Novità diagnostico terapeutiche nel carcinoma renale e prostatico
Campobasso, 19 Settembre 2019

I tumori del rene:

Gestione delle tossicità da TKI e immunoterapia

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Issues

- TKI
  - Sunitinib
  - Pazopanib
  - Axitinib
  - Cabozantinib
- Gestione delle tossicità da TKI
  - Cardiovascolare, ipertensione
  - HFSR
  - Gastrointestinale, epatica

Issues

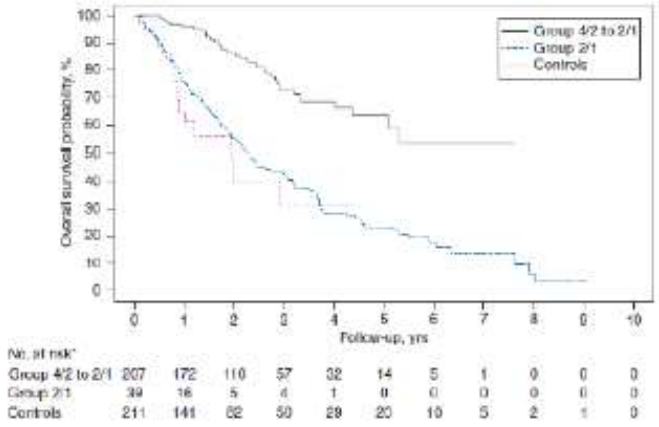
- Immunoterapia
  - Nivolumab
  - Combinazioni
    - Nivolumab/Ipilimumab
- Gestione della tossicità immunocorrelata
  - Polmonare
  - Gastrointestinale/epatica
  - Endocrinopatia
  - Neurologica
  - Renale
  - Cutanea

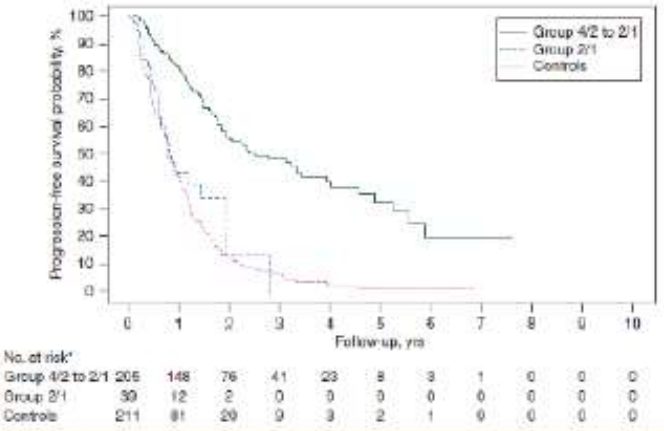
mRCC: Toxicity of TKI and Immunotherapy
Treatment discontinuation due to Adverse Events

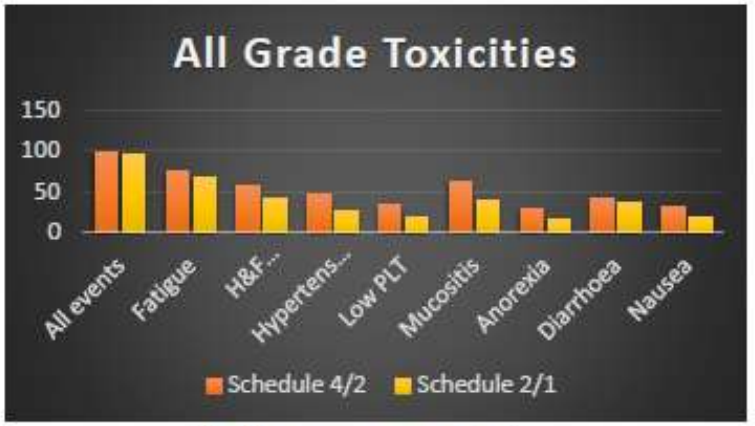
	n. pts	Treatment	Discontinuation due to AEs (%)
Motzer (2007)	375	sunitinib	8
	375	interferon	13
Motzer (2008) Record-1	269	everolimus	10
	135	placebo	2
Sternberg (2010)	290	pazopanib	14
	143	placebo	3
Motzer (2013) COMPARZ trial	548	sunitinib	20
	554	pazopanib	24
Motzer (2013)	361	axitinib	8
	362	sorafenib	14
Motzer (2015) ChekMate-025 trial	410	nivolumab	8
	411	everolimus	13
Choueiri (2016) METEOR	331	cabozantinib	12
	322	everolimus	11
Motzer (2018) CheckMate-214 trial	550	nivolumab/ipilimumab	22
	546	sunitinib	12

Role of old and new TKIs in mRCC

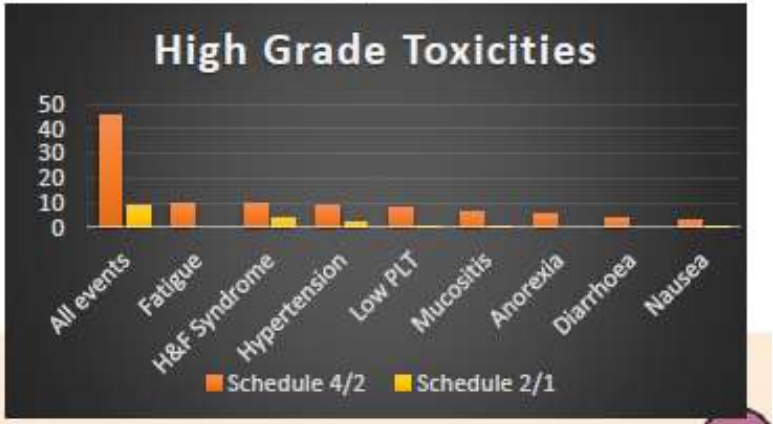
The correct management of toxicities





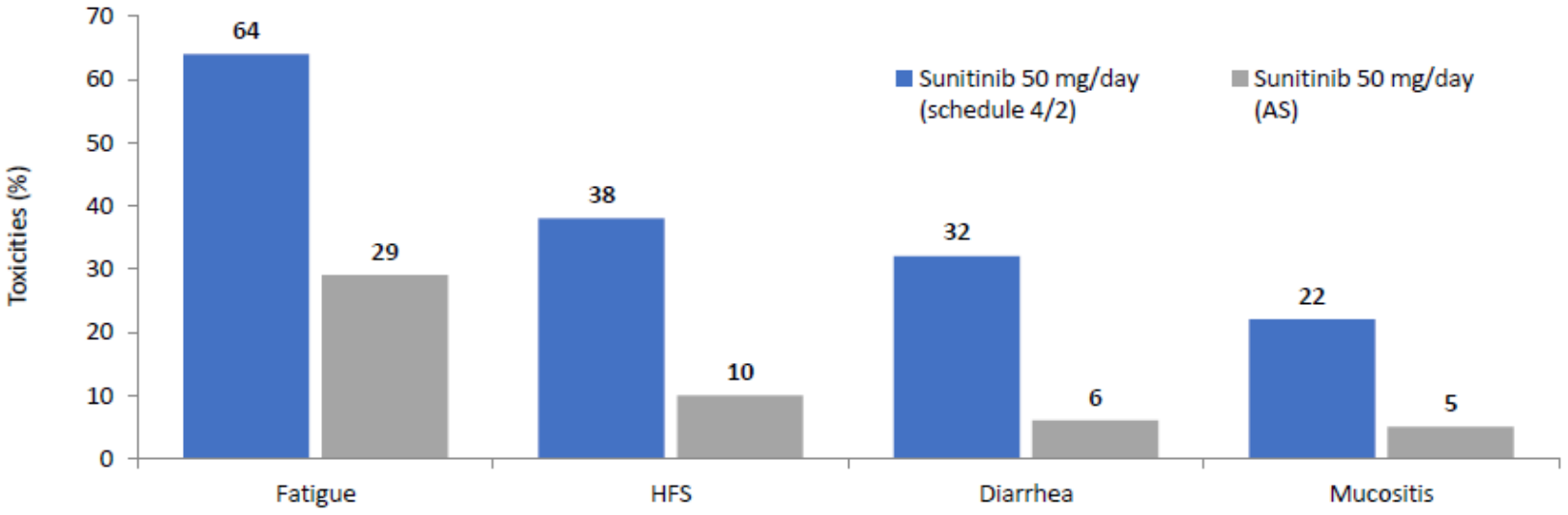


All data are expressed in %



Bracarda et al. Ann Oncol 2015; 26: 2107–2113.

Clinical outcomes for pts with mRCC treated with alternative Sunitinib Schedules



MD Anderson Cancer Center
Madrid • España

Atkinson BJ, et al. J Urol. 2014

Safety

	Pazopanib (n = 554)	Sunitinib (n = 548)
Dose interruptions (≥7 days), %	44	49
Dose reductions, %	44	51
Discontinuations due to AEs, %	24	20

AE = adverse event

Motzer RJ, et al. *N Engl J Med*. 2013;369(8):722-731.

COMPARZ: AEs Affecting ≥30% of Patients in Either Group[1]

	Pazopanib (n=554), %		Sunitinib (n=548), %	
	All grades	Grade 3/4	All grades	Grade 3/4
Any event*	>99	59 / 15	>99	57 / 17
Diarrhoea	63	9 / 0	57	7 / <1
Fatigue	55	10 / <1	63	17 / <1
Thrombocytopaenia	41	3 / <1	78	6 / 0
Hypertension	46	15 / <1	41	15 / <1
Nausea	45	2 / 0	46	2 / 0
Decreased appetite	37	1 / 0	37	3 / 0
ALT increased	31	10 / 2	18	2 / <1
Hair colour changes	30	0 / 0	10	<1 / 0
Hand–foot syndrome	29	6 / 0	50	11 / <1
Taste alteration	26	<1 / 0	36	0 / 0

Risk greater for sunitinib and 95% CI for relative risk does not cross 1

Risk greater for pazopanib and 95% CI for relative risk does not cross 1

1. Motzer *et al. New Engl J Med* 2013;369:722–31 (supplementary material).

COMPARZ: Laboratory Abnormalities Affecting ≥35% of Patients in Either Group: Lower Incidence of Grade 3/4 AEs with Pazopanib

		Pazopanib (n = 554), %		Sunitinib (n = 548), %	
		All grades	Grade 3 / 4	All grades	Grade 3/4
Clinical chemistry	ALT increase	60	15 / 2	43	4 / <1
	AST increase	61	11 / 1	60	3 / 0
	Hypoalbuminemia	33	<1 / 0	42	2 / 0
	Hyperbilirubinemia	36	3 / <1	27	2 / <1
	Creatinine increase	32	<1 / 0	46	<1 / <1
	Hyperglycaemia	54	5 / 0	57	4 / <1
	Hypophosphatemia	36	4 / 0	52	8 / <1
Haematology	Leucopoenia	43	1 / 0	78	6 / 0
	Naeutropenia	37	4 / <1	68	19 / 1
	Thrombocytopaenia	41	3 / <1	78	18 / 4
	Lymphocytopaenia	38	5 / 0	55	14 / <1
	Anaemia	31	1 / <1	60	6 / 1

Risk greater for sunitinib and 95% CI for relative risk does not cross 1
Risk greater for pazopanib and 95% CI for relative risk does not cross 1

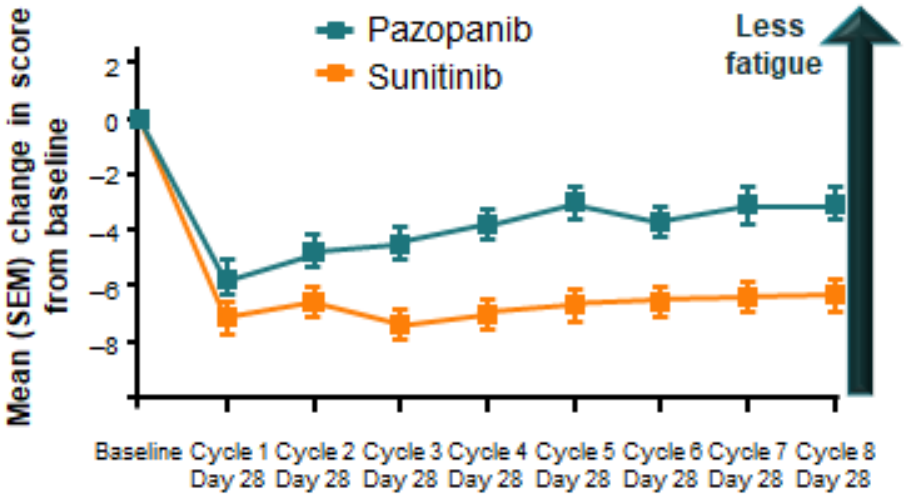
Reprinted from Motzer RJ et al. *N Engl J Med* 2013;369:722-731. Supplementary data online: http://www.nejm.org/doi/full/10.1056/NEJMoa1303989.

COMPARZ Data Show That AEs Can Also Impact QoL

- Less fatigue and foot soreness with pazopanib vs sunitinib

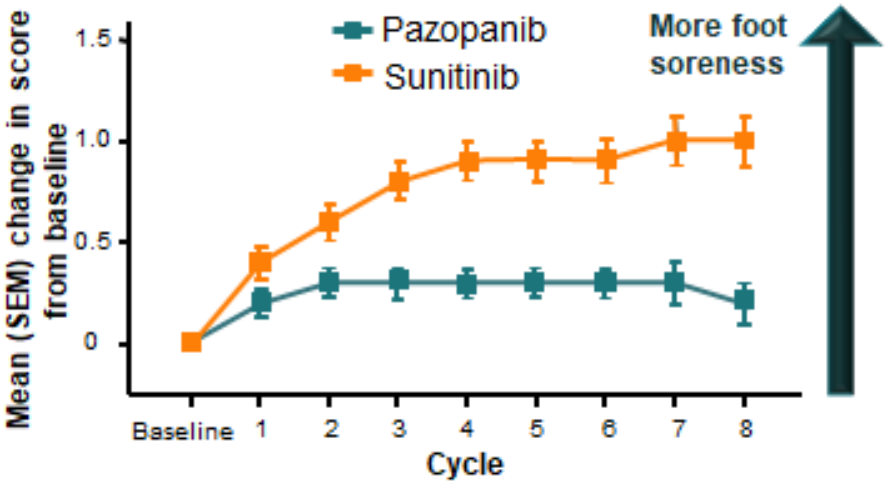
FATIGUE

Change in FACIT-F Scores from Baseline



FOOT SORENESS[a]

Change in SQLQ during First 12 Months

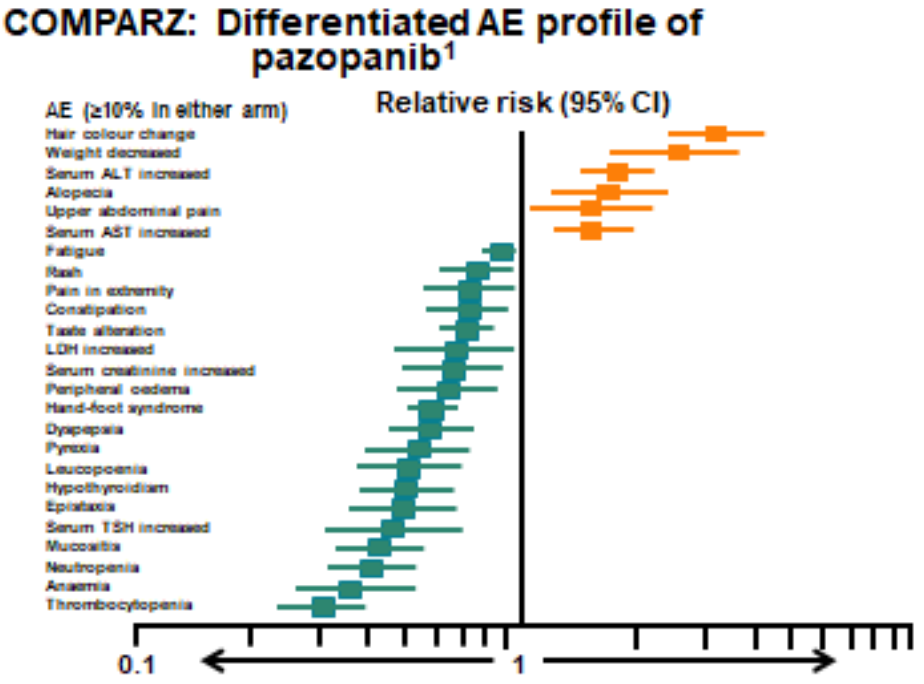


[a]Similar results with hand and mouth soreness

FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; SEM, standard error of the mean; SQLQ, Supplementary Quality of Life Questionnaire.

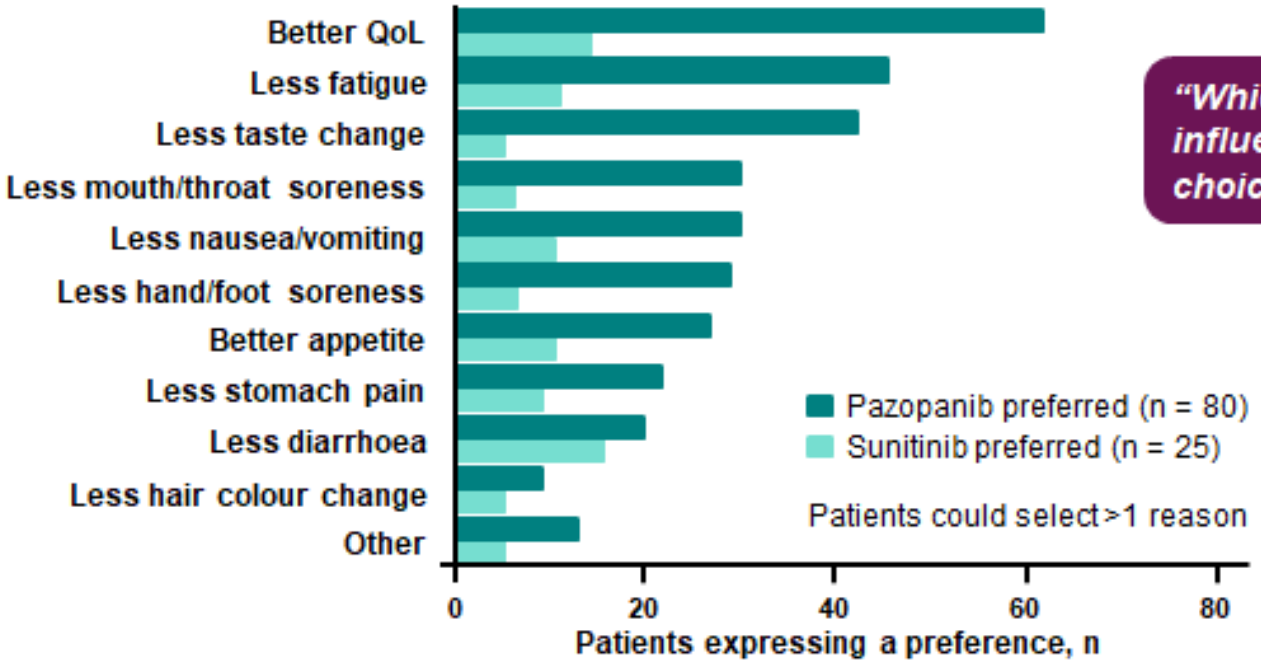
Reprinted from Motzer RJ et al. *N Engl J Med.* 2013;369:722-731.

Efficacy and Differentiated Adverse Event Profile of Pazopanib



AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; LDH lactate dehydrogenase; TSH, thyroid stimulating hormone.

PISCES: Patients Preferred a VEGFR-TKI with a Better QoL Profile and Fewer Symptomatic Adverse Events



"Which factors had an influence on your choice of treatment?"

Escudier B et al. *J Clin Oncol*. 2014;32:1412-1418.

Reported Grade 3/4 AEs with First-Line Pazopanib

Grade 3/4 AEs	%
Asthenia	7.7
Hypertension	4
Diarrhoea	3.6
Emesis	1.1
Mucositis	0.8
Anorexia	0.7
Dysgeusia	0.4
Renal failure	0.4
Stroke	0.4
Proteinuria	0.4

Laboratory grade 3/4 AEs	%
ALT elevation	7.8
AST elevation	3.9
Anaemia	2.6
Uric acid	0.7
Hypophosphatemia	0.7
Neutropenia	0.4
Thrombocytopenia	0.4
Bilirubin	0.4
Amylase	0.4
Lipase	0.4

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Phase 3 METEOR Study: Adverse Events Reported in ≥25% of Patients in Either Arm (Safety Population)

	Cabozantinib (n=331)		Everolimus (n=322)	
Adverse event, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any AE	100	71	>99	60
Diarrhoea	75	13	29	2
Fatigue	59	11	48	7
Nausea	52	5	29	<1
Decreased appetite	47	3	35	<1
PPE syndrome	43	8	6	<1
Hypertension	37	15	8	4
Vomiting	34	3	13	-
Weight loss	34	3	15	<1
Constipation	27	<1	20	<1
Anaemia	18	6	39	17
Cough	21	<1	34	<1
Dyspnea	20	3	30	4
Rash	16	<1	29	<1

PPE, palmar-plantar erythrodysaesthesia

1. Choueiri TK, et al. *J Clin Oncol* 2016;34(Suppl):abstract 4506;
2. Choueiri TK, et al. *Lancet Oncol* 2016;17:917–27

Phase 3 METEOR Study: Grade 3/4 Adverse Events Reported in ≥5% of Patients in Either Arm (Safety Population) by Tumour Burden

Grade 3/4 adverse event, %	Patients With Low Tumour Burden		Patients With High Tumour Burden	
	Cabozantinib (n=166)	Everolimus (n=161)	Cabozantinib (n=165)	Everolimus (n=160)
Any AE	73	58	69	62
Hypertension	17	4	12	4
Diarrhoea	13	2	13	2
Fatigue	11	7	10	8
PPE syndrome	7	1	9	1
Anaemia	5	11	7	23
Hyperglycaemia	2	4	0	5

PPE, palmar-plantar erythrodysaesthesia

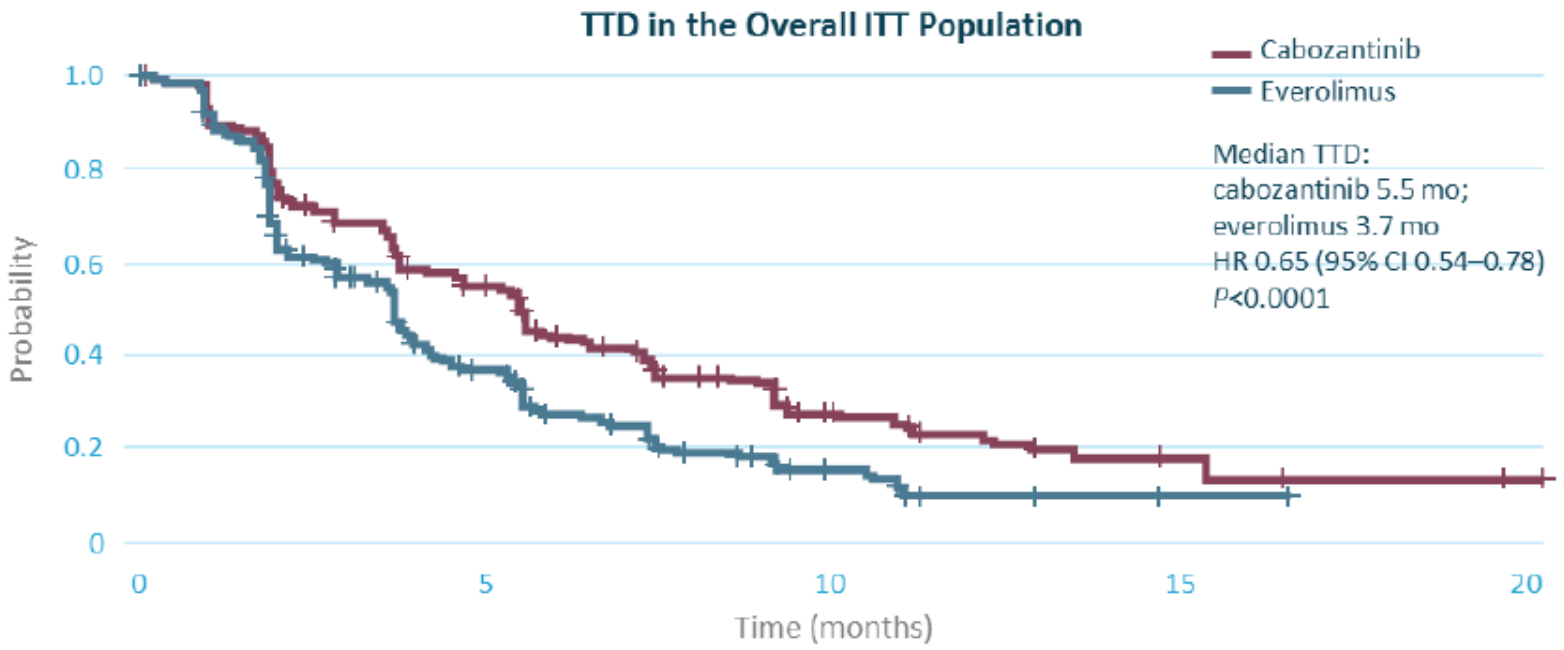
1. Powles T, et al. ESMO 2016; Poster 814P

Phase 3 METEOR Study: Serious Adverse Events (Safety Population)

	Cabozantinib (n=331)	Everolimus (n=322)
Grade ≥3 serious adverse events, n (%)	130 (39)	129 (40)
Most common Grade ≥3 serious adverse events, n (%)		
Abdominal pain	9 (3)	3 (1)
Pleural effusion	8 (2)	7 (2)
Pneumonia	7 (2)	13 (4)
Pulmonary embolism	7 (2)	1 (<1)
Anaemia	5 (2)	10 (3)
Dyspnoea	4 (1)	10 (3)
Deaths during the adverse event reporting period, n (%)	26 (8)	25 (8)
Deaths assessed as treatment-related, n	1	2

1. Choueiri TK, et al. *Lancet Oncol* 2016;17:917–27

Phase 3 METEOR Study QoL: Time to Deterioration (TTD)



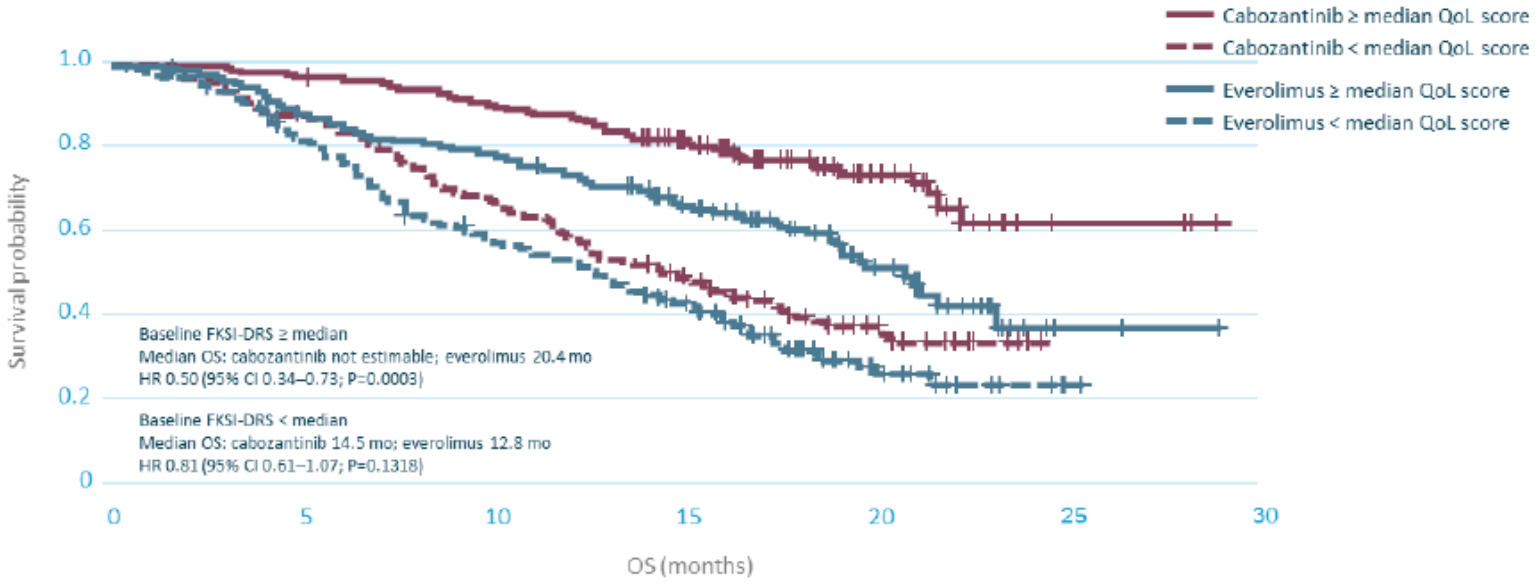
No. at risk																						
Cabozantinib	330	299	244	221	184	172	119	111	75	70	40	37	20	11	9	4	3	2	2	2	1	0
Everolimus	328	291	198	171	121	100	61	54	34	31	20	14	7	4	3	1	1	0				

- Cabozantinib treatment improved TTD compared with everolimus in the ITT population

CI, confidence interval; HR, hazard ratio; ITT, intenti-to-treat; mo, months; TTD, time to deterioration
TTD was defined as earlier of death, rPD, or ≥4-point FKSI-DRS (9-item) decrease in score from baseline

Cella D, et al. *J Clin Oncol* 2018

Phase 3 METEOR Study QoL: Baseline QoL as a Prognostic Factor for Overall Survival



No. at risk																
Cabozantinib	≥ Median	169	169	166	162	158	150	145	134	92	68	43	18	5	3	2	0
	< Median	155	150	137	129	114	101	89	78	56	36	19	6	1	0		
Everolimus	≥ Median	162	159	149	137	133	127	118	105	71	53	33	13	4	2	1	0
	< Median	151	147	132	114	94	85	77	64	44	26	15	5	3	0		

Cella D, et al. *J Clin Oncol* 2018

Phase 2 CABOSUN Study: Exposure and Dose Reductions(Safety Population)

	Cabozantinib (n=78)	Sunitinib (n=72)
Median duration of exposure, months (IQR)	**6.5 (2.8–16.5)**	**3.1 (2.0–8.2)**
Still on therapy, n (%)	10 (13)	2 (3)
Any dose reduction, n (%)	36 (46)	25 (35)
Discontinued due to AE, n (%)	16 (21)	16 (22)

Median follow-up: 25 months

Choueiri TK, et al. *Eur J Cancer* 2016;94:115–125.

Phase 2 CABOSUN Study: All-Causality High-Grade Adverse Events

	Cabozantinib (n=78)	Sunitinib (n=72)
Grade 3, n (%)	45 (58)	42 (58)
Grade 4, n (%)	8 (10)	5 (7)
Grade 5, n (%)	3 (4)	7 (10)
Possibly, probably, or definitely related,* n	2	4

Data cut-off: September 15, 2016
*Two grade 5 AEs in cabozantinib arm were related: renal failure acute and sepsis. Four grade 5 AEs in sunitinib arm were related: angiopathy, sepsis, respiratory failure, sudden death)

Choueiri TK, *et al. Eur J Cancer* 2016;94:115–125

CheckMate 025 Treatment-Related AEs in ≥10% of Patients

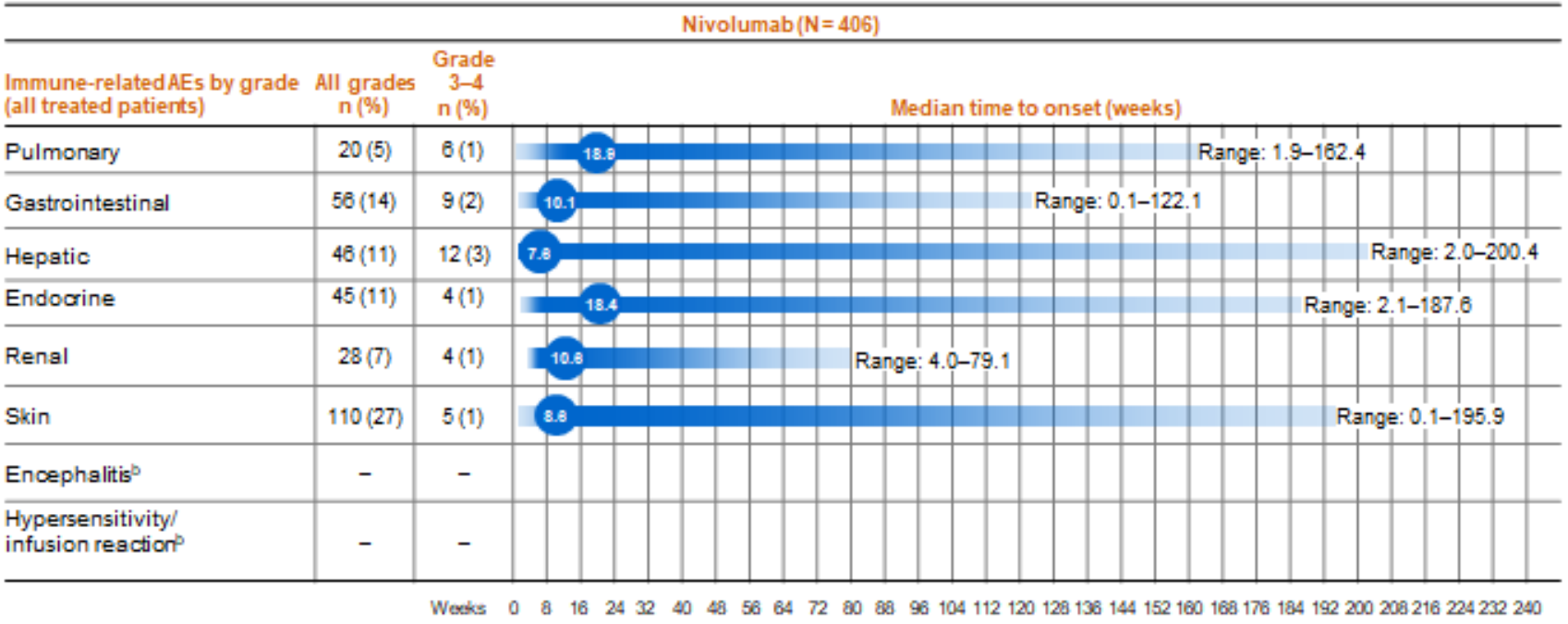
%	Nivolumab N=406			Everolimus N=397		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Treatment-related AEs	79	18	1	88	33	4
Fatigue	33	2	0	34	3	0
Nausea	14	<1	0	17	1	0
Pruritus	14	0	0	10	0	0
Diarrhea	12	1	0	21	1	0
Decreased appetite	12	<1	0	21	1	0
Rash	10	<1	0	20	1	0
Cough	9	0	0	19	0	0
Anemia	8	2	0	24	8	<1
Dyspnea	7	1	0	13	<1	0
Edema peripheral	4	0	0	14	<1	0
Pneumonitis	4	1	<1	15	3	0
Mucosal inflammation	3	0	0	19	3	0
Dysgeusia	3	0	0	13	0	0
Hyperglycemia	2	1	<1	12	3	<1
Stomatitis	2	0	0	29	4	0
Hypertriglyceridemia	1	0	0	16	4	1
Epistaxis	1	0	0	10	0	0

- No treatment-related deaths were reported with nivolumab, and 2 deaths were reported with everolimus (1 from septic shock and 1 from bowel ischemia)

Reported as of June 2015.

AE, adverse event.

Nivolumab in Patients With Advanced RCC: Frequency and Onset of IRAEs in CheckMate 025



[b]IRAE information is not available.
AE, adverse event; IRAE, immune-related adverse event; RCC, renal cell carcinoma.
Sharma P, et al. Presented at the 33rd Deutscher Krebskongress 2018; P764.

Summary of TRAEs in CheckMate 374 and CheckMate 025

- **The table shows a summary of the most common TRAEs in CheckMate 374 with the flat 240-mg nivolumab dose and those reported with 3 mg/kg nivolumab in CheckMate 025[a1]**

	CheckMate 374 (N=142)	CheckMate 025[1] (N=406)
≥1 event (any grade)	68%	79%
Fatigue	20%	33%
Nausea	12%	14%
Decreased appetite	7%	12%
≥1 event (grade 3–4)	16%	19%
Fatigue	2%	2%
Nausea	0	<1%
Decreased appetite	0	<1%

mRCC: Real Life Data
Safety

CheckMate 025

- Treatment-related grade 3–4 AEs occurred in 21% of patients
- No treatment-related deaths were reported with nivolumab

	Nivolumab N = 406		Everolimus N = 397	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related AEs, %	80	**21**	89	37
Treatment-related AEs leading to discontinuation, %	8	5	13	7
Treatment-related deaths, n	0		2	

Italian Program

- Treatment-related grade 3–4 AEs occurred in 7% of patients
- No treatment-related deaths were reported

	Nivolumab N = 389	
	Any Grade	Grade 3-4
Treatment-related AEs, %	32	**7**
Treatment-related serious AEs leading to discontinuation, %	5.7	
Treatment-related deaths, n	0	

Adapted from: poster presented by Sharma P et al. IKCS 2017; De Giorgi U et al. BJU Int 2018

NIVOLUTION LiveAround

RCC Real Life Data Safety

	Checkmate 025				Italian Program	
	Everolimus N=397		Nivolumab N=406		Nivolumab N=389	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Treatment-related AEs, %	**88**	**37**	**79**	**19**	**32**	**7**
Fatigue	34	3	33	2	13	2
Pyrexia	NR	NR	NR	NR	3	0
Nausea	17	1	14	<1	0	0
Pruritus	10	0	14	0	0	0
Diarrhoea	21	1	12	1	5	1
Decreased appetite	21	1	12	<1	1	<1
Rash	20	1	10	<1	9	<1
Hypothyroidism	NR	NR	NR	NR	2	0
Hyperthyroidism	NR	NR	NR	NR	2	0
Hypophysitis	NR	NR	NR	NR	<1	<1
Hypertransaminases	NR	NR	NR	NR	1	0
Cough	19	0	9	0	0	0
Anaemia	24	8	8	2	2	<1
Dyspnoea	13	<1	7	1	3	1
Oedema peripheral	14	<1	4	0	0	0
Pneumonitis	15	3	4	1	2	<1
Mucosal inflammation	19	3	3	0	0	0
Dysgeusia	13	0	3	0	0	0
Hyperglycaemia	12	3	2	1	0	0
Stomatitis	29	4	2	0	0	0
Hypertriglyceridaemia	16	4	1	0	0	0
Epistaxis	10	0	1	0	0	0

Adapted from: poster presented by Verzoni E et al. ESMO 2018

Adapted from De Giorgi U et al. BJU Int 2018

mRCC: Real Life Data
Safety

Drug-related AEs (drAEs): AE classified by the investigators as potentially related to treatment. Any grade drAEs were reported in 124 (32%) patients, the most common were fatigue (13%) and rash (9%).

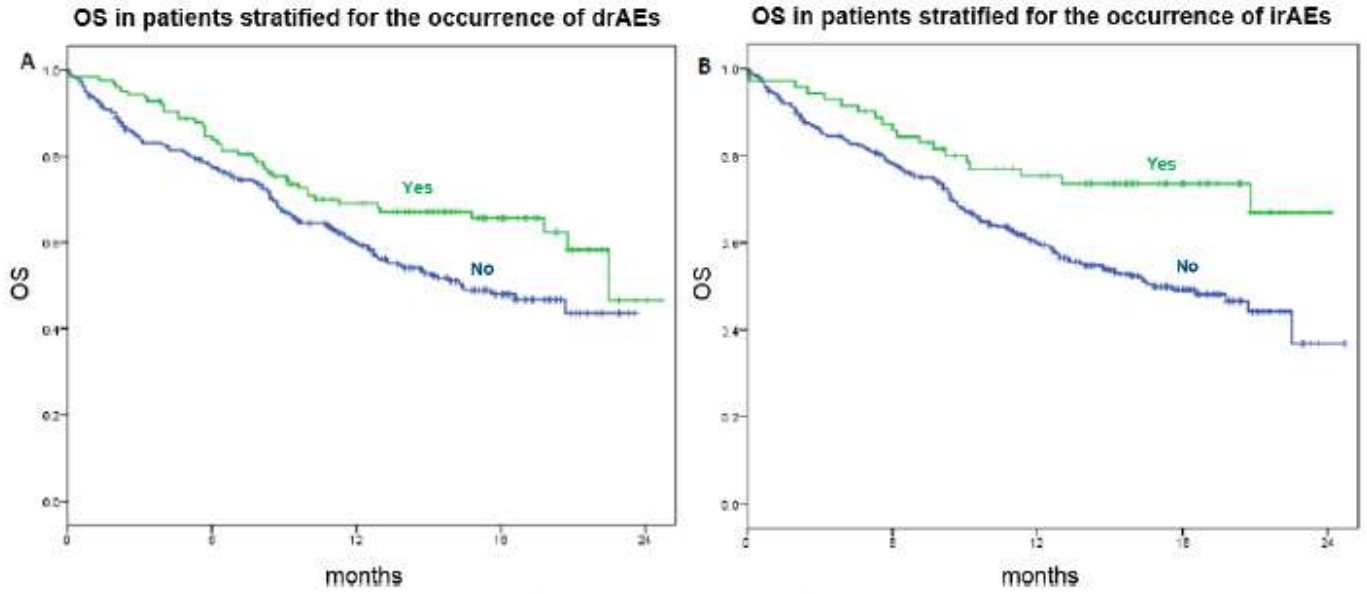
Immune-related (ir)AEs: drAEs showing a certain, likely or possible correlation with immunotherapy, specifically considering 5 categories: cutaneous, endocrine, hepatic, gastro-intestinal and pulmonary. Any grade irAEs occurred in 76 patients (20%).

irAEs	G1 %	G2 %	G3 %	G4 %	Any grade %
Cutaneous	4	3	1	0	8
Endocrine	3	1	<1	<1	4
Hepatic	1	1	0	0	2
Gastro-intestinal	2	2	1	0	5
Pulmonary	<1	<1	1	0	1

22 Grade ≥ 2 drAEs led to treatment discontinuation, 10 (45%) of them were considered irAEs: grade 4 hyperglicemia (n=1), grade 3 diarrhea (n=1), grade 3 pneumonitis (n=1), grade 3 bronchiolitis obliterans organising pneumonia (BOOP), grade 3 fatigue (n=1), grade 3 skin toxicity (n=1), grade 3 tremor (n=1), grade 2 eyelid ptosis (n=2), grade 2 liver toxicity (n=1), grade 2 hypotiroidism (n=1).

Adapted from: poster presented by Verzoni E et al. ESMO

mRCC: Real Life Data
Safety



- Patients experiencing drAEs had a significantly longer survival than those without drAEs (median OS 22.5 versus 16.4 months, p=0.01);
- Patients with irAEs had a more significant survival benefit than patients without irAEs (median OS not reached versus 16.8 months, p=0.002);
- The occurrence of irAEs displayed a strong association with OS in univariable (HR 0.48, p=0.003) and multivariable (HR 0.55, p=0.02) analysis.

Adapted from: poster presented by Verzoni E et al. ESMO 2018

mRCC: Checkmate 214
Treatment-related Adverse Events

	NIVO + IPI N = 547		SUN N = 535	
Event, %	Any grade	Grade 3–5	Any grade	Grade 3–5[a]
Treatment-related adverse events in ≥25% of patients	**93**	**46**	**97**	**63**
Fatigue	37	4	49	9
Pruritus	28	<1	9	0
Diarrhea	27	4	52	5
Nausea	20	2	38	1
Hypothyroidism	16	<1	25	<1
Decreased appetite	14	1	25	1
Dysgeusia	6	0	33	<1
Stomatitis	4	0	28	3
Hypertension	2	<1	40	16
Mucosal inflammation	2	0	28	3
Palmar-plantar erythrodysesthesia syndrome	1	0	43	9
Treatment-related AEs leading to discontinuation, %	22	15	12	7
Treatment-related deaths	n = 7[b]		n = 4[c]	

[a]Two patients had grade 5 cardiac arrest. [b]Pneumonitis, immune mediated bronchitis, lower GI hemorrhage, hemophagocytic syndrome, sudden death, liver toxicity, lung infection. [c]Cardiac arrest (n = 2), heart failure, multiple organ failure

Escudier ESMO 2017

mRCC: Toxicity Nivo-Ipi vs SUN

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

Motzer et al NEJM March 21, 2018

Table 3. Treatment-Related Adverse Events Occurring in 15% or More of Treated Patients in Either Group.*

Event	Nivolumab plus Ipilimumab (N=547)		Sunitinib (N=535)	
	Any Grade†	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients (percent)			
All events	509 (93)	250 (46)	521 (97)	335 (63)
Fatigue	202 (37)	23 (4)	264 (49)	49 (9)
Pruritus	154 (28)	3 (<1)	49 (9)	0
Diarrhea	145 (27)	21 (4)	278 (52)	28 (5)
Rash	118 (22)	8 (1)	67 (13)	0
Nausea	109 (20)	8 (1)	202 (38)	6 (1)
Increased lipase level	90 (16)	56 (10)	58 (11)	35 (7)
Hypothyroidism	85 (16)	2 (<1)	134 (25)	1 (<1)
Decreased appetite	75 (14)	7 (1)	133 (25)	5 (<1)
Asthenia	72 (13)	8 (1)	91 (17)	12 (2)
Vomiting	59 (11)	4 (<1)	110 (21)	10 (2)
Anemia	34 (6)	2 (<1)	83 (16)	24 (4)
Dysgeusia	31 (6)	0	179 (33)	1 (<1)
Stomatitis	23 (4)	0	149 (28)	14 (3)
Dyspepsia	15 (3)	0	96 (18)	0
Mucosal inflammation	13 (2)	0	152 (28)	14 (3)
Hypertension	12 (2)	4 (<1)	216 (40)	85 (16)
Palmar–plantar erythrodysesthesia	5 (<1)	0	231 (43)	49 (9)
Thrombocytopenia	2 (<1)	0	95 (18)	25 (5)

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Discontinuation due to Toxicity

Stop per toxicity: 22 % (N+I) vs 12% (sun)*

*in Comparz trial
20% sun/24% paz

21% dei pts non ha completo 4 cicli NIVO+ IPI

35% hanno ricevuto steroidi a dosi > 40 mg/die

Decessi correlati al trattamento

8 pts (1.4%) N+I (eventi polmonari/epatici/emorragia intestinale)
vs
4pts SUN (0.7%) * (cause cardiache)

*1% in COMPARZ (SUN o PAZ)

Motzer et al NEJM March 21, 2018

Trattamento degli irAEs

60% dei pazienti NIVO+IPI hanno ricevuto steroidi

3% immunosoppressori di II livello

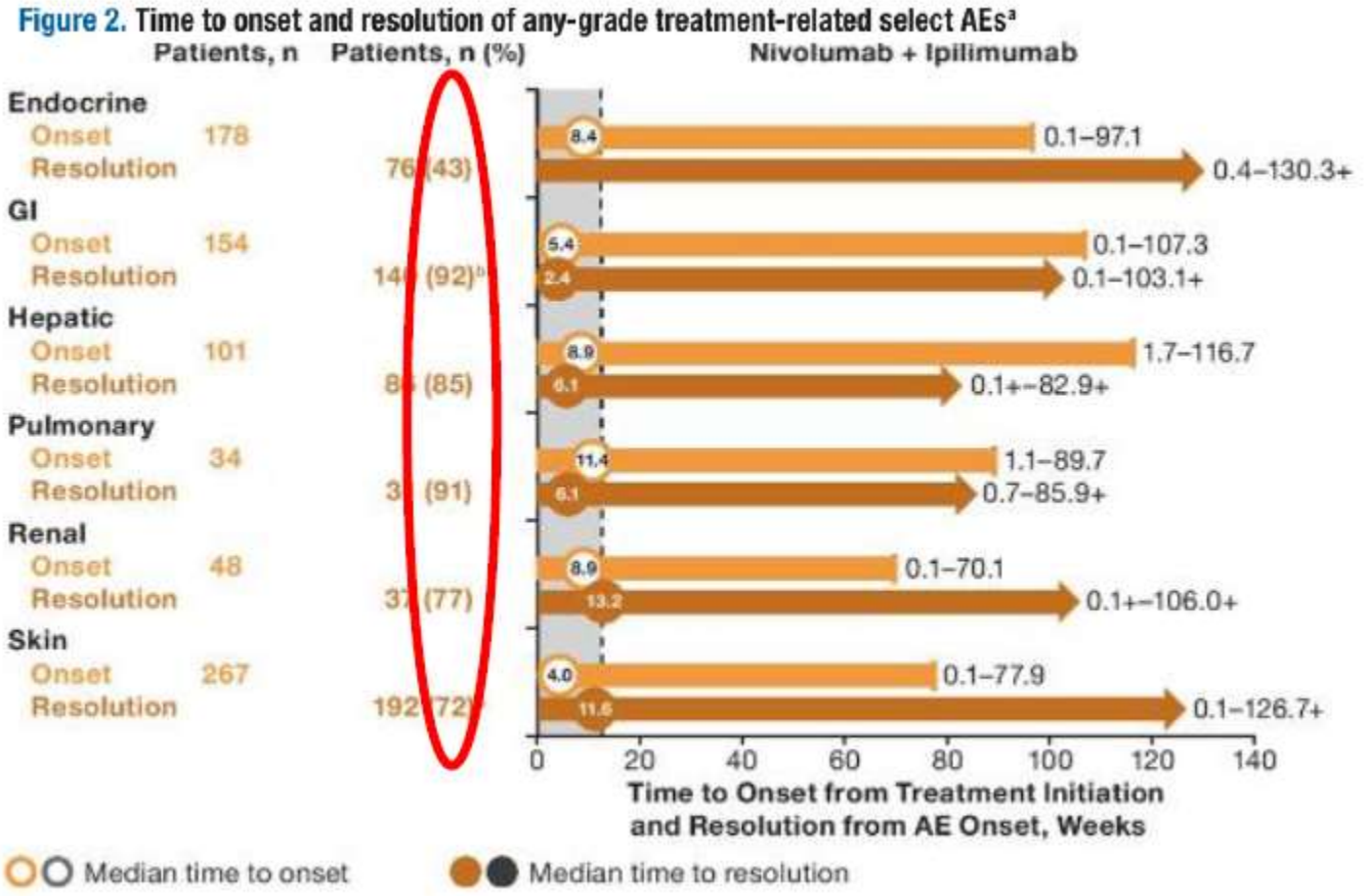
Table 4. Concomitant IMM for treatment-related select AE management[a,b]

System	N+I		S	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Endocrine	n = 178	n = 38	n = 163	n = 1
Patients who received IMM, %	38	76	0	0
Patients who received HDCS, %	25	53	0	0
Duration of HDCS, median (min, max), weeks	2.14 (0.1, 24.3)	1.21 (0.1, 9.3)	–	–
GI	n = 154	n = 27	n = 278	n = 28
Patients who received IMM, %	31	78	0	0
Patients who received HDCS, %	26	70	0	0
Duration of HDCS, median (min, max), weeks	3.14 (0.1, 99.6)	3.00 (0.7, 98.4)	–	–
Hepatic	n = 101	n = 45	n = 77	n = 20
Patients who received IMM, %	39	64	1	5
Patients who received HDCS, %	35	53	0	0
Duration of HDCS, median (min, max), weeks	4.00 (0.1, 97.1)	4.64 (0.4, 97.1)	–	–
Pulmonary	n = 34	n = 6	n = 1	n = 0
Patients who received IMM, %	62	100	100	–
Patients who received HDCS, %	59	100	0	–
Duration of HDCS, median (min, max), weeks	2.36 (0.6, 14.0)	3.86 (1.1, 7.4)	–	–
Renal	n = 48	n = 7	n = 46	n = 6
Patients who received IMM, %	40	57	2	0
Patients who received HDCS, %	27	29	0	0
Duration of HDCS, median (min, max), weeks	2.14 (0.6, 25.7)	13.14 (0.6, 25.7)	–	–
Skin	n = 267	n = 20	n = 304	n = 53
Patients who received IMM, %	37	90	19	17
Patients who received HDCS, %	7	60	0	0
Duration of HDCS, median (min, max), weeks	2.29 (0.1, 100.3)	2.17 (0.1, 17.0)	–	–

[a]Treated patients who experienced ≥1 treatment-related select AE from the category and had treatment-related AEs
[b]Patients may have received IMM for AE management at non-study institutions, therefore complete IMM usage records were not available
HDCS = high-dose corticosteroid (at a dose ≥40 mg prednisone or equivalent)

Tannir et al ASCO GU 2018

Tempi di Risoluzione eventi avversi



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- **Signs and symptoms of pneumonitis may include:[1–3]**
  - Shortness of breath
  - Chest pain
  - New cough
  - Dyspnea
  - New or worsening hypoxia
  - Fever
  - Radiologic features including cryptogenic organizing pneumonia-like, ground glass opacities, interstitial, hypersensitivity, and pneumonitis not otherwise specified

IRAE, immune-related adverse event.

1. Naidoo J, et al. *J Clin Oncol* 2016;35:709–717. *2.* Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 3. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575.

- **Signs and symptoms of gastrointestinal adverse reactions may include:[1–3]**
  - Diarrhea defined as increased stool frequency
  - Colitis
  - Enteritis
  - Abdominal pain
  - Bloody stools
  - Peritoneal signs
  - Nausea
  - Constipation

IRAE, immune-related adverse event.

1. Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575. 3. Weber JS, et al. *Oncologist* 2016;21:1230–1240.

- **Signs and symptoms of hepatitis may include:[1,2]**
  - Asymptomatic elevations in AST and ALT
  - Increased bilirubin
  - Radiological appearance of hepatomegaly, periportal edema, and periportal lymphadenopathy

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRAE, immune-related adverse event.

1. Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575.

- **Signs and symptoms of endocrinopathies (especially in the thyroid, pituitary, adrenal glands, and pancreas) may include:[1–3]**
  - Hypophysitis
  - Hypothyroidism
  - Hyperthyroidism
  - Thyroiditis
  - Adrenal insufficiency
  - Fatigue
  - Headache
  - Visual field defects
  - Hypotension
  - Dehydration
  - Hyponatremia
  - Hyperkalemia
  - Nausea
  - Amenorrhea

IRAE, immune-related adverse event.

1. Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575. 3. Weber JS, et al. *Oncologist* 2016;21:1230–1240.

- **Signs and symptoms of neurologic adverse reactions may include:[1,2]**
  - Transverse myelitis
  - Enteric neuropathy
  - Aseptic meningitis
  - Guillain–Barre syndrome
  - Myasthenia gravis
  - Posterior reversible encephalopathy syndrome

IRAE, immune-related adverse event.

1. Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575.

- **Signs and symptoms of renal dysfunction and nephritis may include:[1–3]**
  - Nephritis
  - Asymptomatic gradually rising creatinine
  - Oliguria
  - Hematuria
  - Ankle oedema
  - Decreased appetite

IRAE, immune-related adverse event.

1. Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575. 3.

- **Signs and symptoms of skin adverse reactions may include:[1–2]**
  - Skin rash
  - Maculopapular rash
  - Papulopustular rash
  - Sweet's syndrome
  - Follicular rash
  - Urticarial dermatitis
  - Pruritus
  - Vitiligo
  - Lichenoid dermatitis
  - Bullous pemphigoid
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis

IRAE, immune-related adverse event.

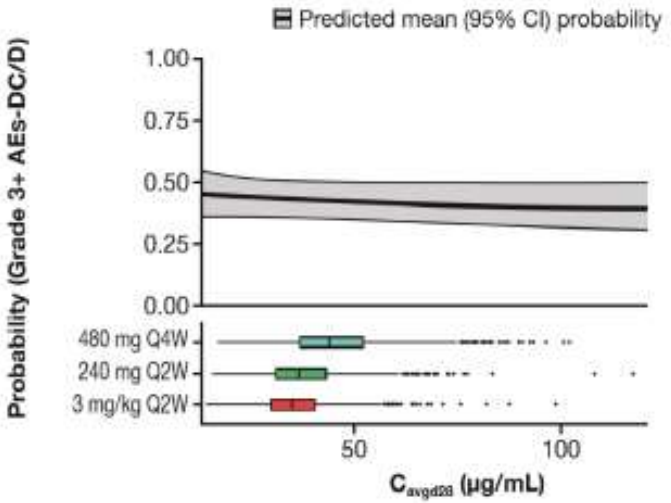
1. Naidoo J, et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J, et al. *Transl Lung Cancer Res* 2015;4:560–575.

- **Signs and symptoms of infusion reactions may include:**
  - Chills
  - Fever
  - Nausea/vomiting
  - Asthenia
  - Headache
  - Skin rash
  - Pruritus/itching
  - Arthralgia/myalgia
  - Bronchospasm
  - Cough
  - Dyspnea
  - Dizziness
  - Fatigue
  - Hypotension/hypertension

Chung CJ, et al. *The Oncologist* 2008;13:725–732.

The Predicted Risk of Grade 3+ AEs-DC/D Was Similar for Nivolumab 480 mg Q4W and Nivolumab 3 mg/kg Q2W

A. E–R of Grade 3+ AEs-DC/D



Predicted risk of Grade 3 or greater AEs was similar between nivolumab 480 mg Q4W and nivolumab 3 mg/kg Q2W*

Persona/Paziente con Neoplasia
Umanizzazione della Gestione clinica

Peculiarità e Criticità

	Indicatori	Rete di Specialisti
▪ Equilibrio Psicologico		Psicologo
▪ Equilibrio Fisico (Fitness)	PS, ADL/IADL	Oncologo/Palliativista/MMG
▫ Età		
▪ Equilibrio Nutritivo		Nutrizionista/Infermiere
▪ Equilibrio Funzionale	CIRS	Oncologo/Specialisti/MMG
▫ Anemia		
▫ Organi ed Apparati		
▪ Segni e Sintomi		
▫ Malattia		
▪ Dolore	VAS/ESAS	Palliativista/MMG
▫ Strategie terapeutiche (Chirurgia, RT, Mediche)	Tossicità	Oncologo/Infermiere/Spec

Persona/Paziente con Neoplasia
Umanizzazione della Gestione clinica

Peculiarità e Criticità

	Indicatori	Rete di Specialisti
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▪ Equilibrio Funzionale	CIRS	Oncologo/Specialisti/MMG
▫ Anemia		
▫ Organi ed Apparati		
▪ Segni e Sintomi		
▫ Malattia		
▪ Dolore	VAS/ESAS	Palliativista/MMG
▫ Strategie terapeutiche (Chirurgia, RT, Mediche)	Tossicità	Oncologo/Infermiere/Spec

Activities of daily living: ADL

Value No.

1. TOILET
   - 4 Cares for self at toilet completely, no incontinence
   - 3 Needs to be reminded, or needs help in cleaning self, or has rare (weekly at most) accidents
   - 2 Soiling or wetting while asleep, more than once a week
   - 1 Soiling or wetting while awake, more than once a week
   - 0 No control of bowels or bladder

2. FEEDING
   - 4 Eats without assistance
   - 3 Eats with minor assistance at meal times, with help preparing food or with help in cleaning up after meals
   - 2 Feeds self with moderate assistance and is untidy
   - 1 Requires extensive assistance for all meals
   - 0 Does not feed self at all and resists efforts of others to feed him

3. DRESSING
   - 4 Dresses, undressed and selects clothes from own wardrobe
   - 3 Dresses and undresses self, with minor assistance
   - 2 Needs moderate assistance in dressing or selection of clothes
   - 1 Needs major assistance in dressing but cooperated with efforts of other to help
   - 0 Completely unable to dress self and resists efforts of others to help

4. GROOMING (neatness, hair, nails, hands, face, clothing)
   - 4 Always neatly dressed and well-groomed, without assistance
   - 3 Grooms self adequately, with occasional minor assistance, e.g., in shaving
   - 2 Needs moderate and regular assistance or supervision in grooming
   - 1 Needs major assistance in dressing but cooperates with efforts of others to help
   - 0 Actively negates all efforts to others to maintain grooming

5. PHYSICAL AMBULATION
   - 4 Goes about grounds or city
   - 3 Ambulates within residence or about one block distant
   - 2 Ambulates with assistance of (check one): ____another person, ____ railing, ____ cane, ____ walker, or ____ wheelchair: ____ gets in and out without help ____ needs help in getting in and out
   - 1 Sits unsupported in chair or wheelchair, but cannot propel self without help
   - 0 Bedridden more than half the time

6. BATHING
   - 4 Bathes self (tub, shower, sponge bath) without help
   - 3 Bathes self, with help in getting in and out of tub
   - 2 Washes face and hands only, but cannot bathe rest of body
   - 1 Does not wash self but is cooperative with those who bathe him
   - 0 Does not travel at all

7. RESPONSIBILITY FOR OWN MEDICATION
   - 2 Is responsible for taking medication in correct dosages at correct time
   - 1 Takes responsibility if medication is prepared in advance in separate dosages
   - 0 Does not try to wash self, and resists efforts to keep him clean

TOTAL SCORE _____

Instrumental activities of daily living: IADL

		Value No.
1.	ABILITY TO USE TELEPHONE	
	3 Operates telephone on own initiative; looks up and dials numbers, etc.	
	2 Dials a few well known numbers	
	1 Answers telephone but does not dial	
	0 Does not use telephone at all	_____
2.	SHOPPING	
	3 Takes care of all shopping needs independently	
	2 Shops independently for small purchases	
	1 Needs to be accompanied on any shopping trip	
	0 Needs to have meals prepared and served	_____
3.	FOOD PREPARATION	
	3 Plans, prepares and serves adequate meals independently	
	2 Prepares adequate meals if supplied with ingredients	
	1 Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	
	0 Needs to have meals prepared and served	_____
4.	HOUSEKEEPING	
	4 Maintains house alone or with occasional assistance (e.g., heavy-work domestic help)	
	3 Performs light daily tasks such as dish-washing and bed-making	
	2 Performs light daily tasks but cannot maintain acceptable level of cleanliness	
	1 Needs help with all home maintenance tasks	
	0 Does not participate in any housekeeping tasks	_____
5.	LAUNDRY	
	2 Does personal laundry completely	
	1 Launders small items; rinses socks, stockings, etc.	
	0 All laundry must be done by others	_____
6.	MODE OF TRANSPORTATION	
	4 Travels independently on public transportation or drives own car	
	3 Arranges own travel via taxi, but does not otherwise use public transportation	
	2 Travels on public transportation when assisted or accompanied by another	
	1 Travel limited to taxi or automobile, with assistance of another	
	0 Does not travel at all	_____
7.	RESPONSIBILITY FOR OWN MEDICATION	
	2 Is responsible for taking medication in correct dosages at correct time	
	1 Takes responsibility if medication is prepared in advance in separate dosages	
	0 Is not capable of dispensing own medication	_____
8.	ABILITY TO HANDLE FINANCES	
	2 Manages financial matters independently (budgets, write checks, pays rent and bills, goes to Bank) collects and keeps track of income	
	1 Manages day-to-day purchases, but needs help with banking, major purchases, etc.	
	0 Incapable of handling money	_____
	TOTAL SCORE	_____

Persona/Paziente con Neoplasia
Umanizzazione della Gestione clinica

Peculiarità e Criticità

	Indicatori	Rete di Specialisti
▪ Equilibrio Psicologico		Psicologo
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▪ Equilibrio Funzionale	CIRS	Oncologo/Specialisti/MMG
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▫ Malattia		
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Comorbidity index CIRS (Cumulative Illness Rating Scale)

Name: _____

Each system is rated as follows:

1 = NONE:	No impairment to that organ/system.
2 = MILD:	Impairment does not interfere with normal activity; treatment may not be required; prognosis is excellent (examples: skin lesions, hernias, hemorrhoids)
3 = MODERATE:	Impairment interferes with normal activity; treatment is needed; prognosis is good (examples: gallstones, diabetes, fractures)
4 = SEVERE:	Impairment is disabling; treatment is urgently needed; prognosis is guarded (examples: respectable carcinoma, pulmonary emphysema, congestive heart failure)
5 = EXTREMELY SEVERE:	Impairment is life threatening; treatment is urgent or of no avail; prognosis is grave (examples: myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, embolus)

Extermann M, et al. J Clin Oncol 1998; 16(4):1582-1587

Comorbidity index CIRS

		Value 1-5
a.	Cardiac (heart only)	___
b.	Hypertension (rating is based on severity; affected systems are rated separately).	___
c.	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics).	___
d.	Respiratory (lungs, bronchi, trachea below the larynx).	___
e.	EENT (eye, ear, nose, throat, larynx).	___
f.	Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees; do no include diabetes).	___
g.	Lower GI (intestines, hernias).	___
h.	Hepatic (liver only).	___
i.	Renal (kidneys only).	___
j.	Other GU (ureters, bladder, urethra, prostate, genitals).	___
k.	Musculo-skeletal-integumentary (muscles, bone, skin)	___
l.	Neurological (brain, spinal cord, nerves; do not include dementia).	___
m.	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)	___
n.	Psychiatric/Behavioral (includes depression, anxiety, agitation, psychosis, not dementia).	___

Extermann M, et al. J Clin Oncol 1998; 16(4):1582-1587

Comorbidity index
CIRS

Stage	Characteristics
Primary	Independent IADL (score ≥ 8) Absent or mild CIRS
Intermediate	Stable CIRS (< 3 mild or moderate cathegories) ± dependent or independent IADL
Secondary	Unstable CIRS (≥ 3 cathegories or 1 severe cathegory) ± dependent IADL
Terminal	

Comorbidity index CIRS
Oncology Territorial Care Unit L'Aquila: Decision-Making

	Medical treatments	
	65-75 years	**>75 years**
Primary	Standard	Standard
Intermediate	Standard	Modified
Secondary	Modified	Modified
Terminal	-	-

Persona/Paziente con Neoplasia
Umanizzazione della Gestione clinica

Peculiarità e Criticità

	Indicatori	Rete di Specialisti
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▫ Strategie terapeutiche (Chirurgia, RT, Mediche)	Tossicità	Oncologo/Infermiere/Spec

Parameters driving treatment strategies

- Patient
  - "Fit": Standard treatment strategies (Triplet or more intensive)
  - "Unfit": Modulated treatment strategies

    Age ("elderly")

    Co-morbidities

Patient's Fitness
Functional condition of the patient

- Elderly status
  - Young-elderly (≥65 <75 years)
  - Old-elderly (≥75 years)
- Comorbidities
- Performance Status
- Functional conditions
- Nutritional conditions

Toxicity Syndromes

Patient-related Clinical Indicator of Individual Toxicity burden induced by Medical Treatments.

Limiting toxicity syndromes (LTS)

- To better evaluate individual safety
- LTS: at least a limiting toxicity associated or not to other limiting or G2 toxicities
  - LTS-single site (LTS-ss): only the limiting toxicity
  - LTS-multiple sites (LTS-ms):
    - ≥2 limiting toxicities or
    - a limiting toxicity associated to other, at least G2, non-limiting toxicities.

Bruera G et al. BMC Cancer 2010;10:567

Bruera G et al. BioMed Res Int 2013;2013:143273

Treatment regimens, clinical outcome, and safety profile

	Metastatic colorectal cancer				Metastatic pancreatic ductal adenocarcinoma		Metastatic gastric cancer	
	FIr-B/FOx		FIr-C/FOx-C		FIr/FOx		FD/FOx	
No.patients	50		29		29		10	
Limiting toxicities (%)								
Diarrhea	28		23		17		-	
Nausea	6		-		3		-	
Vomiting	4		8		3		-	
Hypoalbuminemia	-		-		3		10	
Mucositis	6		-		6		10	
Asthenia	6		15		14		20	
Ipokaliemia	2		-		7		-	
Hypertransaminasemia	4		8		7		-	
Neutropenia	10		-		17		50	
Thrombocytopenia	-		-		3		-	
Anemia	-		-		3		-	

Bruera G et al, BMC Cancer 2010;10:567; Bruera G et al, BioMed Res Int 2013:143273 Bruera G et al, Oncotarget 2017;8(23):37875-37883; Bruera G et al, Ther Adv Med Oncol 2019 0;11:175883591984642l; Bruera G et al, Oncotarget 2018;9(61):31861-31876; Bruera G et al, Oncotarget 2018 ;9(29):20339-20350

Individual Toxicity Syndromes: overall LTS, LTS-ms and LTS-ss, according to triplet chemotherapy-based regimen

	Metastatic colorectal cancer				Metastatic pancreatic ductal adenocarcinoma		Metastatic gastric cancer	
	FIr-B/FOx		FIr-C/FOx-C		FIr/FOx		FD/FOx	
	N.	%	N.	%	N.	%	N.	%
Overall patients	50		29		29		10	
Toxicity Syndromes	22	**44**	19	**65.5**	8	**27.5**	3	**30**
LTS-ms	12	**24**	17	**59**	7	**24.1**	3	30
LTS-ss	10	**20**	2	**7**	1	3.4	-	-
Young-elderly patients	28	42	6	24	13	34.4	4	40
Toxicity Syndromes	13	**46**	5	**83**	5	**38.4**	1	**25**
LTS-ms	11	**39**	4	**67**	5	**38.4**	1	25
LTS-ss	2	**7**	1	**17**	-	-	-	-

Abbreviation: LTS, limiting toxicity syndromes; LTS-ms, LTS multiple sites; LTS-ss, LTS single site.

Bruera G et al, BMC Cancer 2010;10:567; Bruera G et al, BioMed Res Int 2013:143273 Bruera G et al, Oncotarget 2017;8(23):37875-37883; Bruera G et al, Ther Adv Med Oncol 2019 0;11:175883591984642l; Bruera G et al, Oncotarget 2018;9(61):31861-31876; Bruera G et al, Oncotarget 2018 ;9(29):20339-20350

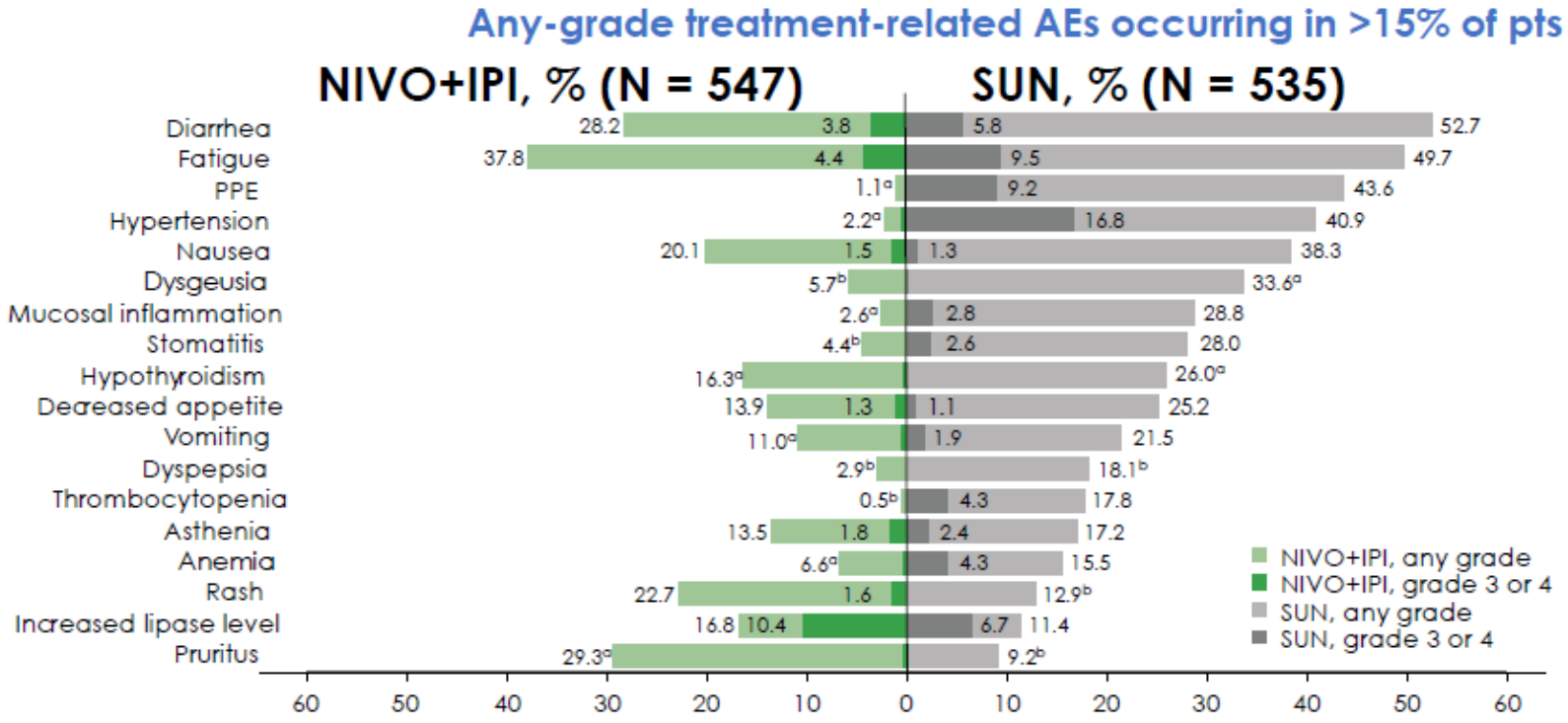
Rete Oncologica…

Azienda Sanitaria Locale
Avezzano, Sulmona, L'Aquila

…insieme,

possiamo fare molto di più!

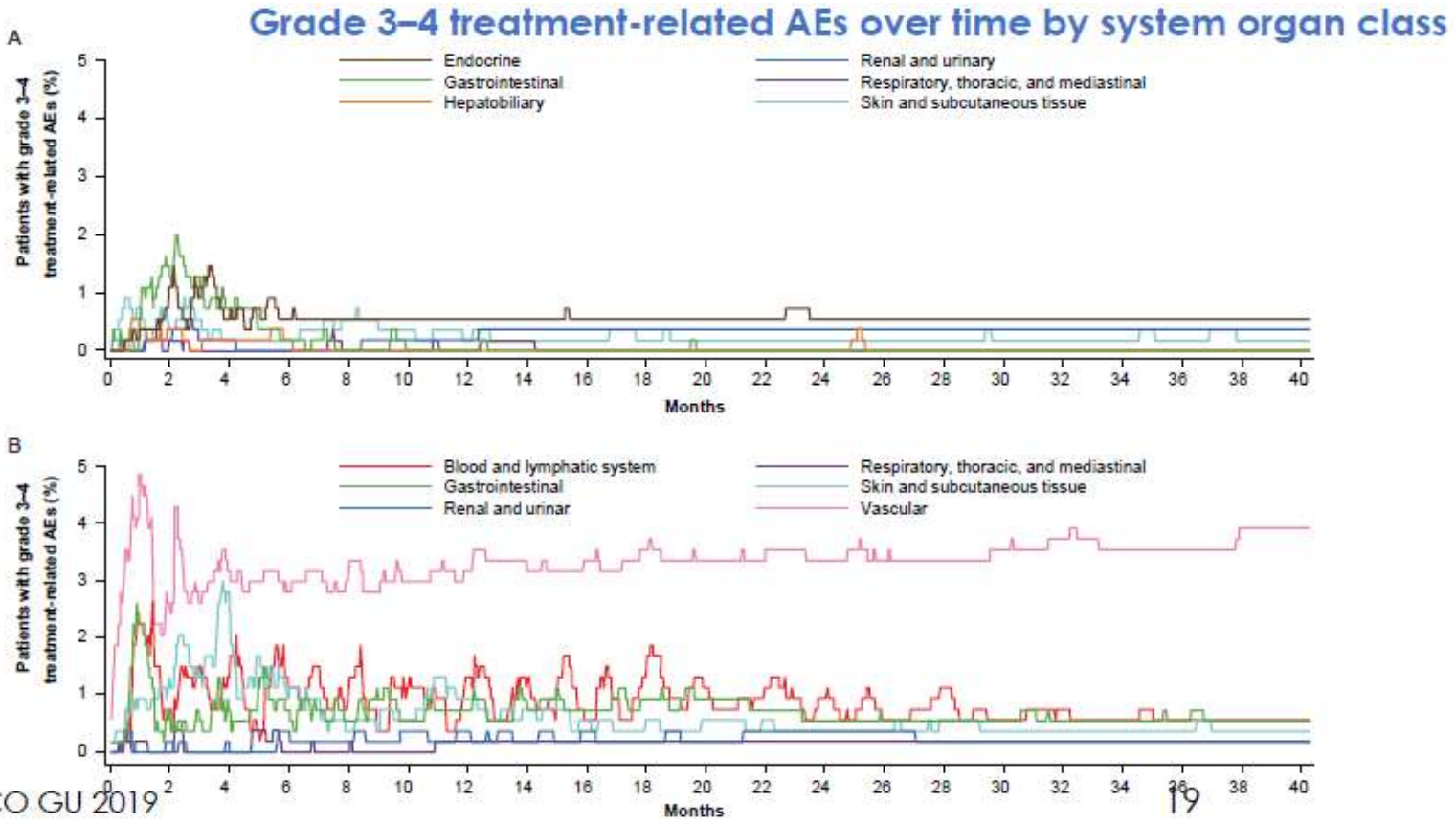
mRCC: Checkmate 214
Update @ 30 months



NB: Cumulative Grade 3–4 AEs **47 %** **vs** **64%** **patients**

Tannir et al, ASCO GU 2019

mRCC: Checkmate 214
Update @ 30 months



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Update @ 30 months

- Among 443 patients in the NIVO+IPI arm with ≥1 treatment-related select (immune-mediated) AE occurring within 30 days of last dose of study therapy, 157 **(35%) patients received high-dose glucocorticoids ([HDCS]; ≥40 mg of prednisone/day or equivalent)**, including 53 (12%) patients who received HDCS for ≥30 days

- **Treatment-related AEs leading to discontinuation** occurred in 1 additional patient in the NIVO+IPI arm and 3 additional patients in the SUN arm compared with the primary analysis: 119 **(22%) patients with NIVO+IPI and 66 (12%) patients with SUN**

- **No additional treatment-related deaths** were reported since the primary analysis: 8 **(1.5%)** patients in the NIVO+IPI arm and 4 **(0.7%)** patients in the SUN arm

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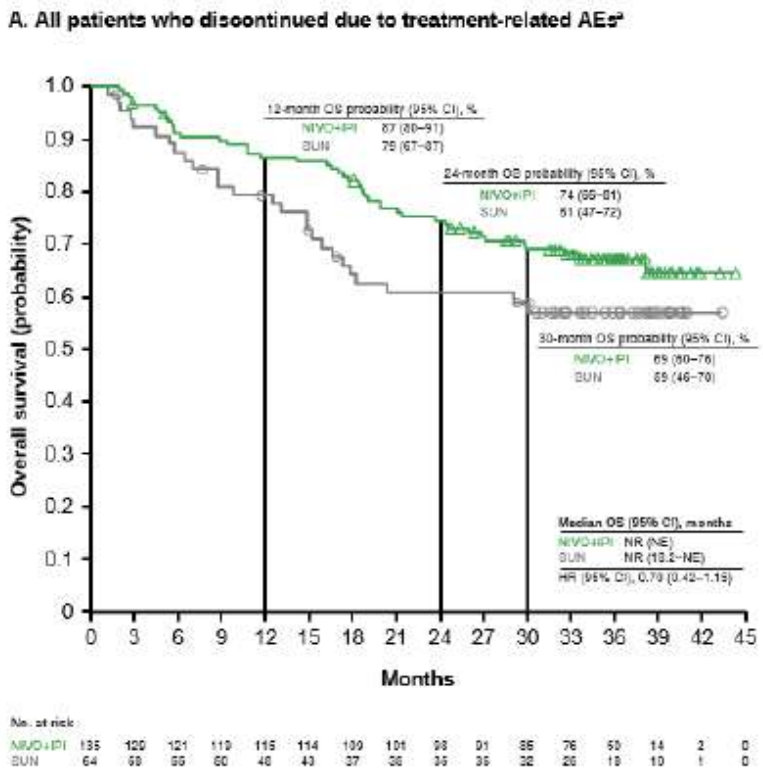
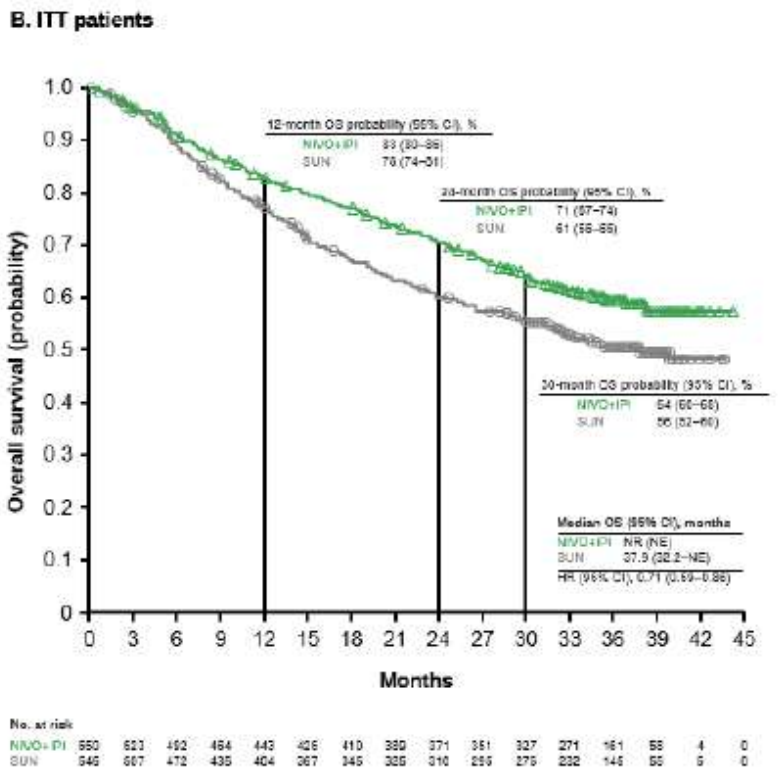
mRCC: Checkmate 214
Update @ 30 months: OS





Tannir et al ASCO GU 2019

Pembrolizumab/axitinib

Powles KN426 ASCO-GU 2019

Summary of Adverse Events

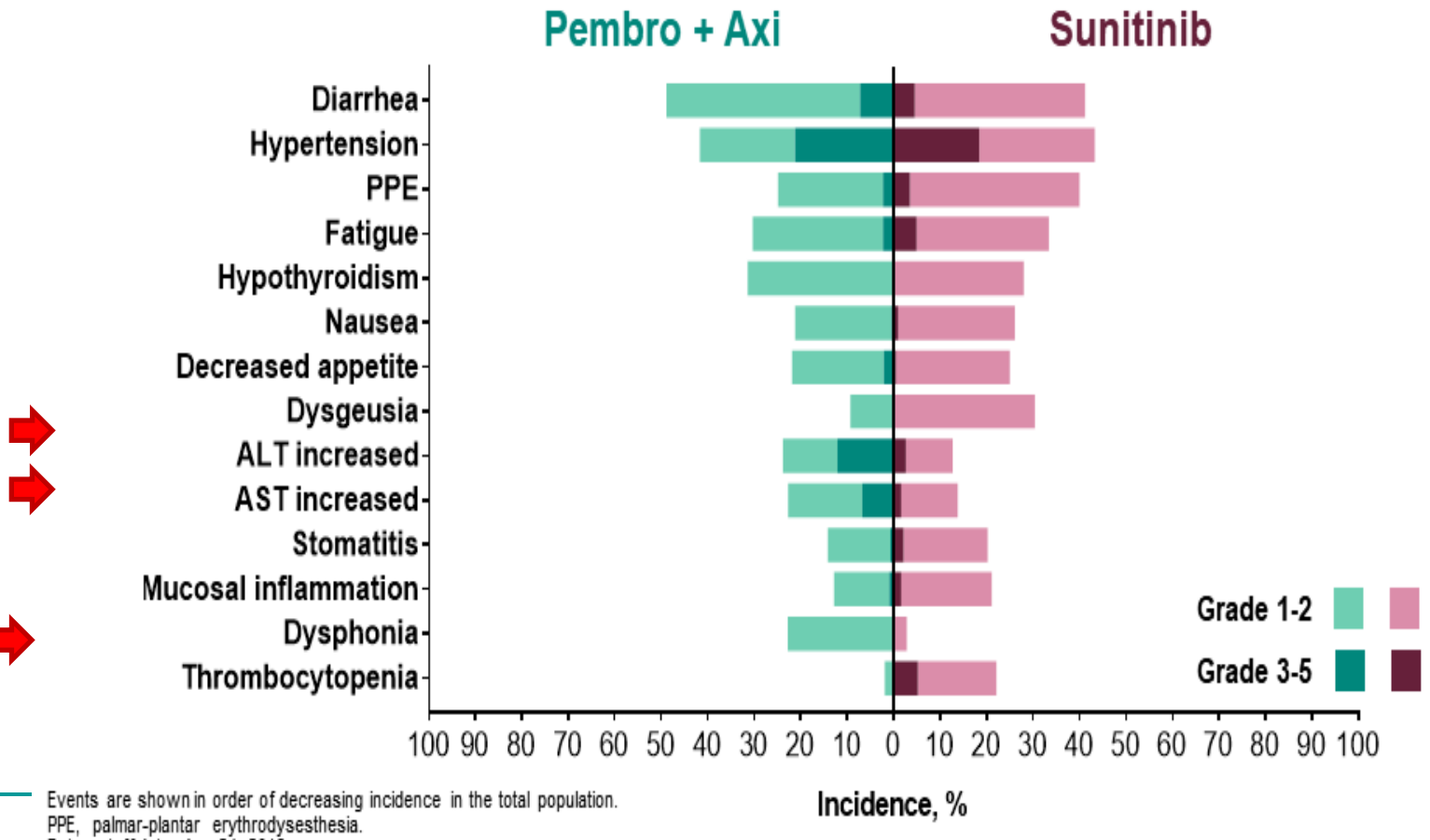
	All Cause		Treatment Related	
	Pembro + Axi N = 429	Sunitinib N = 425	Pembro + Axi N = 429	Sunitinib N = 425
Any	98.4%	99.5%	96.3%	97.6%
Grade 3-5	75.8%	70.6%	62.9%	58.1%
Led to death	2.6%	3.5%	0.9%[a]	1.6%[b]
Led to discontinuation of any treatment	30.5%	13.9%	25.9%	10.1%
Led to discontinuation of both pembro and axi	10.7%	—	8.2%	—
Led to axi or sunitinib dose reduction	20.3%	30.1%	20.0%	28.5%
Led to interruption of any treatment	69.9%	49.9%	62.2%	40.2%

[a]One patient each from myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis.
[b]One patient each from acute myocardial infarction, cardiac arrest, fulminant hepatitis, gastrointestinal hemorrhage, intracranial hemorrhage, malignant neoplasm progression, and pneumonia.
Data cutoff date: Aug 24, 2018.

Pembrolizumab/axitinib

Powles KN426 ASCO-GU 2019

Treatment-Related Adverse Events: Incidence ≥20%



Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

Pembrolizumab/axitinib

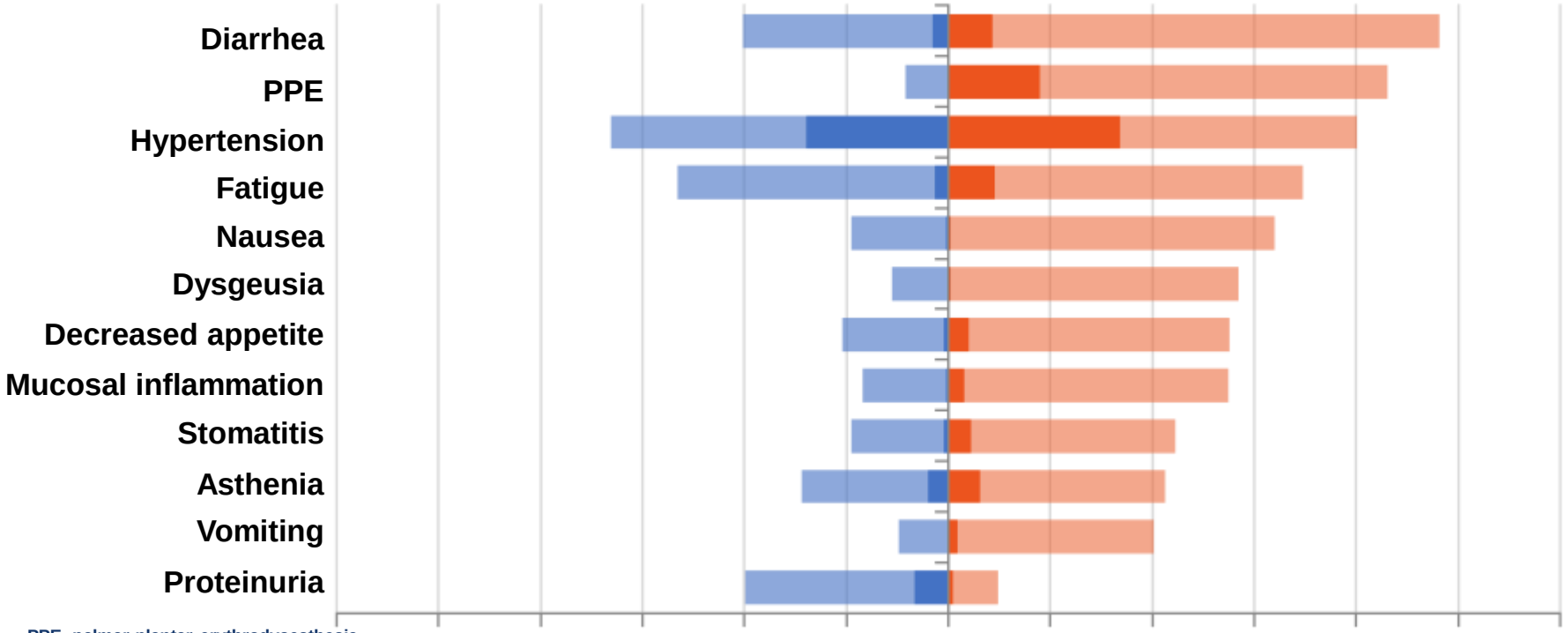
Powles KN426 ASCO-GU 2019

Adverse Events of Interest: Incidence ≥1%

	Pembro + Axi (N = 429)		Sunitinib (N = 425)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any	51.3%	10.7%	36.2%	1.9%
Hypothyroidism	35.4%	0.2%	31.5%	0.2%
Hyperthyroidism	12.8%	1.2%	3.8%	0
Adrenal insufficiency	3.0%	0.7%	0.2%	0
Hepatitis	2.8%	2.3%	0.5%	0.2%
Pneumonitis	2.8%	0.5%	0.2%	0
Thyroiditis	2.8%	0.2%	0.5%	0
Colitis	2.6%	1.9%	0.7%	0
Severe skin reactions	1.9%	1.2%	1.4%	0.7%
Infusion reactions	1.6%	0.2%	0.9%[a]	0.2%[a]
Nephritis	1.4%	0.2%	0.2%	0
Hypophysitis	1.2%	0.9%	0	0

[a]Includes the preferred terms "anaphylactic reaction" and "hypersensitivity," which were experienced by patients in the sunitinib arm.
Events are listed in order of incidence in the pembro + axi arm and are included regardless of attribution to study treatment or immune relatedness by the investigator. The specific events are based on a list of terms specified by the sponsor. In addition to the specific terms listed, related terms were also included. Data cutoff date: Aug 24, 2018.

Atezolizumab/bevacizumab Treatment-Related Aes ≥ *20% Frequency in Either Arm and > 5% Difference Between Arms*



PPE, palmar-plantar erythrodysesthesia.

Avelumab/axitinib

Secondary endpoint

TRAEs in all treated patients (N = 873)

	Avelumab + Axitinib (N = 434)		Sunitinib (N = 439)	
	All grades	Grade 3 (4)	All grades	Grade 3 (4)
All TRAEs, %	**95**	**51 (4)**	**96**	**48 (7)**
Diarrhea	54	5 (0)	45	3 (0)
Hypertension	48	24 (0)	32	15 (0)
Fatigue	36	3 (0)	36	4 (0)
Hand-foot syndrome	33	6 (0)	34	4 (0)
Dysphonia	27	1 (0)	3	0 (0)
Nausea	25	1 (0)	34	1 (0)
Hypothyroidism	24	< 1 (0)	13	< 1 (0)
Stomatitis	22	2 (0)	23	1 (0)
Decreased appetite	20	2 (0)	26	1 (0)
Dysgeusia	13	0 (0)	32	0 (0)
Increased alanine aminotransferase	13	4 (1)	10	2 (0)
Thrombocytopenia	3	< 1 (0)	18	5 (1)
Anemia	2	< 1 (0)	17	5 (< 1)
Neutropenia	1	< 1 (0)	18	7 (1)
TRAEs leading to discontinuation of all study drugs, %*	**4**		**8**	
TRAEs leading to death, %†	**1**		**< 1**	

Treatment-related adverse events (TRAEs) of any grade occurring in ≥ 20% of patients or grade 3-4 in ≥ 3% of patients are shown. * No events occurred in ≥ 1% of patients. † Grade 5 events occurred in 3 patients in the avelumab + axitinib arm (myocarditis, necrotizing pancreatitis, sudden death; n = 1 each); in 1 patient in the sunitinib arm (intestinal perforation).

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Avelumab/axitinib

AEs of special interest in all treated patients

Secondary endpoint

	Avelumab + Axitinib (N = 434)	
	All grades	**Grade 3 (4)**
All immune-related AEs, %	**38**	**8 (1)**
Hypothyroidism	21	< 1 (0)
Liver function test abnormalities	5	4 (< 1)
Adrenal insufficiency	2	1 (0)
Diarrhea	2	1 (0)
Acute kidney injury	1	1 (0)
Colitis	1	1 (0)
Hepatotoxicity	1	1 (0)
Infusion-related reaction, %	**12**	**1 (0)**

High-dose corticosteroids* were administered to 11% of patients who experienced an immune-related AE.

Immune-related AEs of any grade occurring in ≥ 5% of patients or grade 3 in ≥ 1% of patients are shown. * ≥40 mg total daily prednisone or equivalent.

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Comorbidity index CIRS (Cumulative Illness Rating Scale)

Name: _____

Each system is rated as follows:

1 = NONE:	No impairment to that organ/system.
2 = MILD:	Impairment does not interfere with normal activity; treatment may not be required; prognosis is excellent (examples: skin lesions, hernias, hemorrhoids)
3 = MODERATE:	Impairment interferes with normal activity; treatment is needed; prognosis is good (examples: gallstones, diabetes, fractures)
4 = SEVERE:	Impairment is disabling; treatment is urgently needed; prognosis is guarded (examples: respectable carcinoma, pulmonary emphysema, congestive heart failure)
5 = EXTREMELY SEVERE:	Impairment is life threatening; treatment is urgent or of no avail; prognosis is grave (examples: myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, embolus)

		Value 1-5
a.	Cardiac (heart only)	___
b.	Hypertension (rating is based on severity; affected systems are rated separately).	___
c.	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics).	___
d.	Respiratory (lungs, bronchi, trachea below the larynx).	___
e.	EENT (eye, ear, nose, throat, larynx).	___
f.	Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees; do no include diabetes).	___
g.	Lower GI (intestines, hernias).	___
h.	Hepatic (liver only).	___
i.	Renal (kidneys only).	___
j.	Other GU (ureters, bladder, urethra, prostate, genitals).	___
k.	Musculo-skeletal-integumentary (muscles, bone, skin)	___
l.	Neurological (brain, spinal cord, nerves; do not include dementia).	___
m.	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)	___
n.	Psychiatric/Behavioral (includes depression, anxiety, agitation, psychosis, not dementia).	___

Extermann M, et al. J Clin Oncol 1998; 16(4):1582-1587

Activities of daily living: ADL
Instrumental activities of daily living: IADL

Value No.

1. TOILET
   - 4 Cares for self at toilet completely, no incontinence
   - 3 Needs to be reminded, or needs help in cleaning self, or has rare (weekly at most) accidents
   - 2 Soiling or wetting while asleep, more than once a week
   - 1 Soiling or wetting while awake, more than once a week
   - 0 No control of bowels or bladder

2. FEEDING
   - 4 Eats without assistance
   - 3 Eats with minor assistance at meal times, with help preparing food or with help in cleaning up after meals
   - 2 Feeds self with moderate assistance and is untidy
   - 1 Requires extensive assistance for all meals
   - 0 Does not feed self at all and resists efforts of others to feed him

3. DRESSING
   - 4 Dresses, undressed and selects clothes from own wardrobe
   - 3 Dresses and undresses self, with minor assistance
   - 2 Needs moderate assistance in dressing or selection of clothes
   - 1 Needs major assistance in dressing but cooperated with efforts of other to help
   - 0 Completely unable to dress self and resists efforts of others to help

4. GROOMING (neatness, hair, nails, hands, face, clothing)
   - 4 Always neatly dressed and well-groomed, without assistance
   - 3 Grooms self adequately, with occasional minor assistance, e.g., in shaving
   - 2 Needs moderate and regular assistance or supervision in grooming
   - 1 Needs major assistance in dressing but cooperates with efforts of others to help
   - 0 Actively negates all efforts to others to maintain grooming

5. PHYSICAL AMBULATION
   - 4 Goes about grounds or city
   - 3 Ambulates within residence or about one block distant
   - 2 Ambulates with assistance of (check one): ____another person, ____ railing, ____ cane, ____ walker, or ____ wheelchair: ____ gets in and out without help ____ needs help in getting in and out
   - 1 Sits unsupported in chair or wheelchair, but cannot propel self without help
   - 0 Bedridden more than half the time

6. BATHING
   - 4 Bathes self (tub, shower, sponge bath) without help
   - 3 Bathes self, with help in getting in and out of tub
   - 2 Washes face and hands only, but cannot bathe rest of body
   - 1 Does not wash self but is cooperative with those who bathe him
   - 0 Does not travel at all

7. RESPONSIBILITY FOR OWN MEDICATION
   - 2 Is responsible for taking medication in correct dosages at correct time
   - 1 Takes responsibility if medication is prepared in advance in separate dosages
   - 0 Does not try to wash self, and resists efforts to keep him clean

TOTAL SCORE ____

Value No.

1. ABILITY TO USE TELEPHONE
   - 3 Operates telephone on own initiative; looks up and dials numbers, etc.
   - 2 Dials a few well known numbers
   - 1 Answers telephone but does not dial
   - 0 Does not use telephone at all

2. SHOPPING
   - 3 Takes care of all shopping needs independently
   - 2 Shops independently for small purchases
   - 1 Needs to be accompanied on any shopping trip
   - 0 Needs to have meals prepared and served

3. FOOD PREPARATION
   - 3 Plans, prepares and serves adequate meals independently
   - 2 Prepares adequate meals if supplied with ingredients
   - 1 Heats and serves prepared meals, or prepares meals but does not maintain adequate diet
   - 0 Needs to have meals prepared and served

4. HOUSEKEEPING
   - 4 Maintains house alone or with occasional assistance (e.g., heavy-work domestic help)
   - 3 Performs light daily tasks such as dish-washing and bed-making
   - 2 Performs light daily tasks but cannot maintain acceptable level of cleanliness
   - 1 Needs help with all home maintenance tasks
   - 0 Does not participate in any housekeeping tasks

5. LAUNDRY
   - 2 Does personal laundry completely
   - 1 Launders small items; rinses socks, stockings, etc.
   - 0 All laundry must be done by others

6. MODE OF TRANSPORTATION
   - 4 Travels independently on public transportation or drives own car
   - 3 Arranges own travel via taxi, but does not otherwise use public transportation
   - 2 Travels on public transportation when assisted or accompanied by another
   - 1 Travel limited to taxi or automobile, with assistance of another
   - 0 Does not travel at all

7. RESPONSIBILITY FOR OWN MEDICATION
   - 2 Is responsible for taking medication in correct dosages at correct time
   - 1 Takes responsibility if medication is prepared in advance in separate dosages
   - 0 Is not capable of dispensing own medication

8. ABILITY TO HANDLE FINANCES
   - 2 Manages financial matters independently (budgets, write checks, pays rent and bills, goes to Bank) collects and keeps track of income
   - 1 Manages day-to-day purchases, but needs help with banking, major purchases, etc.
   - 0 Incapable of handling money

TOTAL SCORE _____

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