

APPENDIX

APPENDIX FIGURES:

1. Types of autoimmune disease symptoms at baseline.
2. Cumulative incidence (solid line) of AD exacerbations at 3-month benchmark by cancer type (A) and baseline symptomatic status (B) with treatment discontinuation due to progression or other reasons without an irAE event as competing events (dotted line). Cumulative incidence (solid line) of new irAEs (C) and AD exacerbation or new irAE (D) at 6-month benchmark by cancer type with treatment discontinuation due to progression or other reasons without an irAE event as competing events (dotted line). 95% confidence intervals were provided for 3- or 6-month cumulative incidence estimates.
3. TTF and OS by cancer type.

Figure 1: Types of autoimmune disease symptoms at baseline.

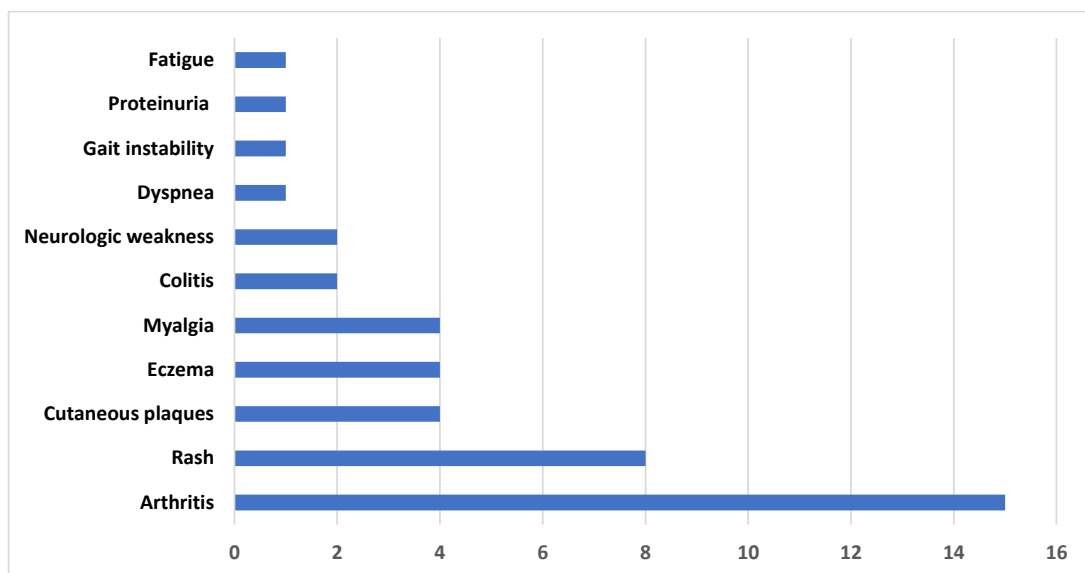
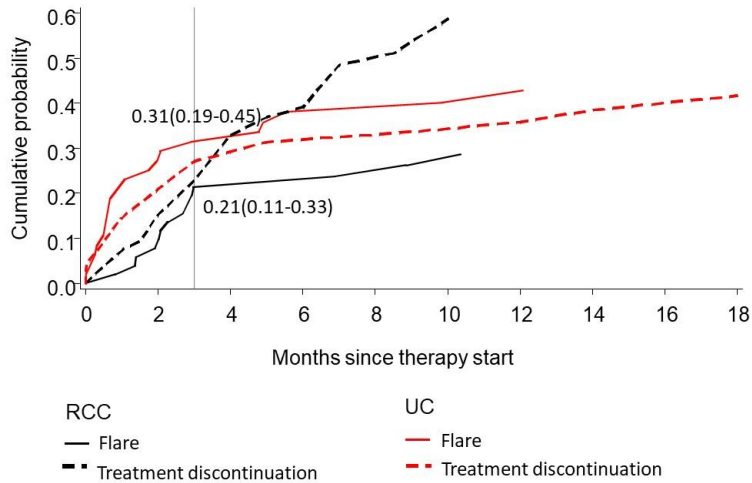
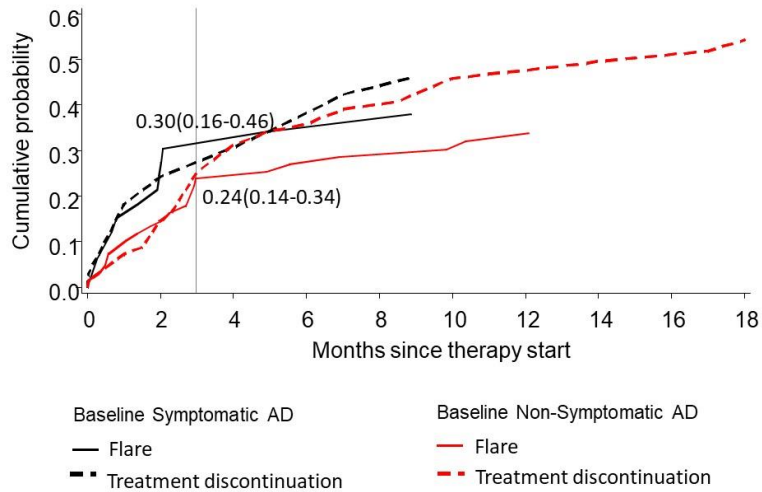


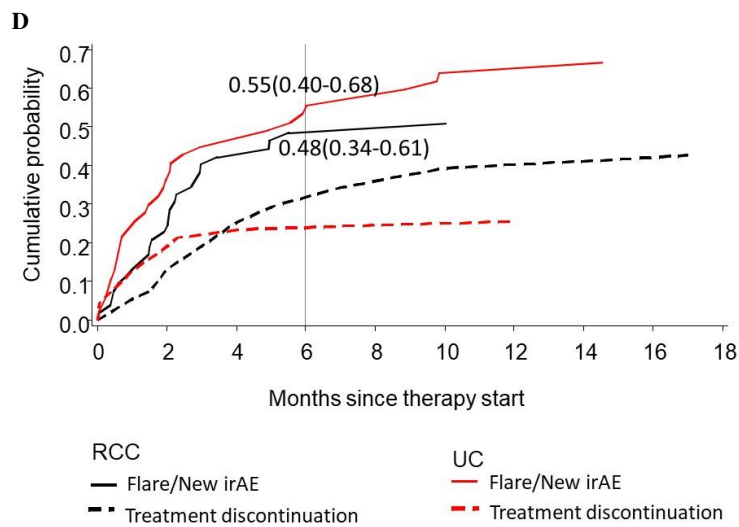
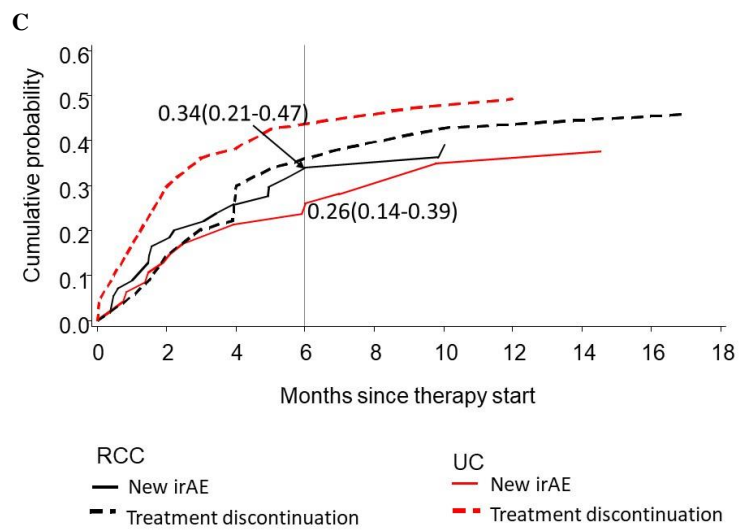
Figure 2: Cumulative incidence (solid line) of AD exacerbations at 3-month benchmark by cancer type (A) and baseline symptomatic status (B) with treatment discontinuation due to progression or other reasons without an irAE event as competing events (dotted line). Cumulative incidence (solid line) of new irAEs (C) and AD exacerbation or new irAE (D) at 6-month benchmark by cancer type with treatment discontinuation due to progression or other reasons without an irAE event as competing events (dotted line). 95% confidence intervals were provided for 3- or 6-month cumulative incidence estimates.

A



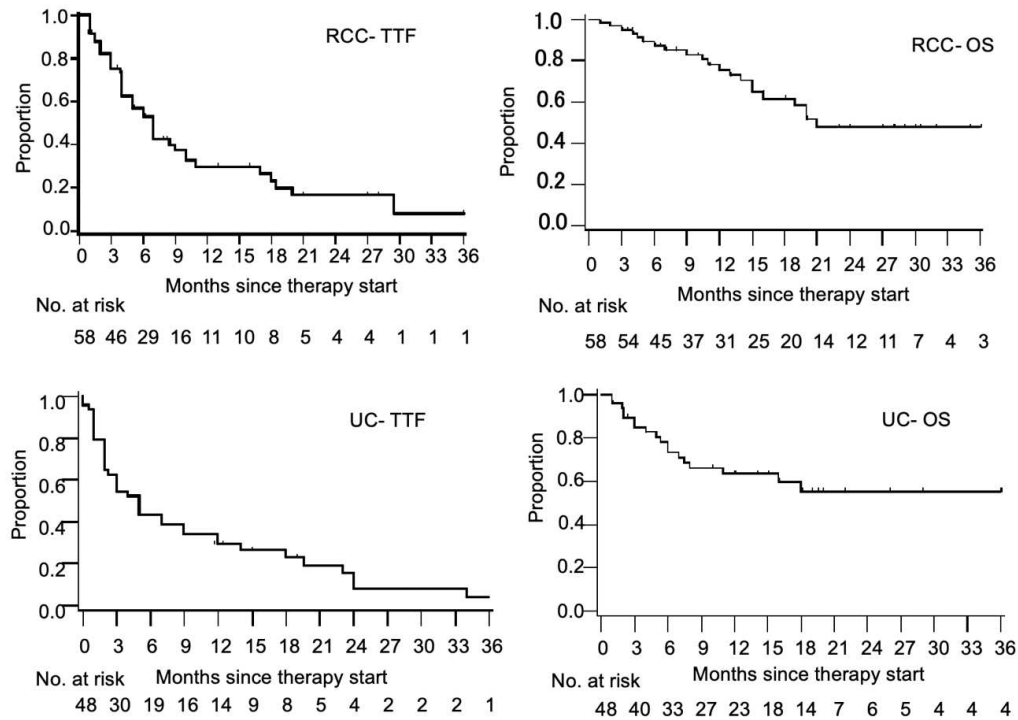
B





Abbreviation – AD: Autoimmune Disorder; RCC: Renal cell carcinoma; UC: Urothelial carcinoma, irAE; immune-related adverse event

Figure 3: TTF and OS by cancer type.



Abbreviations – TTF: Time to treatment failure; OS: Overall survival; No: Numbers; RCC: Renal cell carcinoma; UC: Urothelial carcinoma.

APPENDIX TABLES:

1. Types of autoimmune disease at baseline.
2. AD exacerbations on CPI by AD type.
3. Types of AD exacerbations and new irAEs on CPI.
4. AD exacerbation in selected clinically significant AD types.
5. Type of subsequent non-CPI systemic treatment after AD exacerbation.
6. List of patients and centers included.

Table 1: Types of autoimmune disease at baseline.

Characteristic	RCC (N = 58) N (%)	UC (N = 48) N (%)	Overall (N = 106) N (%)
AD Types, n (%)			
Rheumatologic	12 (21%)	23 (48%)	35 (33%)
- Rheumatoid arthritis	5 (9%)	7 (15%)	12 (11%)
- Polymyalgia rheumatica	3 (5%)	5 (10%)	8 (8%)
- Seronegative arthritis	1 (2%)	3 (6%)	4 (4%)
- Psoriatic arthritis	1 (2%)	0 (0%)	1 (1%)
- Ankylosing spondylitis	0 (0%)	2 (4%)	2 (2%)
- Systemic lupus erythematosus	0 (0%)	4 (8%)	4 (4%)
- Sarcoidosis	2 (3%)	0 (0%)	2 (2%)
- Vasculitis ¹	0 (0%)	2 (4%)	2 (2%)
Dermatologic	19 (33%)	13 (27%)	32 (30%)
- Psoriasis	17 (29%)	7 (15%)	24 (23%)
- Discoid lupus erythematosus	1 (2%)	2 (4%)	3 (3%)
- Bullous pemphigoid	1 (2%)	2 (4%)	3 (3%)
- Lichen planus	0 (0%)	2 (4%)	2 (2%)
Endocrine	19 (33%)	6 (13%)	25 (24%)
- Graves' disease	3 (5%)	2 (4%)	5 (5%)
- Hashimoto's thyroiditis	3 (5%)	0 (0%)	3 (3%)
- Autoimmune thyroiditis	11 (19%)	3 (6%)	14 (13%)
- Addison's disease	0 (0%)	1 (2%)	1 (1%)
- Type 1 diabetes	2 (3%)	0 (0%)	2 (2%)
Gastrointestinal	3 (5%)	3 (6%)	6 (6%)
- Ulcerative colitis	2 (3%)	1 (2%)	3 (3%)
- Crohn's disease	1 (2%)	2 (4%)	3 (3%)
Neurological	2 (3%)	2 (4%)	4 (4%)
- Multiple sclerosis	2 (3%)	1 (2%)	3 (3%)
- Guillain Barre syndrome	0 (0%)	1 (2%)	1 (1%)
Nephrological	2 (3%)	1 (2%)	3 (3%)
- IgA nephropathy	1 (2%)	1 (2%)	2 (2%)
- IgG4-related sclerosing disease	1 (2%)	0 (0%)	1 (1%)
Hematologic	1 (2%)	0 (0%)	1 (1%)
- Immune thrombocytopenic purpura	1 (2%)	0 (0%)	1 (1%)

¹Vasculitis includes one patient with giant cell arteritis (temporal arteritis) and one patient with granulomatosis with polyangiitis (GPA)

Abbreviations – AD: Autoimmune disorder; RCC: Renal cell carcinoma; UC: Urothelial carcinoma

Table 2: AD exacerbations on CPI by AD type.

AD TYPE	EXACERBATION N
<u>Rheumatologic disorders</u>	<u>18</u>
-Rheumatoid arthritis	4
-Polymyalgia rheumatic	7
-Seronegative arthritis	3
-Psoriatic arthritis	1
-Systemic lupus erythematosus	1
-Giant cell arteritis (temporal arteritis)	1
-Granulomatosis with polyangiitis	1
<u>Dermatologic disorders</u>	<u>14</u>
-Psoriasis	12
-Discoid lupus erythematosus	1
-Bullous pemphigoid	1
<u>Endocrine disorders</u>	<u>5</u>
-Autoimmune thyroiditis	3
-Grave's disease	2
<u>Gastrointestinal disorders</u>	<u>1</u>
-Ulcerative colitis	1
<u>Neurological disorders</u>	<u>1</u>
-Guillain-Barre Syndrome	1

Abbreviations – AD: Autoimmune disorder; CPI: Checkpoint inhibitor

Table 3: Types of AD exacerbations and new irAEs on CPI.

Characteristic	RCC (N = 58) N (%)	UC (N = 48) N (%)	Overall (N = 106) N (%)
AD Exacerbations Types			
Arthritis	6(10)	11(23)	17(16)
Myalgia	2(3)	3(6)	5(5)
Rash	7(12)	3(6)	10(9)
Cutaneous plaques	3(5)	2(4)	5(5)
Eczema	4(7)	3(6)	7(7)
Hypothyroidism	1(2)	0	1(1)
Hyperthyroidism	1(2)	0	1(1)
Adrenal insufficiency	0	0	0
Colitis	1(2)	0	1(1)
Hepatitis	0	0	0
Nephritis	0	0	0
Pneumonitis	0	0	0
Uveitis	0	0	0
Neuropathy	0	4(8)	4(4)
New irAEs Types			
Arthritis	4(7)	2(4)	6(6)
Myalgia	0	0	0
Rash	4(7)	4(8)	8(8)
Cutaneous plaques	0	0	0
Eczema	0	0	0
Hypothyroidism	4(7)	3(6)	7(7)
Hyperthyroidism	0	0	0
Adrenal insufficiency	2(3)	1(2)	3(3)
Colitis	7(12)	2(4)	9(9)
Hepatitis	3(5)	0	3(3)
Nephritis	0	3(6)	3(3)
Pneumonitis	0	4(8)	4(4)
Uveitis	1(2)	0	1(1)
Neuropathy	0	1(2)	1(1)
Hypophysitis	0	1(2)	1(1)

Abbreviations – AD: Autoimmune disorder; CPI: Checkpoint inhibitor, irAE: immune-related adverse event; RCC: Renal cell carcinoma; UC: Urothelial carcinoma

Table 4: Details of AD exacerbation in selected AD of clinical significance.

AD type	Baseline symptoms and CTCAE grade	Baseline immunosuppressive treatment	Type CPI treatment	AD Exacerbation	CTCAE Grade AD Exacerbation	Time to onset of AD Exacerbation symptoms (days)	Treatment for AD Exacerbation symptoms	CPI management
Gastrointestinal disorders								
Crohn's disease	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Crohn's disease	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Ulcerative Colitis	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Ulcerative Colitis	Yes (G1)	Sulfasalazine	PD(L)-1 single agent	No	NA	NA	NA	NA
Crohn's disease	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Ulcerative Colitis	Yes (G2)	Mesalamine	PD(L)-1 single agent	Yes	G3	43	Systemic corticosteroids	Permanently discontinued
Neurological disorders								
Multiple sclerosis	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Multiple sclerosis	Yes (G1)	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Guillain Barre syndrome	No	No	PD(L)-1 single agent	Yes	G3	18	Systemic corticosteroids	Permanently discontinued
Multiple sclerosis	Yes (G2)	Teriflunomide	PD(L)-1 single agent	No	NA	NA	NA	NA
Renal disorders								
IgA nephropathy	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
IgG-related sclerosing disease	Yes (G1)	No	PD(L)-1 single agent	No	NA	NA	NA	NA
IgA nephropathy	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Other								
ITP	No	No	Dual CPI PD(L)-1+ CTLA-4	No	NA	NA	NA	NA
Systemic Lupus	No	No	PD(L)-1 single agent	Yes	G2	150	Systemic corticosteroids	Temporarily discontinued
Systemic Lupus	Yes (G1)	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Systemic Lupus	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Systemic Lupus	Yes (G1)	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Sarcoidosis	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA
Sarcoidosis	No	No	PD(L)-1+ VEGF inhibitor	No	NA	NA	NA	NA
Giant cell arteritis	No	No	PD(L)-1 single agent	Yes	Unknown	368	Systemic corticosteroids	Permanently discontinued
Granulomatosis with polyangiitis [15]	No	No	PD(L)-1 single agent	Yes	G3	10	Systemic corticosteroids and Rituximab	Permanently discontinued
Addison disease	No	No	PD(L)-1 single agent	No	NA	NA	NA	NA

[15] Nabel CS, Severgnini M, Hung YP, et al. Anti-PD-1 Immunotherapy-Induced Flare of a Known Underlying Relapsing Vasculitis Mimicking Recurrent Cancer. *Oncologist*. 2019. doi: 10.1634/theoncologist.2018-0633. [Epub ahead of print]

Abbreviations – AD: Autoimmune disorder; CPI: Checkpoint inhibitor; G: Grade; ITP: immune thrombocytopenic purpura; NA: Not applicable

Table 5: Type of subsequent non-CPI systemic treatment after AD exacerbation.

TYPE SUBSEQUENT TREATMENT	N
RENAL CELL CARCINOMA	
Cabozantinib	3
Pazopanib	1
Clinical Trial	1
UROTHELIAL CARCINOMA	
Platinum-based chemotherapy	3
Clinical Trial ¹	2

¹Including one patient treated with Enfortumab.

Abbreviations – AD: Autoimmune disorder; CPI: Checkpoint inhibitor

Table 6: List of centers and patients included.

INSTITUTION	NUMBER OF PATIENTS INCLUDED
Dana-Farber Cancer Institute [25]	52
The Ohio State University Comprehensive Cancer Center, Columbus, OH	16
Duke Cancer Center, Durham, NC, USA	11
University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA	6
Jules Bordet Institute, Université Libre de Bruxelles, Belgium	5
Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA	4
University of Colorado Cancer Center, Aurora, CO, USA	4
Leuven Cancer Institute, University Hospitals Leuven, Belgium	4
Moore's Cancer Center, UC San Diego, La Jolla, CA, USA	3
Stanford Cancer Institute, Palo Alto, CA, USA	1

[25] Martinez Chanza N, Xie W, Kaymakcalan MD, et al. Safety and efficacy of immune checkpoint inhibitors (CPI) in metastatic renal cell carcinoma (RCC) and urothelial carcinoma (UC) patients (pts) with pre-existing autoimmune disorders (AD). DOI: 10.1200/JCO.2019.37.7_suppl.653 Journal of Clinical Oncology 37, no. 7_suppl (March 1 2019) 653-653