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Cancer Immunotherapy in Practice: Toxicities Associated with Combination Therapies

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1



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Disclosures

- **Consultant:** Astellas; AstraZeneca; Eisai; Exelixis; Janssen, EMD Serono; Dendreon; Pfizer, Seattle Genetics, BMS, Bayer, Guardant Health; Caris Life Sciences
- **Contracted Research:** AstraZeneca, Merck, Caris Life Sciences, ESSA Pharma
- **Research Grant:** BlueEarth Diagnostics, Merck, Exelixis
- **Speaker's Bureau (Unbranded):** Bayer, Caris Life Sciences, Natera, Pfizer, Myovant

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2



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Which of the following statements is true regarding toxicities associated with Combination Therapies

- A. The use of high dose corticosteroids (≥ 40 mg prednisone equivalent) is usually needed in less than 10% of the cases
- B. Treatment-related adverse events are expected usually after 6 months of therapy
- C. Quality of Life assessment is comparable among with different combination regimens
- D. Treatment-related adverse events can happen at any time after initiation of treatment and time to resolution can be very long

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3



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Combination Therapies in GU

- RCC → IO-IO and IO-TKI
- UC → EV-pembrolizumab

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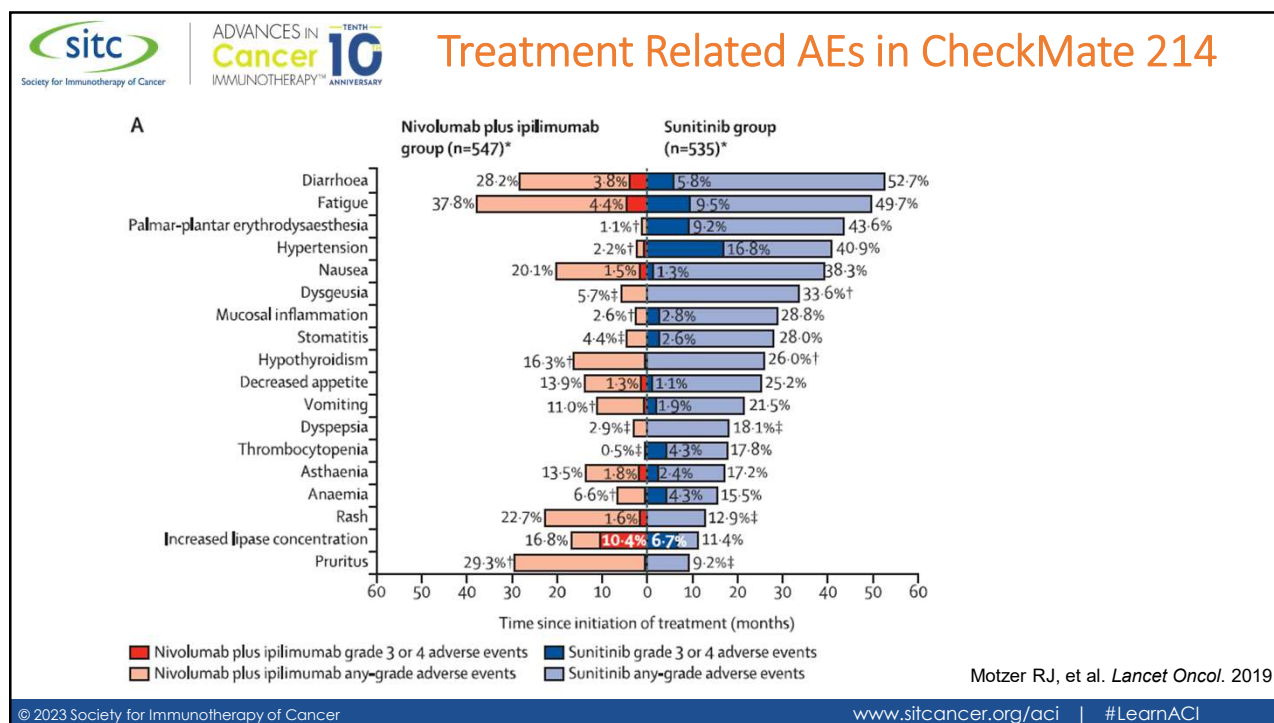
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Front Line Treatment Options in Metastatic RCC

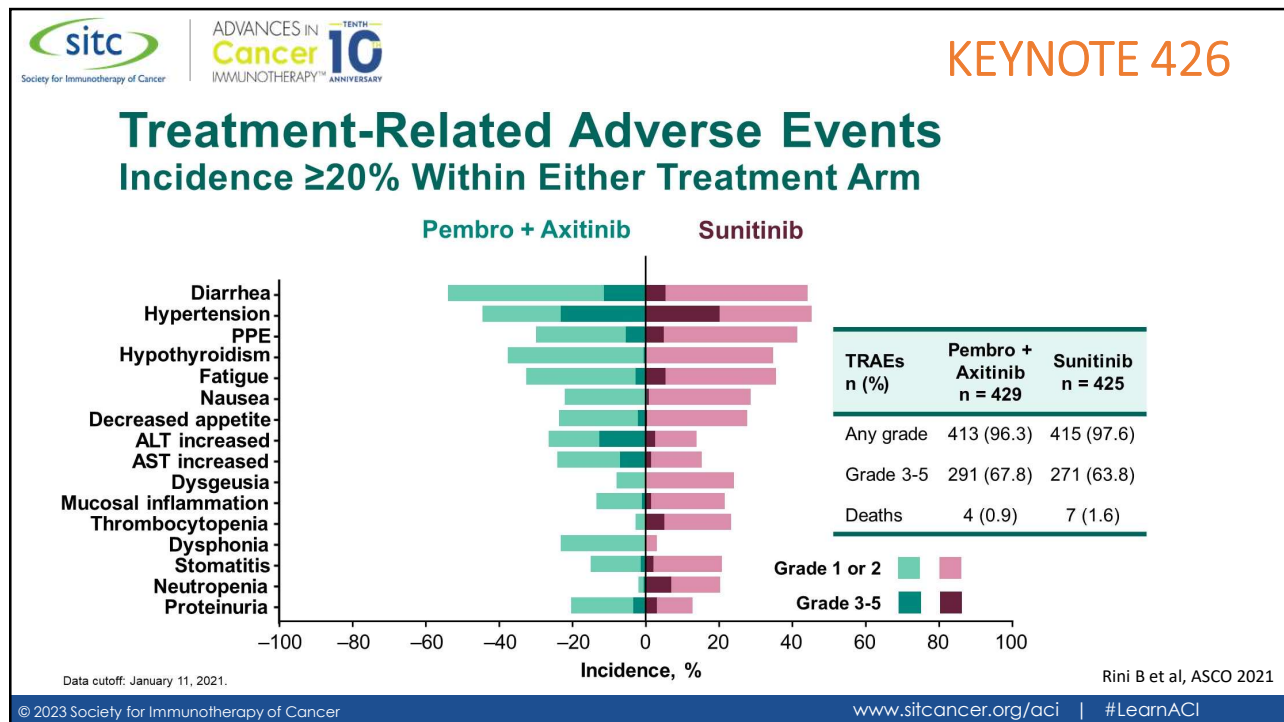
IO-IO	IO-VEGF	VEGF
<ul style="list-style-type: none"> Nivolumab + Ipilimumab 	<ul style="list-style-type: none"> Pembrolizumab + Axitinib Avelumab + Axitinib Nivolumab + Cabozantinib Pembrolizumab + Lenvatinib 	<ul style="list-style-type: none"> Cabozantinib Sunitinib Pazopanib

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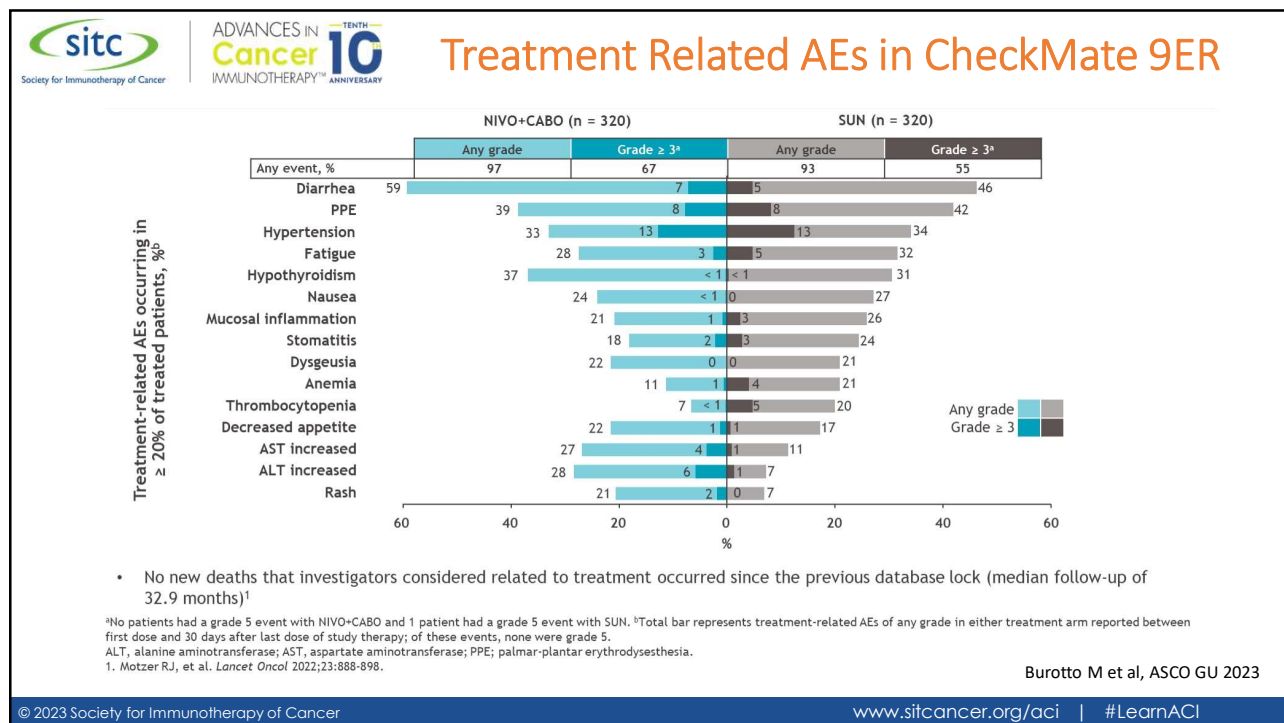
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6

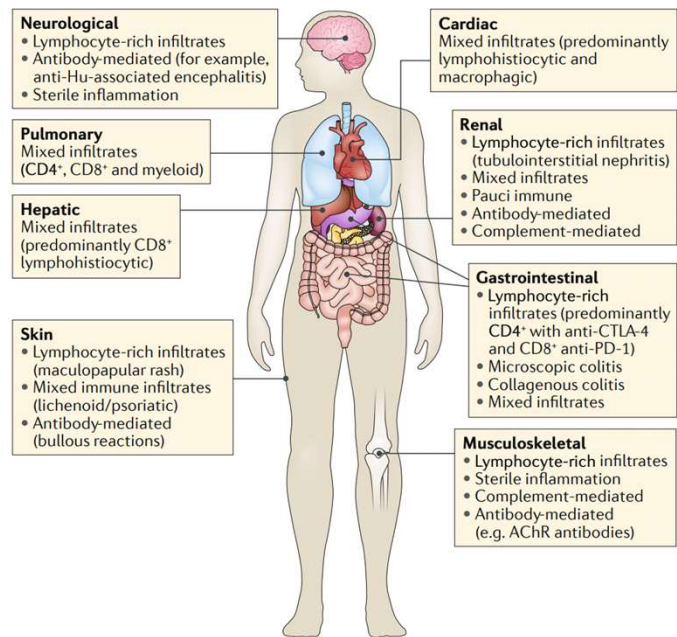


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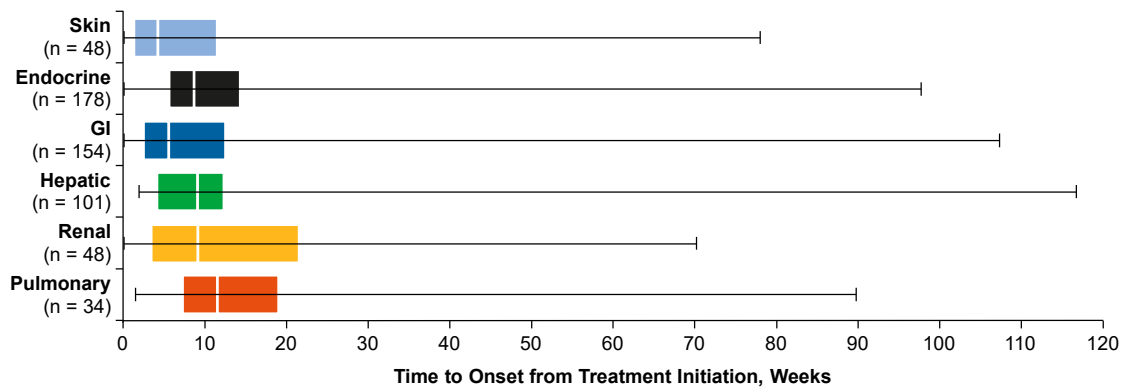
Spectrum of Immune Related AEs



Esfahani K, et al. *Nat Rev Clin Oncol.* 2020;17(8):504-515.

11

Time to Onset of Any-Grade Treatment-Related Select AEs in the N+I Arm



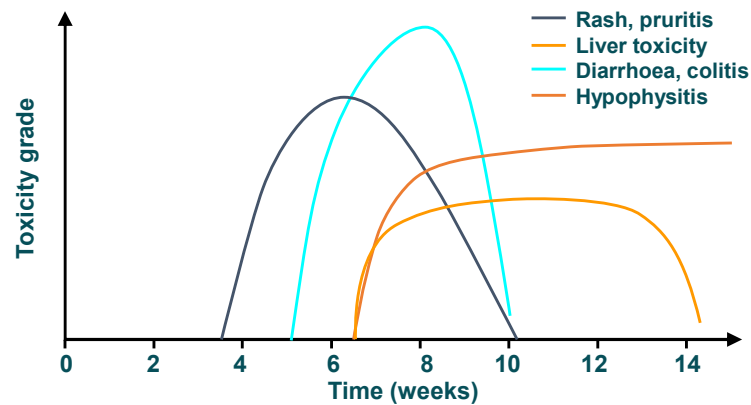
Colored boxes indicate interquartile range (Q1, Q3); center vertical line indicates median; outer vertical lines indicate range (minimum to maximum).

Tannir et al, IKCS 2018.

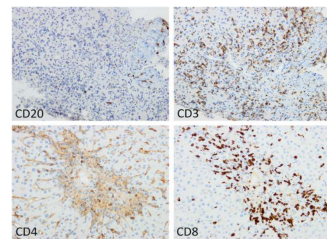
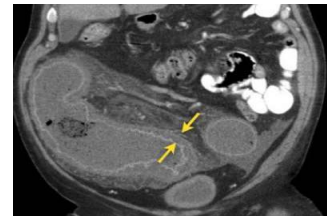
12

Immune Checkpoint Inhibitors: Immune-related Adverse Event (irAE) Onset

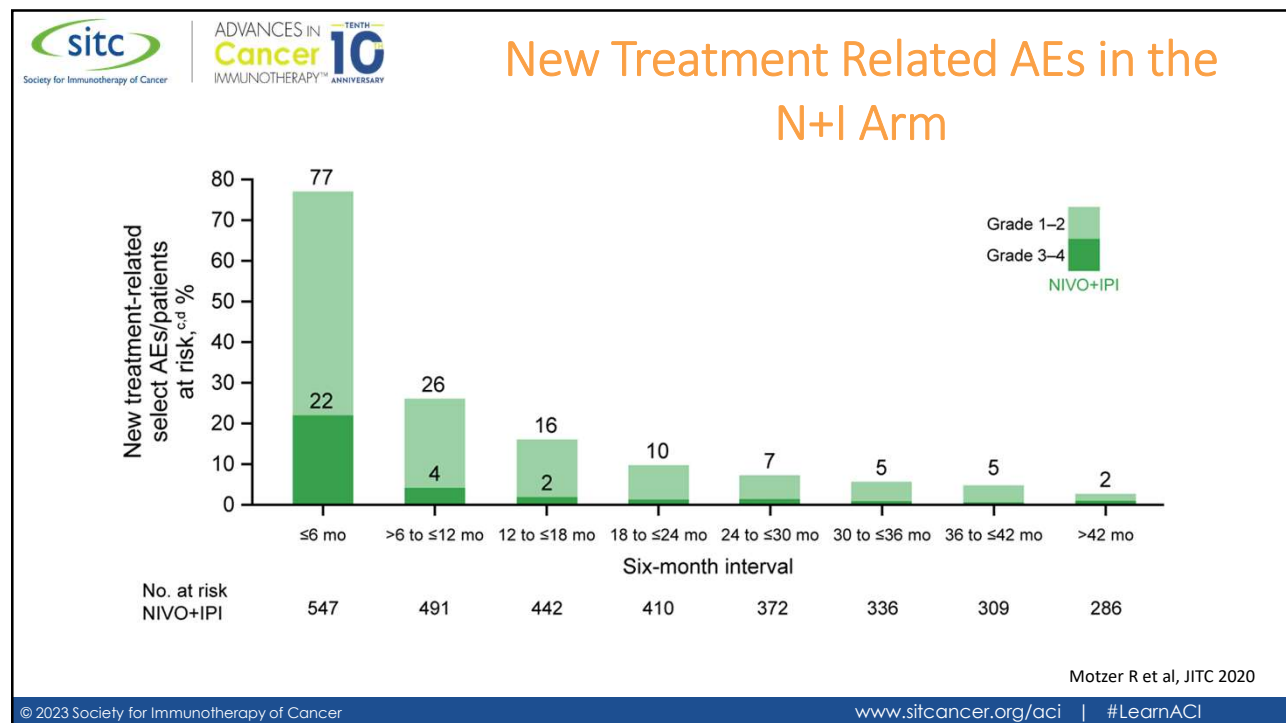
- Each irAE has different kinetics of onset
- Rash first, followed by colitis, hypophysitis and finally hepatitis



Weber JS, et al. *J Clin Oncol.* 2012;30:2691–2697.



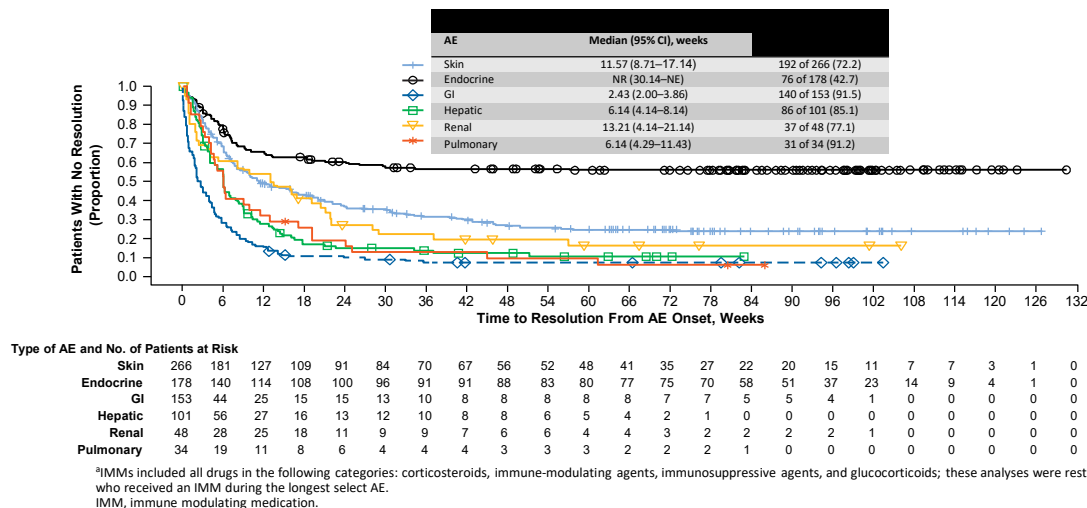
13



14

Time to Resolution of Any-Grade Treatment-Related Select AEs in the N+I Arm

- Of the 436 patients treated with N+I who experienced an any-grade treatment-related select AE, **35%** received high-dose glucocorticoids (≥ 40 mg of prednisone per day or equivalent)

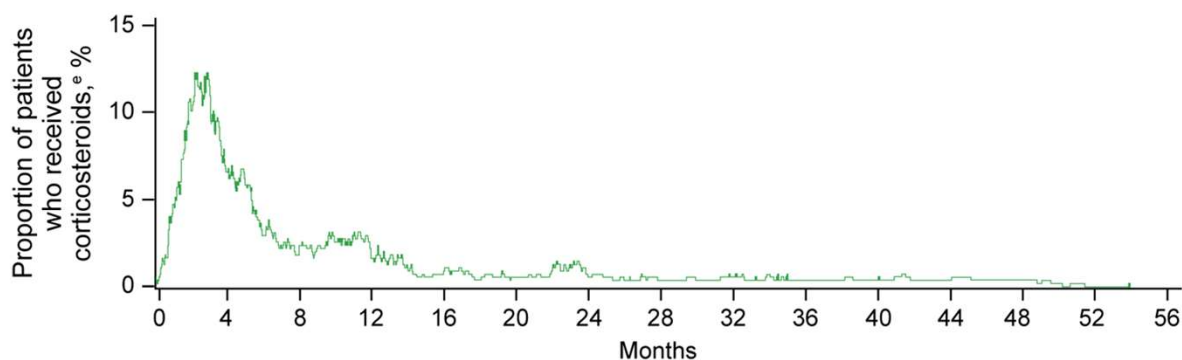


Tannir et al, IKCS 2018.

15



Corticosteroid Use Over Time in the N+I Arm



Motzer R et al, JITC 2020

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16

What about Quality of Life?

	CheckMate-214		Keynote-426		Checkmate-9ER		Clear		
	Nivolumab + Ipilimumab	Sunitinib	Pembrolizumab + Axitinib	Sunitinib	Nivolumab + Cabozantinib	Sunitinib	Pembrolizumab + Lenvatinib	Lenvatinib + Everolimus	Sunitinib
	Intermediate/Poor		All Risk		All Risk		All Risk		
FKSI-19	↑				↑				
FKSI-DRS			=				=/↑	=/↓	
EQ-5D-3L	↑		=		↑		=/↑	=/↓	
EORTC QLQ-C30			=				=/↑	=/↓	
FACT-G	↑								

FKSI-19=Functional Assessment of Cancer Therapy—Kidney Symptom Index; FKSI-DRS=Functional Assessment of Cancer Therapy-Disease related symptoms; EPRTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; FACT-G=Functional Assessment of Cancer Therapy—General.

Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277-1290.

Rini BI, et al. *N Engl J Med.* 2019;380(12):1116-1127.

Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-1115.

Motzer RJ, et al. *N Engl J Med.* 2021;384(14):1289-1300.



17

Quality of Life Evaluation Methodology

- Evaluation uses different instruments in different study patients at different time-points

	CheckMate-214	Keynote-426	Checkmate-9ER	CLEAR
FKSI-19 (19 items)	Q 3 weeks (C1-2) Q 4 weeks (\geq C3)		Q 2 weeks	
FKSI-DRS (15 items)	-	Q 3 weeks (C1-8) Q 6 weeks (C9-18) Q 12 weeks (\geq C19)	-	Q 3 weeks
EQ-5D-3L (5 items / 3 levels)	Q 3 weeks Q 4 weeks (\geq C3)	Q 3 weeks (C1-8) Q 6 weeks (C9-18) Q 12 weeks (\geq C19)	Q 2 weeks	Q 3 weeks
EORTC QLQ-C30 (30 items)	-	Q 3 weeks (C1-8) Q 6 weeks (C9-18) Q 12 weeks (\geq C19)	-	Q 3 weeks
FACT-G (27 items)	Q 3 weeks Q 4 weeks (\geq C3)		-	-

Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277-1290.; Rini BI, et al. *N Engl J Med.* 2019;380(12):1116-1127.

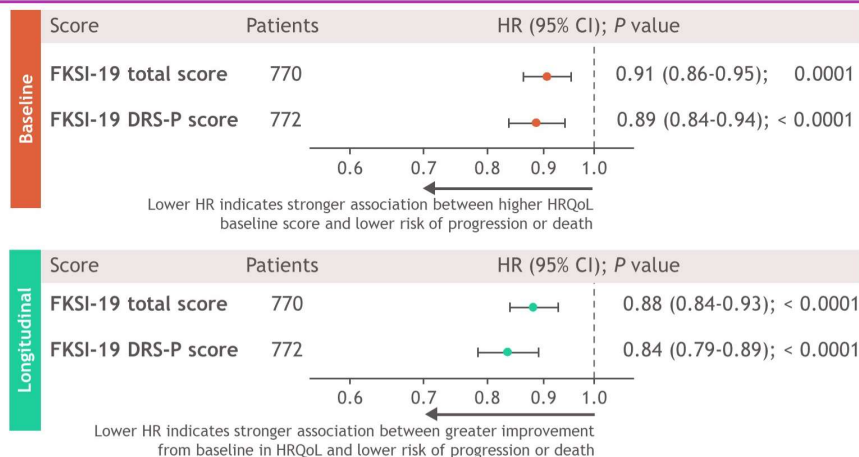
Motzer RJ, et al. *N Engl J Med.* 2019;380(12):1103-1115; Motzer RJ, et al. *N Engl J Med.* 2021;384(14):1289-1300.



18

HRQoL and Clinical Outcomes

Baseline/longitudinal HRQoL scores and Progression-Free Survival



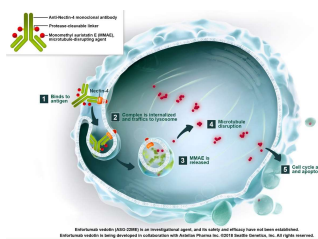
HR is calculated as risk of progression per X-point improvement in HRQoL score; X is defined as 5 points for FKSI-19 total score and 4 points for FKSI-19 DRS-P. CI, confidence interval.

Cella D et al, ASCO 2022

10

19

Enfortumab vedotin + pembrolizumab in advanced urothelial carcinoma (EV-103)



Cohort A
EV + pembro
cis-ineligible
1L


- 93% tumor reduction
- 73.3% ORR
- mPFS – 12.3 months

Treatment-Related Adverse Events (TRAEs)

TRAEs by preferred term	Patients (N=45) n (%)	
	Any Grade ≥20% of patients	≥Grade 3 ≥10% of patients
Overall	43 (96)	26 (58)
Fatigue	22 (49)	4 (9)
Alopecia	22 (49)	–
Peripheral sensory neuropathy	22 (49)	2 (4)
Diarrhea	20 (44)	3 (7)
Decreased appetite	17 (38)	0
Dysgeusia	15 (33)	–
Rash maculo-papular	14 (31)	4 (9)
Nausea	13 (29)	0
Pruritus	13 (29)	1 (2)
Anemia	9 (20)	3 (7)
Weight decreased	9 (20)	0
Lipase increased	8 (18)	8 (18)

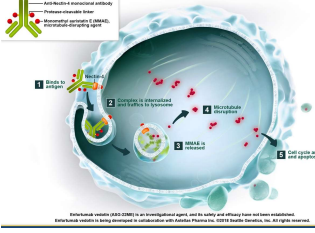
Hoimes C et al, JCO 2023

20



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Enfortumab vedotin + pembrolizumab in advanced urothelial carcinoma (EV-103)



Cohort A
EV + pembro

cis-ineligible 1L

Treatment-Related Adverse Events of Clinical Interest (AECl)


AECl: categorized by related MedDRA terms	Patients (N=45) n (%)		Time to first onset (months) median (min, max)
	Any Grade	≥Grade 3*	
Peripheral neuropathy	25 (56)	2 (4)	2.3 (1, 9)
Rash	28 (62)	6 (13)	0.8 (0, 12)
Hyperglycemia†	5 (11)	3 (7)	0.5 (0, 4)
AECl: determined by investigator			
Immune-mediated AE requiring systemic steroids	13 (29)	8 (18)*	

Hoimes C et al, JCO 2023

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21



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22