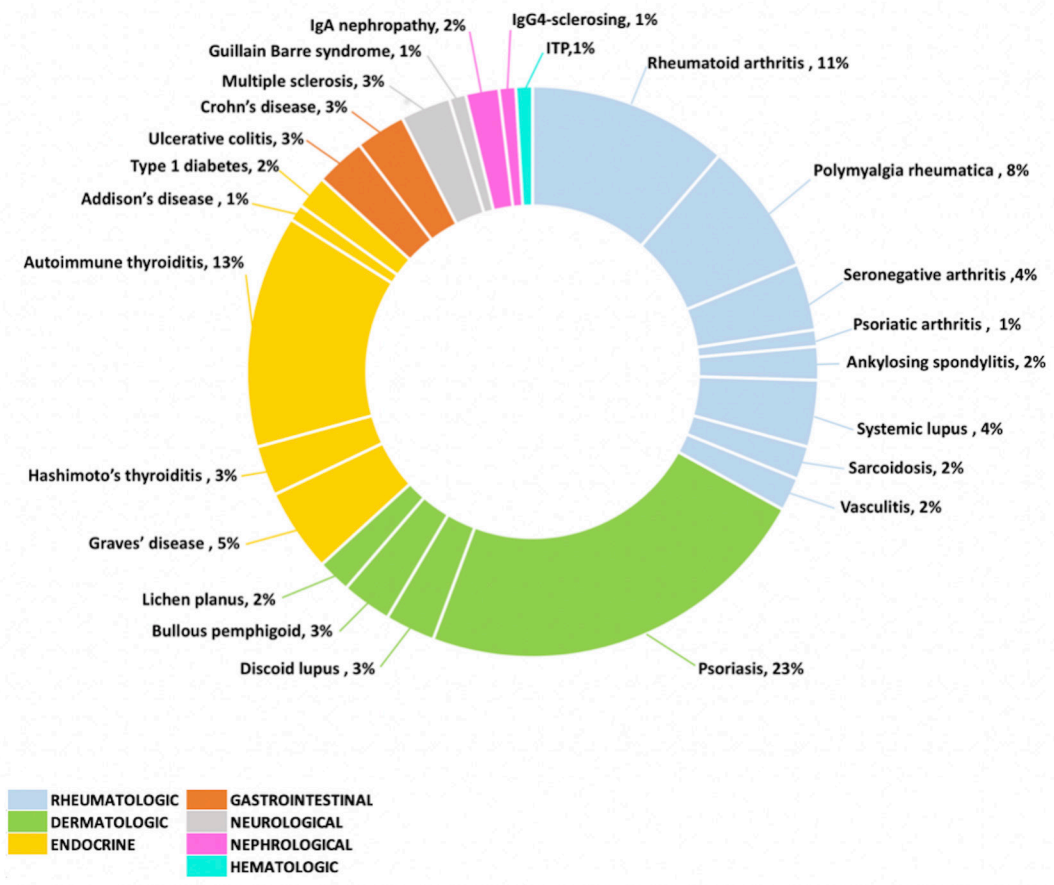


**Figure 1** Autoimmune disorder types at baseline. IgA, Immunoglobulin A; ITP, immune thrombocytopenic purpura.

(unknown grade). Corticosteroids were required in 17/38 (45%) patients, of whom 3 (8%) became steroid refractory: 1 patient was on mesalamine at baseline for ulcerative colitis and 2 required rituximab and methotrexate for granulomatosis with polyangiitis and polymyalgia rheumatica exacerbations, respectively. On analysis, six patients had ongoing exacerbations: one was receiving systemic corticosteroids, two topical corticosteroids, two supportive care and one had discontinued CPI. Ten patients received subsequent non-CPI systemic therapy (online supplementary table 5).

### New onset irAEs (unrelated to primary AD)

New onset irAEs occurred in 40 (38%) patients with pre-existing AD with similar frequencies among the RCC (n=22, 38%) and UC cohorts (n=18, 38%). Median time after CPI initiation was 56 days (range: 2–305) and 120 days (range: 12–443), respectively (table 3, figure 2). The cumulative incidence was 22% (95% CI 15% to 30%) at 3 months and 32% (95% CI 23% to 41%) at 6 months in the overall cohort.

The most frequent new irAEs were colitis (n=9, 8%), rash (n=8, 8%) and hypothyroidism (n=7, 7%) (online supplementary table 3). Grade 3 events occurred in 12 patients (30%) including colitis (n=4), nephritis (n=2), adrenal insufficiency (n=1), hypophysitis (n=1), arthritis (n=1), pneumonitis (n=1), rash (n=1) and hepatitis (n=1). One patient developed grade 4 hepatitis. No grade 5 irAEs occurred.

Of the 40 patients who developed new irAEs, 22 (55%) received corticosteroids with only one steroid-refractory case of grade 3 colitis requiring infliximab. CPI was discontinued in 22 (55%) patients: 14 (35%) temporarily and 8 (20%) permanently. The AEs types necessitating permanent discontinuation were colitis (n=3), pneumonitis (n=3), adrenal insufficiency (n=1) and rash (n=1); all events were grade 3 with the exception of one unknown grade pneumonitis. On analysis, 11 (28%) patients had an ongoing but resolving irAE and 27 (68%) had experienced complete resolution.

### Risk of any AD exacerbation and/or new irAE

The cumulative incidence of AD exacerbation and/or new irAE was 45% (95% CI 35% to 54%) and 53% (95% CI 43% to 62%) at 3 and 6 months, respectively (online supplementary figure 2) with 16 (15%) patients developing both event types (AD exacerbation and new irAE; figure 2). There was a slightly higher rate of AD exacerbations in patients who also developed a new irAE (n=16/40, 40%) compared with those who experienced only AD exacerbation (n=24/68, 35%). Similarly, risk for a new irAE was higher in patients who also experienced an AD exacerbation (n=16/38, 42%) compared with patients who had a new irAE but no AD exacerbation (24/68,

**Table 2** Autoimmune disorders (AD) symptoms and management at baseline

| Characteristic | RCC (n=58) N (%) | UC (n=48) N (%) | Overall (n=106) N (%) |
|---|---|---|---|
| AD symptoms | | | |
| Asymptomatic | 41 (71) | 30 (63) | 71 (67) |
| Symptomatic | 17 (29) | 18 (38) | 35 (33) |
| Severity of baseline AD symptoms* | | | |
| Grade 0 (asymptomatic) | 41 (71) | 30 (63) | 71 (67) |
| Grade 1 | 13 (22) | 13 (27) | 26 (25) |
| Grade 2 | 3 (5) | 3 (6) | 6 (6) |
| Grade 3–4 | 0 (0) | 0 (0) | 0 (0) |
| Unknown | 1 (2) | 2 (4) | 3 (3) |
| Concurrent AD treatment at CPI initiation | | | |
| Topical corticosteroids | 1 (2) | 2 (4) | 3 (3) |
| Systemic corticosteroids | 2 (3) | 3 (6) | 5 (5) |
| Immunomodulatory agents† | 4 (7) | 1 (2) | 5 (5) |

*Only the worst grade for the same symptom is captured.
†Five patients received one of the following treatments: hydroxychloroquine (rheumatoid arthritis), mesalamine (ulcerative colitis), sulfasalazine (ulcerative colitis), teriflunomide (multiple sclerosis) and methotrexate (psoriatic arthritis).
CPI, checkpoint inhibitor; RCC, renal cell carcinoma; UC, urothelial carcinoma.

35%). At time of analysis, the new irAE had resolved or was controlled in all 16 patients and the AD exacerbation in 14 patients. Two patients with symptomatic AD exacerbations (arthralgias and hypothyroidism) were still receiving CPI and supportive treatment for grade 1 events. CPI was permanently discontinued in five patients due to the new irAE and in two due to AD exacerbation.

### Clinical outcomes

For the RCC cohort, ORR was 31% (95% CI 20% to 45%) including four CRs. Five non-evaluable patients were included as non-responders. Median follow-up was 13 months (range: 1–52). Forty-one (71%) discontinued treatment because of radiological/clinical progression (n=30, 73%), toxicity (n=6, 15%) or physician choice (n=5, 12%). Median TTF was 7 months (95% CI 4 to 10) with 1-year OS of 78% (95% CI 63% to 87%; online supplementary figure 3).

For the UC cohort, ORR was 40% (95% CI 26% to 55%) with six CRs. The eight non-evaluable patients were included as non-responders. Median follow-up was 15 months (range: 1–53). CPI was discontinued in 41 (85%) patients due to PD (n=18, 44%), toxicity (n=10, 24%), physician choice (n=7, 17%), patient choice (n=3, 7%),and therapy completion (n=3, 7%). Median TTF was 5 months (95% CI 2 to 9) with 1-year OS of 63% (95% CI 47% to 76%; online supplementary figure 3).

Subgroup analysis across RCC and UC by baseline symptom status, treatment lines and types of treatment was analyzed with no significant differences (table 4).

## DISCUSSION

Leveraging a large international collaboration, we captured real-world evidence of the safety profile and efficacy of CPI in RCC and UC patients with pre-existing AD. Based on pivotal trials showing significant improvements in ORR and OS, CPI are now broadly employed in advanced RCC and UC to treat both treatment-naïve and previously treated disease.[20–24] To minimize the risk of heightened treatment-related toxicity, most prospective studies excluded patients with pre-existing AD. There is a meager although growing literature mostly comprised cases series and retrospective experiences of CPI in patients with AD with melanoma or non-small cell lung cancer (NSCLC) which describe rates of irAEs ranging from 23% to 42%.[8–12] To our knowledge, we report the largest series of the CPI administration in patients with pre-existing AD and specifically evaluate patients with urological cancer. In our study, the rates of AD exacerbations and new irAEs were similar at 36% and 38%, respectively, and in line with the reported melanoma and NSCLC series.

While irAEs can develop at any time, including after CPI cessation, they generally appear within the first few weeks to months.[3] In our AD cohort, the median time to development of an irAE was <3 months from CPI initiation and similar in time frame, 61 and 68 days, across the two cancers. In phase 3 RCC and UC studies evaluating single agent CPIs, irAE were generally reversible with grade 3/4 events ranging from 15% to 19% and treatment discontinuation due to toxicity in 6%–8%.[20 21] In our analyses, toxicity severity was comparable for AD exacerbations with 16% being grade 3/4. However, we observed higher rates of new irAEs (33% grade 3/4) and CPI interruption (16% for AD exacerbations, 20% for new irAEs) than the phase 3 studies. Corticosteroid use was similar for exacerbations and new irAEs (45% vs 55%) in our series.

Our intensive chart review permitted evaluation of detailed information on subset populations. CPI combinations are standard of care in treatment-naïve patients with RCC resulting in higher rates of irAEs, but also higher efficacy than monotherapy. In our series, while combinations induced more AD exacerbations or new irAEs, only one patient permanently discontinued anti-PD-L1+VEGF due to polymyalgia rheumatica exacerbation. More frequent exacerbations were seen among those with clinically active AD at baseline and in patients receiving chronic immunosuppressants. With respect to ADs of clinical concern, such as neurological (eg, multiple sclerosis, Guillain-Barré syndrome) or IBD, exacerbations did not appear more frequent but perhaps were more aggressive as most resulted in CPI discontinuation (online supplementary table 4),[15] although this latter finding could be biased by physician comfort level and experience.

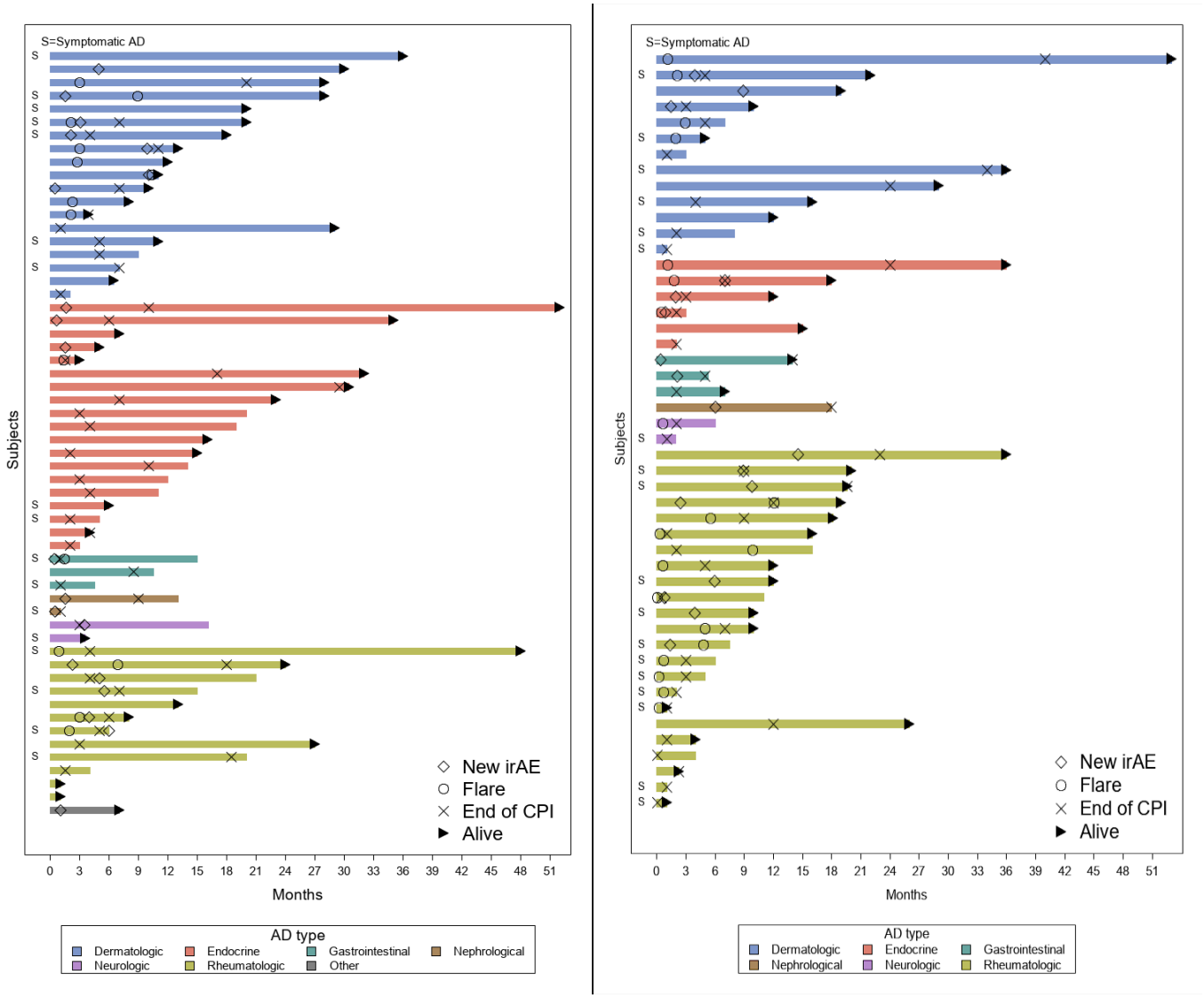


**Figure 2** Swimmers plot denoting time on checkpoint inhibitors (CPI) treatment in patients with (A) renal cell carcinoma and (B) urothelial carcinoma with pre-existing autoimmune disorder (AD) with time to onset of AD exacerbation and/or new immune-related adverse event (irAE) and time of CPI discontinuation.

Robust clinical activity was observed in our AD cohort. One hypothesis is that CPI may have greater efficacy in patients with AD (especially those not on immune suppression) due to a propensity for immune stimulation.[1 2] However, in the Dana-Farber single institution experience evaluating CPI in 52 patients with AD (11%) compared with a control cohort of 442 patients without AD, we did not find statistically significant differences in the cumulative incidence of new irAEs at 6 months (55% vs 37%, p=0.69 for RCC; 33% vs 27%, p=0.64 for UC, respectively, for AD and non-AD) or in efficacy outcomes.[25] Toxicity was generally mild and manageable in this asymptomatic or mildly symptomatic AD population at baseline. Another retrospective study of patients with different solid tumors, mostly NSCLC and melanoma, treated with PD-1 inhibitors compared the incidence of irAEs in patients with pre-existing AD (n=85) to a control cohort without AD (n=666).[14] While incidence of any grade irAEs was higher in patients with AD (66% vs 40%) with a significant rate of AD exacerbations (47%), there was no difference in survival outcomes. However, multiple pooled analyses of non-AD patients with a variety of solid tumors support enhanced checkpoint blockade efficacy in patients who experience irAEs.[26–28]

Clinical experiences capturing real-world evidence in patients who are under-represented in clinical trials are critical to optimize CPI management in these populations. The SAUL (NCT02928406) study prospectively evaluated atezolizumab in patients with metastatic urinary tract tumors and complex comorbidities who are often excluded from the pivotal trials.[29] Only 35 patients with AD were included, and degree of AD severity was limited (most frequent was psoriasis, n=15). Investigators described consistent efficacy, more common treatment-related AEs (69%) but low rates of treatment discontinuation (9%). To our knowledge, our series of 106 patients is

**Table 3** Characteristics and management of autoimmune disorder (AD) exacerbations and new immune-related adverse events (irAEs) on checkpoint inhibitors (CPI)

| | RCC | | UC | | Overall | |
|---|---|---|---|---|---|---|
| | AD flare | New irAE | AD flare | New irAE | AD flare | New irAE |
| **In all patients** | (n=58) | | (n=48) | | (n=106) | |
| Total events, N (%) | 18 (31%) | 22 (38%) | 20 (42%) | 18 (38%) | 38 (36%) | 40 (38%) |
| Cumulative incidence, % (95% CI) | | | | | | |
| At 3 months | 21 (11 to 33) | 22 (12 to 34) | 31 (19 to 45) | 17 (8 to 29) | 29 (20 to 38) | 22 (15 to 30) |
| At 6 months | 21 (11 to 33) | 34 (21 to 47) | 38 (24 to 52) | 26 (14 to 39) | 32 (23 to 41) | 32 (23 to 41) |
| **In patients with irAE** | (n=18) | (n=22) | (n=20) | (n=18) | (n=38) | (n=40) |
| Median time from CPI start to event, days (range) | 76 (25–315) | 56 (2–305) | 33 (1–368) | 120 (12–443) | 61 (1–368) | 68 (2–443) |
| Severity of symptoms*, N (%) | | | | | | |
| Grade 1 | 6 (33%) | 7 (32%) | 2 (10%) | 3 (17%) | 8 (21%) | 10 (25%) |
| Grade 2 | 7 (39%) | 8 (36%) | 12 (60%) | 7 (39%) | 19 (50%) | 15 (38%) |
| Grade 3–4 | 2 (11%) | 7 (32%) | 4 (20%) | 6 (33%) | 6 (16%) | 13 (33%) |
| Unknown | 3 (17%) | 0 (0%) | 2 (10%) | 2 (11%) | 5 (13%) | 2 (5%) |
| Received topical corticosteroids, N (%) | | | | | | |
| Yes | 9 (50%) | 0 (0%) | 3 (15%) | 2 (6%) | 12 (32%) | 2 (5%) |
| No | 9 (50%) | 22 (100%) | 17 (85%) | 16 (94%) | 26 (68%) | 38 (95%) |
| Received systemic corticosteroids, N (%) | | | | | | |
| Yes | 5 (28%) | 11 (50%) | 12 (60%) | 11 (61%) | 17 (45%) | 22 (55%) |
| No | 13 (72%) | 11 (50%) | 8 (40%) | 7 (39%) | 21 (55%) | 18 (45%) |
| Received immunomodulatory agents†, N (%) | | | | | | |
| Yes | 1 (6%) | 0 (0%) | 1 (5%) | 0 (0%) | 2 (5%) | 0 (0%) |
| No | 17 (94%) | 22 (100%) | 19 (95%) | 18 (100%) | 36 (95%) | 40 (100%) |
| CPI management, N (%) | | | | | | |
| Continued | 13 (72%) | 11 (50%) | 11 (55%) | 7 (39%) | 24 (63%) | 18 (45%) |
| Temporarily discontinued | 3 (17%) | 8 (36%) | 5 (25%) | 6 (33%) | 8 (21%) | 14 (35%) |
| Permanently discontinued | 2 (11%) | 3 (14%) | 4 (20%) | 5 (28%) | 6 (16%) | 8 (20%) |
| irAE outcome‡, N (%) | | | | | | |
| Ongoing but controlled | 7 (39%) | 6 (27%) | 12 (60%) | 5 (28%) | 19 (50%) | 11 (28%) |
| Ongoing but uncontrolled | 3 (17%) | 0 (0%) | 3 (15%) | 0 (0%) | 6 (16%) | 0 (0%) |
| Resolved | 8 (44%) | 16 (73%) | 5 (25%) | 11 (61%) | 13 (34%) | 27 (68%) |
| Unknown | 0 (0%) | 0 (0%) | 0 (0%) | 2 (11%) | 0 (0%) | 2 (5%) |

*Only the worst grade for the same symptom is captured. No grade 5 events occurred.
†Two patients received one of the following treatments: methotrexate (polymyalgia rheumatica), rituximab (granulomatosis with polyangiitis).
‡Controlled was defined as a now asymptomatic adverse event still requiring immunosuppression agents. Uncontrolled was defined as an irAE that was still symptomatic at the time of the analysis.
RCC, renal cell carcinoma; UC, urothelial carcinoma.

the largest to provide real-world evidence highlighting the potential benefit and tolerability of CPI among patients with urological cancer with well-controlled, pre-existing AD. It highlights the moderate risk of AD exacerbations and new irAEs, especially in patients with active conditions at baseline or in those receiving CPI combinations. However, irAEs tended to be low grade, manageable with corticosteroids and <20% required treatment discontinuation. Prospective efforts to elucidate the interplay between AD and enhanced risk of CPI toxicity are underway such as studies evaluating nivolumab in patients with pre-existing AD (NCT03656627, NCT03816345).

In the absence of consensus guidelines for the relatively large population with pre-existing AD and as we await prospective results, retrospective real-world evidence can provide reassurance that CPI generally can be administered safely and that patients with well-controlled AD should not be denied the potential significant clinical

**Table 4** Efficacy outcomes: subset analyses based on autoimmune disorder (AD) baseline symptom status, treatment line and type of treatment

| | ORR | | | TTF | | OS | |
|---|---|---|---|---|---|---|---|
| | Total | N | % (95% CI) | No of events | Median TTF, months (95% CI) | No of events | 12-month OS rate, % (95% CI) |
| **RCC** | | | | | | | |
| Overall | 58 | 18 | 31 (20 to 45) | 41 | 7 (4 to 10) | 21 | 78 (63 to 87) |
| Baseline symptomatic | | | | | | | |
| Yes | 17 | 7 | 41 (18 to 67) | 12 | 7 (2 to 19) | 8 | 68 (40 to 86) |
| No | 41 | 11 | 27 (14 to 43) | 29 | 7 (4 to 10) | 13 | 82 (63 to 91) |
| Treatment line | | | | | | | |
| First line | 20 | 10 | 50 (27 to 73) | 14 | 7 (4 to 20) | 3 | 86 (54 to 96) |
| Second line or more | 38 | 8 | 21 (10 to 37) | 27 | 6 (3 to 9) | 18 | 73 (55 to 85) |
| Type of treatment | | | | | | | |
| Anti-PD-1/PD-L1 | 38 | 8 | 21 (10 to 37) | 25 | 7 (4 to 11) | 16 | 74 (55 to 85) |
| Anti-PD-1/PD-L1 +anti-CTLA-4 | 9 | 2 | 22 (3 to 60) | 6 | 6 (2 to 10) | 1 | 100 |
| Anti-PD-1/PD-L1 +anti-VEGF | 11 | 8 | 73 (39 to 94) | 10 | 5 (4 to 18)* | 4 | 82 (45 to 95) |
| **UC** | | | | | | | |
| Overall | 48 | 19 | 40 (26 to 55) | 41 | 5 (2 to 9) | 18 | 63 (47 to 76) |
| Baseline symptomatic | | | | | | | |
| Yes | 18 | 5 | 28 (10 to 53) | 14 | 4 (1 to 20) | 8 | 49 (23 to 71) |
| No | 30 | 14 | 47 (28 to 66) | 27 | 5 (2 to 12) | 10 | 71 (51 to 85) |
| Treatment line | | | | | | | |
| First line | 22 | 8 | 36 (17 to 59) | 17 | 5 (2 to 9) | 6 | 69 (43 to 85) |
| Second line or more | 26 | 11 | 42 (23 to 63) | 24 | 3 (2 to 12) | 12 | 59 (37 to 76) |

*Reasons of discontinuation among the eight patients who achieved complete response or partial response: toxicity (n=3), physician choice (n=2), progressive disease (n=2) and unknown (n=1).
CTLA-4, cytotoxic T lymphocyte associated protein-4; irAE, immune-related adverse event; ORR, overall response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand-1; RCC, renal cell carcinoma; TTF, time-to-treatment failure; UC, urothelial carcinoma; VEGF, vascular endothelial growth factor.

benefit. Further study is needed to confirm these findings and extend the experience to more symptomatic or severe cases or disorders not captured in our study that may be more clinically risky. Until then, we recommend carefully weighing the risk/benefit ratio with the patient, designing a thoughtful multidisciplinary monitoring strategy, and developing a proactive treatment plan in concert with the AD subspecialist in anticipation of exacerbations.

Limitations of our study included the retrospective nature with potential selection bias of patients with generally well-controlled, non-life-threatening AD. However, inclusion of a heterogeneous population with different types of immunotherapy and lines of treatment also enhances the generalizability of our results. Patients with more severe and rare types of AD were under-represented. Most AD patients at CPI initiation were asymptomatic or mildly symptomatic, with good performance status and not on immunosuppression. Nevertheless, the population included is representative of that commonly seen in clinical practice, and patients with severe AD treated with multiple biological therapies or who have life-threatening diseases would need a highly personalized multidisciplinary approach that is unlikely to be captured in even in the ongoing prospective studies. Despite this being the largest series yet reported, relatively short follow-up and small numbers limited the assessment of delayed AEs as well as safety and efficacy by prognostic risk and treatment subgroups. The study lacked central radiographic review, which may have impacted response assessment. TTF was employed rather than progression free survival as a metric that better reflects real-world practice given that treatment discontinuation generally encompasses toxicity, tolerability and subjective physician judgment of clinical benefit in addition to progressive disease.

## CONCLUSIONS

Patients with RCC and UC with well-controlled AD can benefit from CPI and experience manageable toxicities

that are consistent with what is expected of a non-AD population. Research collaborations and support of prospective clinical trials including more severe AD types are warranted to evaluate clinical outcomes and the risk–benefit profile in this understudied population. In the absence of available prospective data, our real-world evidence study supports the cautious use of CPI across the AD spectrum with close monitoring and proactive multidisciplinary care in concert with the AD specialist.

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