La gestione della tossicità

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Disclosures

- No pertinent C.O.I. with this presentation
- Advisory Boards/Honoraria/Consultant for:
  - Astellas
  - BMS
  - Janssen
  - Novartis
  - Pfizer
  - Roche

New toxicity profile for novel immunotherapy agents: focus on immune-checkpoint inhibitors

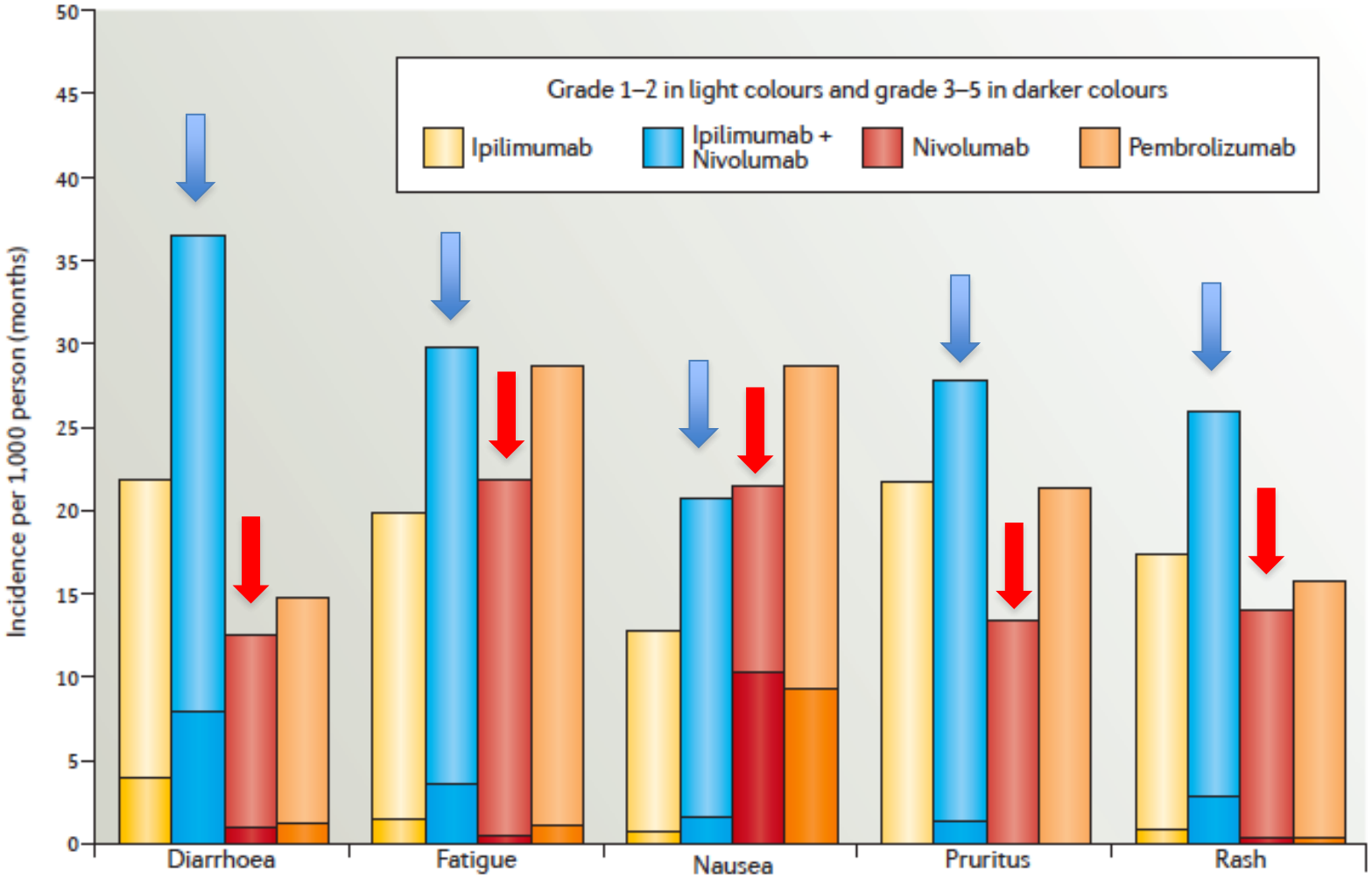
C Ciccarese[*], S Alfieri[*], M Santoni, D Santini, M Brunelli, C Bergamini, L Licitra, R Montironi, G Tortora[††] & F Massari[†††]

- *A focus on immunotoxicity is important in the education of clinicians and will improve patient safety.*

- *There is a willingness to tailor specific immune-therapies to each cancer patient, and to stimulate researchers through understanding of the physiopathogenesis, using the hypothesis that immune-mediated toxicities can be used as predictors of response or a prognostic sign of survival, thereby guiding therapeutic decisions.*

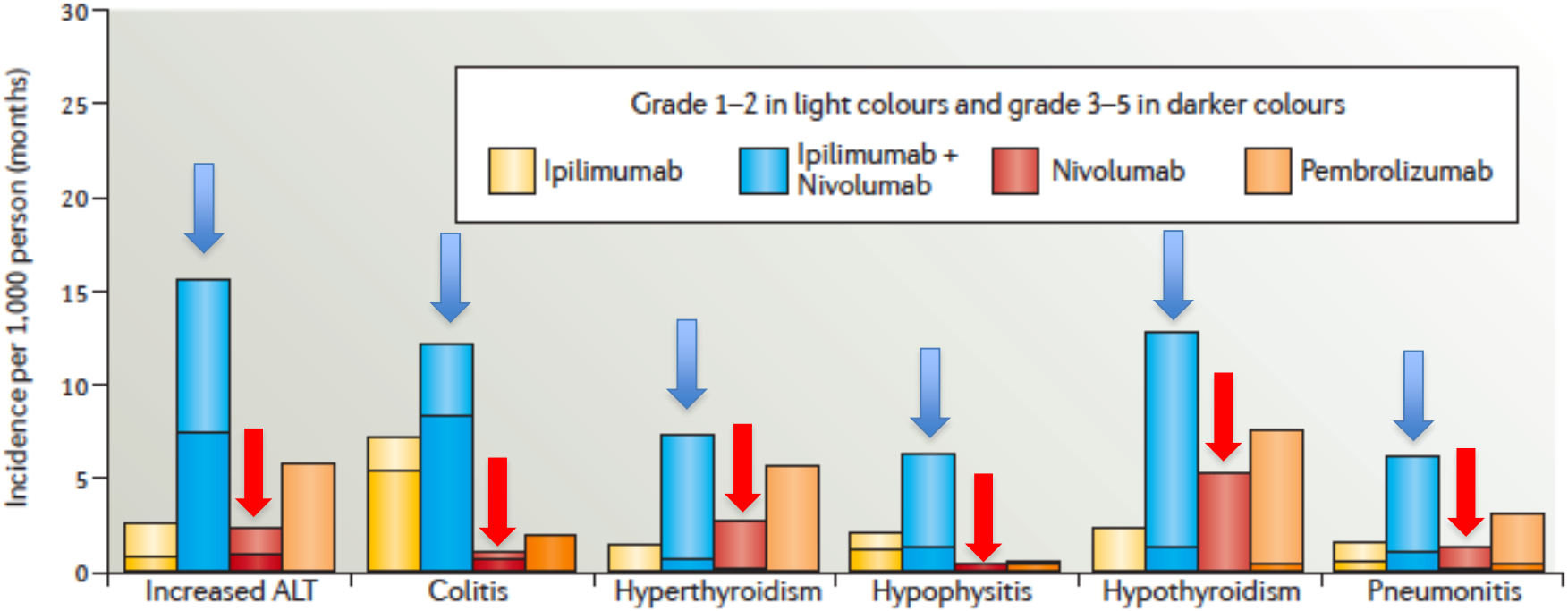
Ciccarese C, et al. Exp Opin Drug Met Tox. 2016;12(1): 57-75

Most common adverse events in patients treated with ipilimumab, pembrolizumab, nivolumab, or ipilimumab plus nivolumab



Boutros, et al. Nat Rev Clin Oncol. 2016;13: 473-486

Adverse events of special interest noted with immune-checkpoint inhibitors.



Boutros, et al. Nat Rev Clin Oncol. 2016;13: 473-486

Nivolumab: adverse events

DRUG DOSE (mg/kg)	Cancer type (N Patiients)	AEs Any Grade	Type Total % (dose-dependent %)	AEs G3-4	Type (Total)	Ir-AEs G3-4 Total % (dose-dependent %)	Treatment discontinuation for AEs
Nivolumab 0.1 mg/kg 0.3 mg/kg 1 mg/kg 3 mg/kg 10 mg/kg	Advanced cancer (296)	70% total 78% 58% 75% 68% 69%	Fatigue 24% (22, 26, 24, 24, 25) Decreased appetite 8% (6, 11, 8, 10, 8) Rash 12% (17, 11, 20, 8, 9) Diarrhea 11% (6, 11, 19, 6, 9) Pruritus 10% (0, 11, 17, 8, 7) Nausea 8% (0, 5, 6, 14, 9)	14%	Fatigue (2%) Diarrhea (1%) Abdominal pain (1%) ALT increased (1%) AST increased (1%) Hypophosphatemia (1%) Pneumonitis (1%) Lymphopenia (1%)	Total G3-4 6% [any G 41%] Pneumonitis 1% (0, 0, 3, 0, 1) AST increased 1% (0, 0, 0, 2, 1) ALT increased 1% (0, 0, 0, 0, 2) Allergic rhinitis 1% (0, 0, 0, 0, 2)	5%
Nivolumab 1 mg/kg 3 mg/kg 10 mg/kg	NSCLC (129)	70.5% total 64% 68% 76%	Fatigue 24% (24, 19, 27) Decreased appetite 12.4% (12, 11, 14) Diarrhea 10% (12, 11, 8.5)	14% total 15% 13.5% 14%	Fatigue (3%) Lymphopenia (2.3%) Pnaumonitis (2.3%)	G3-4 4.7% [Any G 41%] GI 0.8% Polmunary 2.3% Hepatic 8.0% Infusion reaction 0.8%	-
Nivolumab 3 mg/kg vs Docetaxel	Squamous NSCLC (272)	58%	Fatigue 16% Decreased appetite 11% Asthenia 10% Nausea 9% Diarrhea 8%	7%	Fatigue (1%) Decreased appetite (1%) Leukopenia (1%)	Nephritis Pneumonitis Colitis	3%
Nivolumab 0.1 mg/kg 0.3 mg/kg 1 mg/kg 3 mg/kg 10 mg/kg	Melanoma (107)	84% total 76.5% 78% 97% 88% 70%	Fatigue 32% (29, 28, 34, 47, 20) Rash 23% (18, 17, 37, 12, 20) Diarrhea 18% (6, 11, 29, 12, 20) Pruritus 13% (0, 6, 23, 18, 10)	22% 29% 17% 14% 35% 25%	Fatigue (1.9%) Diarrhea (1.9%) Abdominal pain (1.9%) Leukopenia (2.8%)	G3-4 5% [any G 54%] Skin 0%[any G 36%] Diarrhea 2% [any G 18%] Colitis 1%[any G 2%] Endocrinopaties 2% [any G 13% Hepatic 1% [any G 6.5%]	-
Nivolumab 3 mg/kg [vs DTIC]	Melanoma (418)	74.3%	Fatigue 19.9% Pruritus 17 % Nausea 16.5%	11.7%	Diarrhea (1%) Rash (0.5%) Pruritus (0.5%) Vomiting (0.5%)	Diarrhea (1%) ALT increased (1%)	6.8%
Nivolumab 3 mg/kg [vs DTIC or CBDCA/TXL]	Melanoma (631)	68%	Fatigue 25% Pruritus 16% Diarrhea 12% Nausea 9%	G3 8% G4 1%	Increased lipase (1%) Fatigue (1%) Anemia (1%) Increased ALT (1%)	G3-4 3% Liver function abnormalities	3%

Ciccarese C, et al. Exp Opin Drug Met Tox. 2016;12(1): 57-75

Nivolumab: adverse events - mRCC

DRUG DOSE (mg/kg)	Cancer type (N Patiients)	AEs Any Grade	Type Total % (dose-dependent %)	AEs G3-4	Type (Total)	Ir-AEs G3-4 Total % (dose-dependent %)	Treatment discontinuation for AEs
Nivolumab 1 mg/kg 10 mg/kg	RCC (36)	85% total 83% 87%	Fatigue 41% (33, 50) Rash 26.5% (39, 12.5) Diarrhea 18% (28, 6) Pruritus 18% (22, 12.5) ALT increased 12% (11, 12.5)	18% total 11% 25%	Pruritus (3%) ALP increased (3%) Hypophosphatemia (6%)	G3-4 9% [any G 56%] Pruritus 2.9% Macular rash 2.9% Increased ALT 2.9% Acute respiratory failure 2.9%	-
Nivolumab 0.3 mg/kg 2 mg/kg 10 mg/kg	RCC (168)	73% total 75% 67% 78%	Fatigue (24, 22, 35) Nausea (10, 13, 13) Pruritus (10, 9, 11) Diarrhea (3, 11, 15) Hypersensitivity (2, 2, 17)	11% total 5% 17% 13%	Nausea (2, 2, 0%) Pruritus (0, 2, 0%) Arthralgia (0, 0, 2%)	Hepatic (2, 4, 0%) Skin (0, 4, 0%) Endocrine (0, 4, 0%) GI (0, 2, 0%)	7% total 2% 11% 7%
Nivolumab 3 mg/kg [Vs Everolimus]	RCC (821)	79% [vs 88%]	Fatigue 33% Pruritus 14% Nausea 14% Diarrhea 12% Decreased appetite 12%	19% [vs 37%]	Fatigue (2%) Anemia (2%) Diarrhea (1%) Pneumonitis (1%) Hyperglycemia (1%)	-	8% [vs 13%]

Ciccarese C, et al. Exp Opin Drug Met Tox. 2016;12(1): 57-75

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ORIGINAL REPORT

Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab

David F. McDermott, Charles G. Drake, Mario Sznol, Toni K. Choueiri, John D. Powderly, David C. Smith, Julie R. Brahmer, Richard D. Carvajal, Hans J. Hammers, Igor Puzanov, F. Stephen Hodi, Harriet M. Kluger, Suzanne L. Topalian, Drew M. Pardoll, Jon M. Wigginton, Georgia D. Kollia, Ashok Gupta, Dan McDonald, Vindira Sankar, Jeffrey A. Sosman, and Michael B. Atkins

- *Grade 3 to 4 treatment-related adverse events occurred in 18% of patients; all were reversible*
- *Toxicities were generally manageable*

McDermott DF, et al. J Clin Oncol 2015; 33:2013-2020

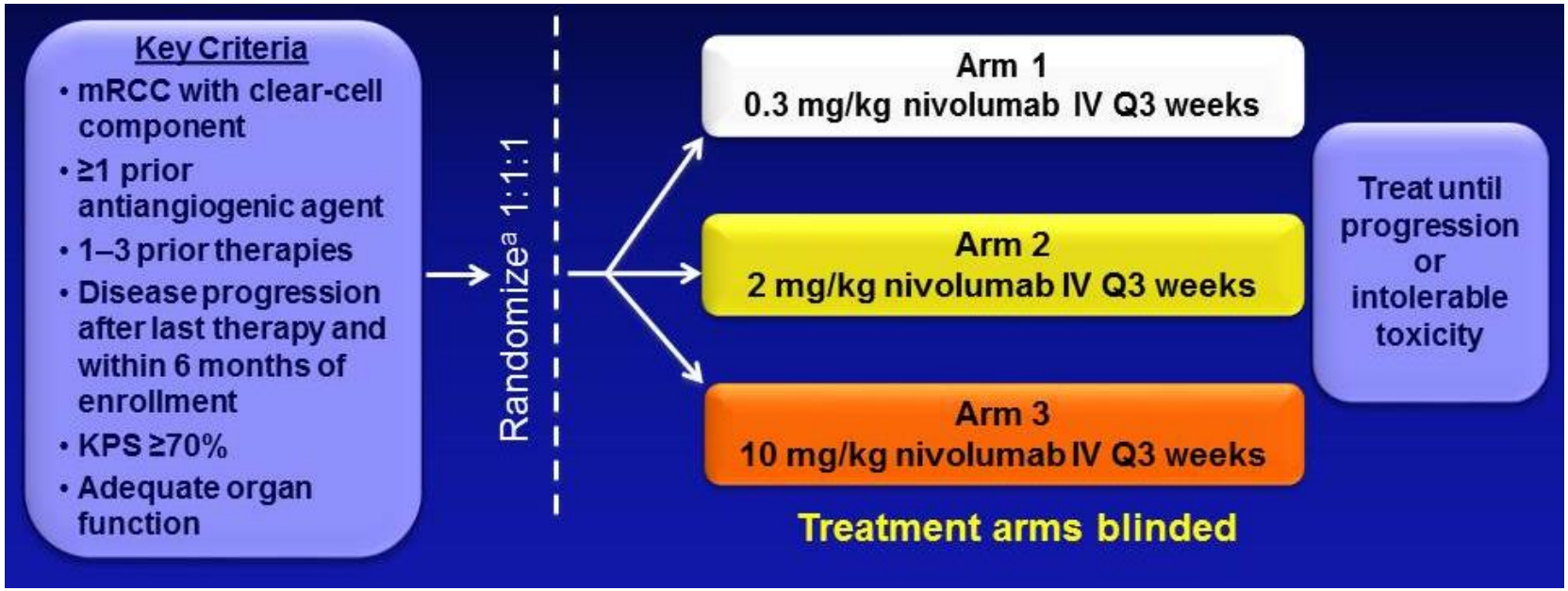
Presentation 810O
Abstract 8020

Randomized, dose-ranging phase II trial of nivolumab for metastatic renal cell carcinoma (mRCC)

R. Motzer, B. Rini, D.F. McDermott, B. Redman, T. Kuzel, M.R. Harrison, U.N. Vaishampayan, H. Drabkin, S. George, T. Logan, K. Margolin, E.R. Plimack, I. Waxman, A. Lambert, H. Hammers

Motzer R et al. ESMO 2014; Abstract 8020 (Presentation 810O)

Phase II study design



- Primary objective
  - To assess whether a dose-response relationship exists in the 0.3, 2 and 10 mg/Kg arms as measured by PFS (RECIST v1.1)
- Secondary objectives
  - To assess PFS, ORR, OS and safety
- Exploratory objectives
  - To assess efficacy by PD-L1 expression

Motzer R et al. ESMO 2014; Abstract 8020 (Presentation 810O)

Treatment-related adverse events

	Nivolumab, mg/kg					
	0.3 (n = 59)		2.0 (n = 54)		10 (n = 54)	
Patients with event, %	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any event	**75**	**5**	**67**	**17**	**78**	**13**
Fatigue	24	0	22	0	35	0
Nausea	10	2	13	2	13	0
Pruritus	10	0	9	2	11	0
Rash	9	0	7	0	13	0
Diarrhea	3	0	11	0	15	0
Appetite decreased	3	0	13	0	4	0
Dry mouth	3	0	6	0	11	0
Dry skin	2	0	6	0	13	0
Hypersensitivity	2	0	2	0	17	0
Arthralgia	2	0	7	0	15	2

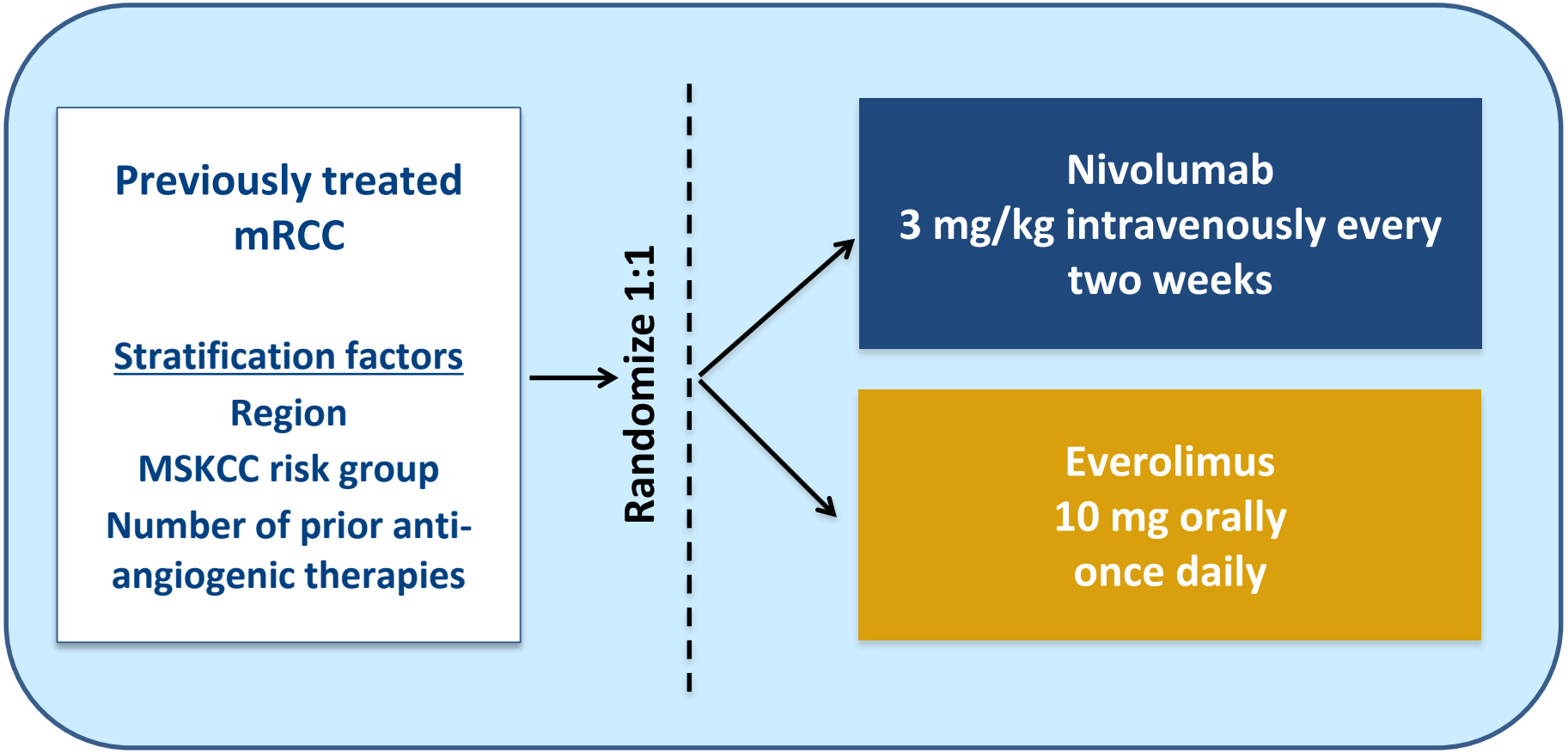
Motzer R et al. ESMO 2014; Abstract 8020 (Presentation 810O)

Phase II Study of Nivolumab in Metastatic RCC: Adverse Events

Treatment-Related AE, n (%)	Nivolumab 0.3 mg/kg (n = 59)		Nivolumab 2 mg/kg (n = 54)		Nivolumab 10 mg/kg (n = 54)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any treatment-related AE	44 (75)	3 (5)	36 (67)	9 (17)	42 (78)	7 (13)
Immune-related AE						
▪ Skin	13 (22)	0	12 (22)	2 (4)	15 (28)	0
▪ Endocrine	4 (7)	0	6 (11)	2 (4)	8 (15)	0
▪ GI	3 (5)	0	6 (11)	1 (2)	8 (15)	0
▪ Pulmonary	3 (5)	0	2 (4)	0	4 (7)	0
▪ Hepatic	2 (3)	1 (2)	4 (7)	2 (4)	3 (6)	0
▪ Renal	1 (2)	0	0	0	1 (2)	0

Motzer RJ, et al. J Clin Oncol. 2014

CheckMate 025



- Patients were treated until progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

MSKCC, Memorial Sloan-Kettering Cancer Center.

Motzer RJ et al, N Engl J Med. 2015; 373(19):1803-13

CheckMate 025 - Safety

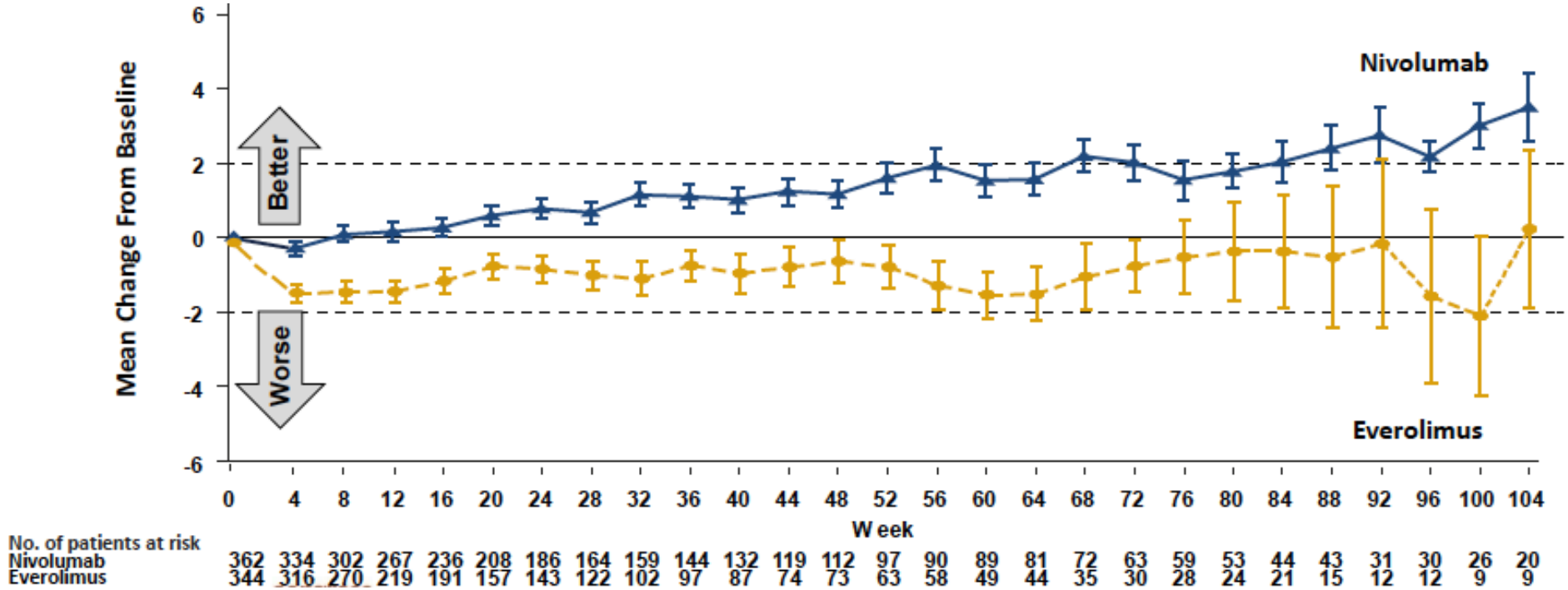
Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.

Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

Motzer RJ et al, N Engl J Med. 2015; 373(19):1803-13

Change from baseline in quality of life scores on FSKI-DRS

A clinically meaningful and statistical improvement from baseline in QoL was seen with nivolumab for the duration of the study



Motzer RJ et al, N Engl J Med. 2015; 373(19):1803-13

Summary of Safety in Phase III CheckMate 025 Study

	Nivolumab N = 406		Everolimus N = 397	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	78.6	18.7	87.9	36.5
Treatment-related AEs leading to discontinuation, %	7.6	4.7	13.1	7.1

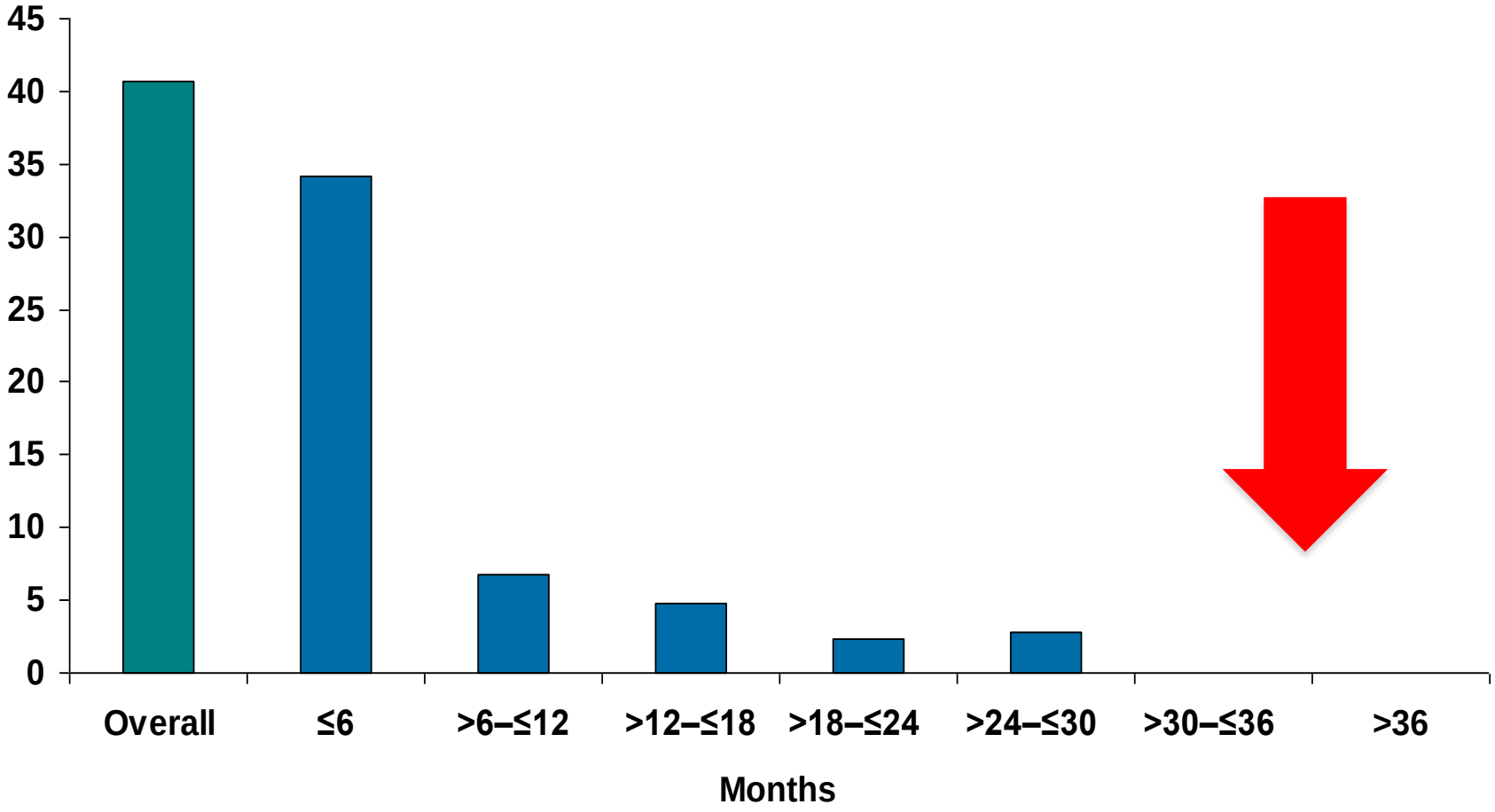
Motzer RJ et al, N Engl J Med. 2015; 373(19):1803-13

Summary of Long-term Safety in Phase I and II Studies

	Phase I N = 34		Phase II N = 167	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AEs, %	85.3	17.6	73.1	14.4
Treatment-related AEs leading to discontinuation, %	8.8	2.9	9.6	3.6

McDermott DF, et al. J Clin Oncol 2015; 33:2013-2020
Motzer RJ, et al. J Clin Oncol. 2014

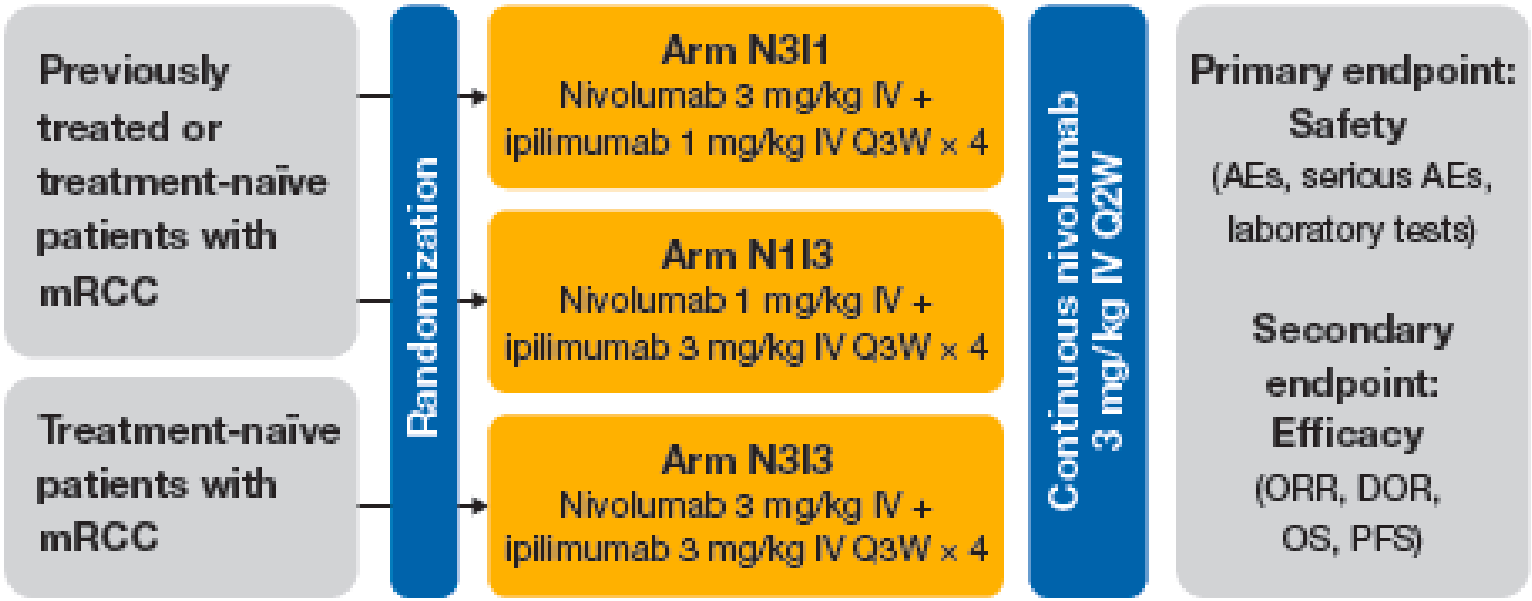
Emergence of Select Treatment-related AEs (Any Grade) Over Time in Phase II Study



Select treatment-related AEs included endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin

McDermott DF, ASCO 2016

Phase I Study of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study



- Long-term follow-up of previously treated and treatment-naïve patients with mRCC treated with nivolumab and ipilimumab demonstrated a manageable safety profile
  - There were no new safety signals
  - Treatment-related AEs and select treatment-related AEs were consistent with those in other studies of nivolumab and ipilimumab
  - Fewer AEs were associated with N3I1 than with N1I3

Hammers HJ et al., Poster 1062P - ESMO Congress 2016

Phase I Study of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma: The CheckMate 016 Study

Preferred term, n (%)	N3I1 (n = 47)		N1I3 (n = 47)	
	All grades	Grade 3/4	All grades	Grade 3/4
Total patients with event	43 (91.5)	18 (38.3)	45 (95.7)	29 (61.7)
Fatigue	24 (51.1)	0 (0)	32 (68.1)	3 (6.4)
Rash	15 (31.9)	0 (0)	12 (25.5)	0 (0)
Pruritus	15 (31.9)	0 (0)	17 (36.2)	0 (0)
Nausea	13 (27.7)	1 (2.1)	21 (44.7)	0 (0)
Arthralgia	12 (25.5)	0 (0)	10 (21.3)	0 (0)
Diarrhea	11 (23.4)	2 (4.3)	21 (44.7)	7 (14.9)
Chills	11 (23.4)	0 (0)	4 (8.5)	0 (0)
Pyrexia	10 (21.3)	2 (4.3)	7 (14.9)	0 (0)
Hypothyroidism	9 (19.1)	0 (0)	13 (27.7)	0 (0)
Increased lipase	9 (19.1)	7 (14.9)	16 (34.0)	13 (27.7)
Increased AST	8 (17.0)	2 (4.3)	15 (31.9)	6 (12.8)
Increased ALT	7 (14.9)	2 (4.3)	14 (29.8)	10 (21.3)
Decreased appetite	6 (12.8)	0 (0)	14 (29.8)	0 (0)
Vomiting	7 (14.9)	1 (2.1)	11 (23.4)	0 (0)

AST = aspartate aminotransferase

Hammers HJ et al., Poster 1062P - ESMO Congress 2016

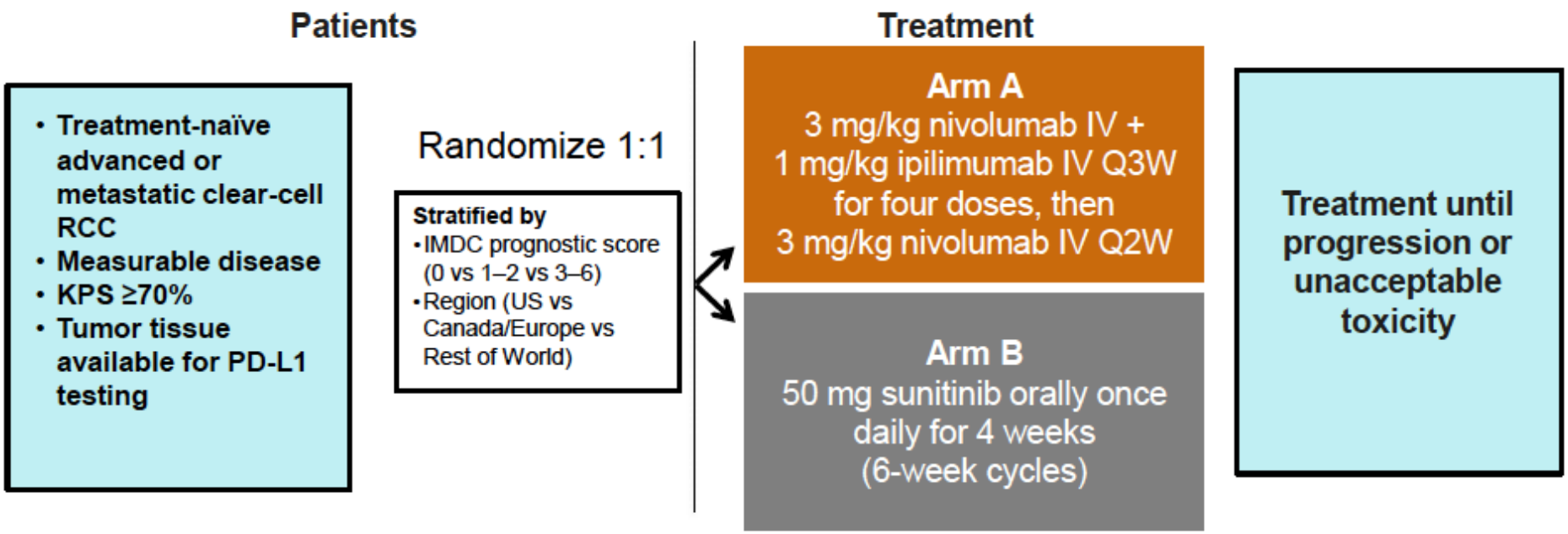
MADRID 2017 ESMO congress

CheckMate 214: Efficacy and Safety of Nivolumab Plus Ipilimumab vs Sunitinib for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma, Including IMDC Risk and PD-L1 Expression Subgroups

Bernard Escudier,[1] Nizar M. Tannir,[2] David F. McDermott,[3] Osvaldo Arén Frontera,[4] Bohuslav Melichar,[5] Elizabeth R. Plimack,[6] Philippe Barthelemy,[7] Saby George,[8] Victoria Neiman,[9] Camillo Porta,[10] Toni K. Choueiri,[11] Thomas Powles,[12] Frede Donskov,[13] Pamela Salman,[14] Christian K. Kollmannsberger,[15] Brian Rini,[16] Sabeen Mekan,[17] M. Brent McHenry,[17] Hans J. Hammers,[18] Robert J. Motzer[19]

Escidier B et al. ESMO 2017; Abstract LBA5

CheckMate 214: Study design



Escidier B et al. ESMO 2017; Abstract LBA5

Treatment-related adverse events: All treated patients

	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]	

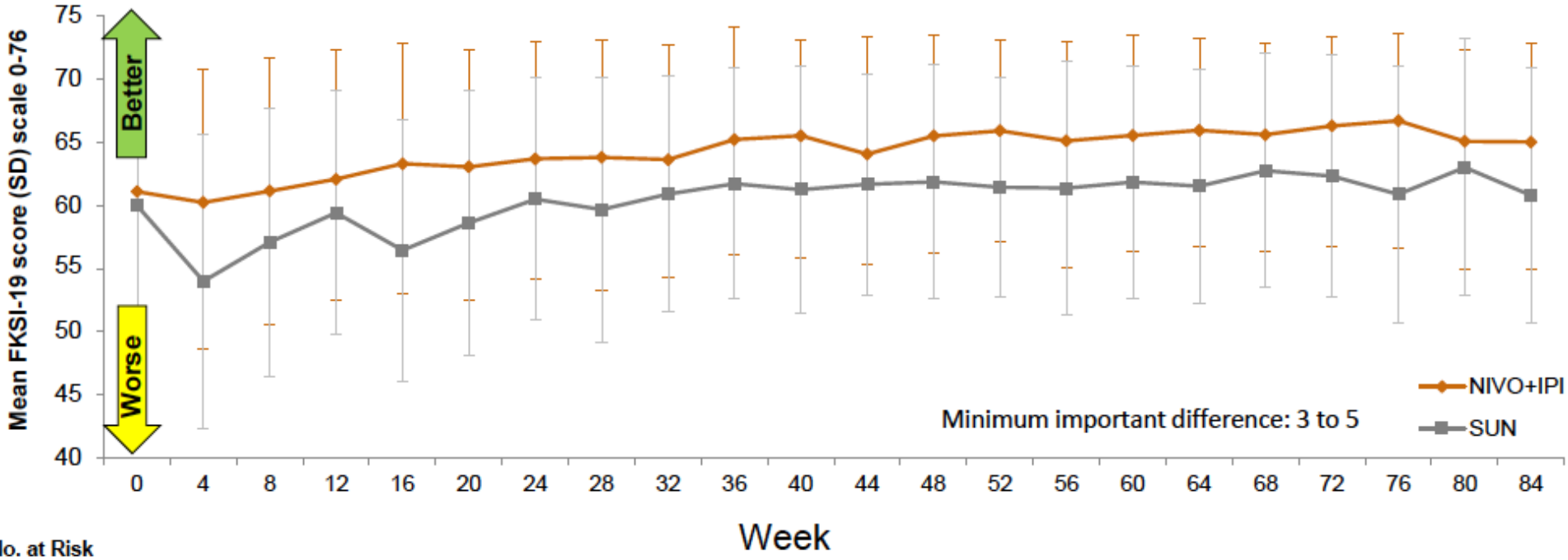
Escidier B et al. ESMO 2017; Abstract LBA5

Immune-mediated adverse events: All treated patients

	NIVO + IPI N = 547	
Category, %	Any grade	Grade 3–4
Rash	17	3
Diarrhea/colitis	10	5
Hepatitis	7	6
Nephritis and renal dysfunction	5	2
Pneumonitis	4	2
Hypersensitivity/infusion reaction	1	0
Hypothyroidism	19	<1
Hyperthyroidism	12	<1
Adrenal insufficiency	8	3
Hypophysitis	5	3
Thyroiditis	3	<1
Diabetes mellitus	3	1

Escidier B et al. ESMO 2017; Abstract LBA5

Health-related quality of life: Intention to treat



No. at Risk

NIVO	532	502	399	350	323	298	288	188	142	190	126	118	154	118	103	114	108	104	119	89	90	103
SUN	515	502	460	402	383	294	311	169	111	215	134	98	173	103	92	156	91	71	132	82	64	106

Escidier B et al. ESMO 2017; Abstract LBA5

MADRID 2014 ESMO congress

Poster Discussant Summary

1052PD
Abstract 7506

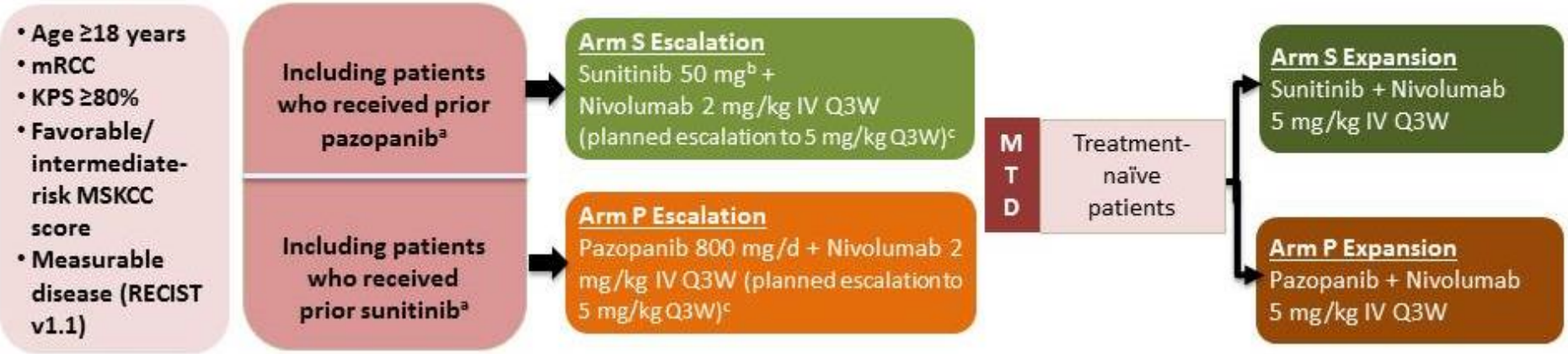
Nivolumab (N) (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib (S) or pazopanib (P) in patients with metastatic renal cell carcinoma (mRCC)

A. Amin, E.R. Plimack, J.R. Infante, M.S. Ernstoff, B. Rini, D.F. McDermott, J. Knox, S.K. Pal, M.H. Voss, P. Sharma, C. Kollmannsberger, D. Heng, J. Spratlin, Y. Shen, J. Kurland, P. Gagnier, H. Hammers

Amin A et al. ESMO 2014; Abstract 7506 (1052PD)

Phase I study design

- Phase I, open-label study



- Primary objective
  - Overall safety and tolerability, the maximum tolerated dose (MTD) and recommended phase II dose
- Secondary objective
  - Preliminary antitumor activity of each combination

Amin A et al. ESMO 2014; Abstract 7506 (1052PD)

Result: safety

Grade 3/4 treatment-related adverse events (AEs) occurring in ≥10% of patients	S + N (n = 33)		P + N (n = 20)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Total patients with an event, n (%)	33 (100)	27 (81.8)	20 (100)	14 (70.0)
Hypertension	16 (48.5)	6 (18.2)	5 (25.0)	2 (10.0)
Elevated alanine aminotransferase	13 (39.4)	6 (18.2)	5 (25.0)	4 (20.0)
Hyponatremia	6 (18.2)	5 (15.2)	0	0
Decreased lymphocyte count	6 (18.2)	5 (15.2)	1 (5.0)	1 (5.0)
Diarrhea	20 (60.6)	3 (9.1)	12 (60.0)	4 (20.0)
Elevated aspartate aminotransferase	12 (36.4)	3 (9.1)	6 (30.0)	4 (20.0)
Fatigue	27 (81.8)	3 (9.1)	12 (60.0)	3 (15.0)

- No grade 5 treatment-related AEs observed
- Treatment-related pneumonitis observed in one patient each arm
- Discontinuation due to treatment-related AEs in 12 patients in arm S + N and 5 patients in arm P + N

Amin A et al. ESMO 2014; Abstract 7506 (1052PD)

Is there any ideal combination?

	ARM S Sunitinib + nivolumab	Arm P Pazopanib 800 mg QD +nivolumab 2 mg/kg Q3W (N2)	(N3+I1) Nivolumab 3mg/kg + Ipilimumab 1mg/kg	(N1 +I3) Nivolumab 1mg/kg + ipilimumab 3mg/kg
Prior therapy	42% prior therapy	100%	77% prior therapy	
Nb.	n=33	n=20	n=21	n=23
MSKCC risk	Favorable/Intermediate (95%)		Favorable/Intermediate (100%)	
ORR (%)	52%	45%	43%	48%
Median DOR range (wks)	54 18.1-80	45 23.1-68.5	31.1 4.1+ – 42.1+	NR 12.1+ – 35.1+
Median PFS (wks)	48.9	31.4	36.6	38.3
Gr. 3/4 Toxicity (%)	24/33 (73%)	12/20 (60%)	5/21 (24%)	14/23 (61%)
	ALT elevation 18% Hypertension 18% Hyponatremia 15%	4 DLTs (stopped) (LFTs=3)	ALT elevation 0% Diarrhea 4.8% Fatigue 0%	ALT elevation 26% Diarrhea 13% Fatigue 8%

Escudier B; ECCO-ESMO 2015

Recognition and Management of Immunotherapy Related Toxicities

Management of immune-related adverse events excluding skin and endocrine toxicities

Grade (CTCAE v4)	Management	Follow-up monitoring
Grade 1	• Continue immunotherapy • Treatment of symptoms	• Frequent monitoring • If worsening: treat as grade 2 or 3/4
Grade 2	• Delay immunotherapy • Treatment of symptoms	• Resume immunotherapy when symptoms improve to grade 1 • Consider glucocorticosteroids 0.5–1 mg/kg per day if symptoms persist more than 5–7 days • If worsening with steroids: treat as grade 3/4
Grade 3–4	• Discontinue immunotherapy except in patients with skin or endocrine toxicities • Initiate glucocorticosteroids 1–2 mg/kg per day • Consider hospitalization	• Continue glucocorticosteroids until grade 1 • Taper dose of steroids over at least one month • If persistent or worsening: consider alternative immunosuppressive therapy

Boutros, et al. Nat Rev Clin Oncol. 2016;13: 473-486

Summary of CTLA-4 Blockade Immune-Mediated Toxicities

- Toxicity related to ipilimumab appears to be dose related
- Toxicity-related death occurred in < 1% of cases

Common (> 20%)

- Rash, pruritus
- Fevers, chills, lethargy
- ***Diarrhea/colitis***

Occasional (3% to 20%)

- Hepatitis/liver enzyme abnormalities
- Endocrinopathies: hypophysitis, thyroiditis, adrenal insufficiency

Rare (< 2%)

- Episcleritis/uveitis
- Pancreatitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Lymphadenopathy (sarcoid)
- Thrombocytopenia
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- Toxicity less common than with anti–CTLA-4 but can be fatal

Occasional (5% to 20%)

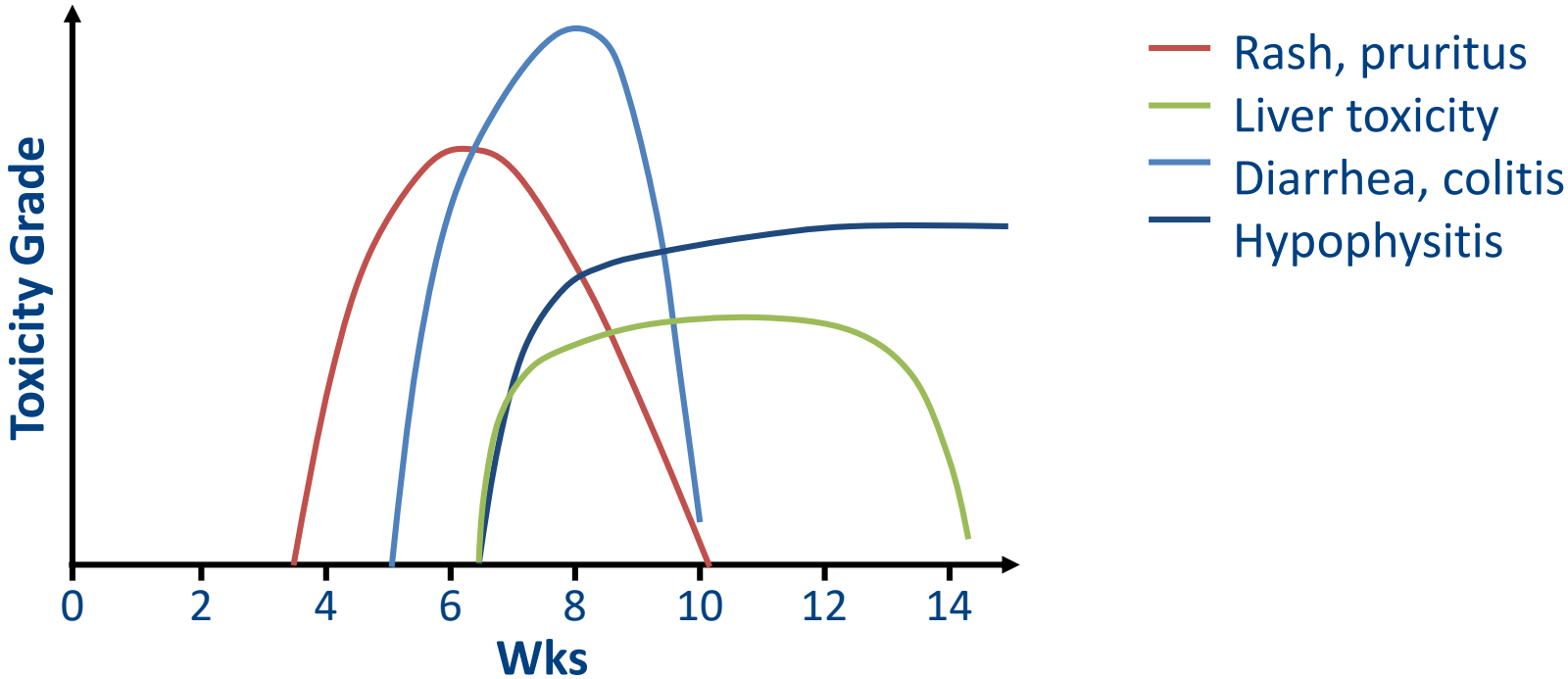
- Fatigue, headache, arthralgia, fevers, chills, lethargy
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- ***Diarrhea/colitis***
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

Rare (< 5%)

- ***Pneumonitis***
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Kinetics of Appearance of irAEs With Checkpoint Blockade



- Data from pts receiving anti–PD-1 antibodies q2w for ≥ 3 yrs show most irAEs occur by Wk 24 (6 mos)
- Toxicities with PD-1/PD-L1 agents may take longer to resolve than with ipilimumab, so long-term surveillance is recommended

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697.
Weber JS, et al. J Clin Oncol. 2015;[Epub ahead of print].

Colitis: Immune Checkpoint Inhibitor Toxicity

- Ulceration in descending colon
- Focal active colitis
- Alterations in crypt epithelium

Maker AV, et al. Ann Surg Oncol. 2005;12:1005-1016.

Management of diarrhea or colitis associated with immunotherapy

Severity[a]	Evaluation	Management	Follow-up
Grade 1: <4 bowel movements over baseline; asymptomatic colitis	Clinical examination; abdominal imaging as indicated	Antimotility agents; oral hydration; consider colitis diet	Close follow-up for worsening symptoms; continue treatment
Grade 2: 4–6 bowel movements per day over baseline; requiring IV fluids for <24 h; abdominal pain; blood in stools; not limiting ADLs	Clinical examination; abdominal imaging as indicated; consider colonoscopy	Hold treatment; antimotility agents; oral/IV hydration; If symptoms persist >5 days, consider prednisone 0.5–1 mg/kg/day; if no improvement after 3–5 days, treat as Grade 3 (1–2 mg/kg steroids)	Close follow up for worsening symptoms; may resume treatment if symptoms improve to < grade 2; if started, taper steroids over ≥1 month
Grade 3: ≥7 bowel movements over baseline; requiring IV fluids for ≥24 h; severe abdominal pain	Hospitalization; GI consult and colonoscopy; abdominal imaging as indicated	Hold treatment; corticosteroids equivalent to 1–2 mg/kg/day of prednisone; IV hydration and electrolyte repletion; consider adding infliximab 5 mg/kg or mycophenolate mofetil if no clinical improvement despite steroids	Surgical interventions as indicated for perforation; permanently discontinue treatment for recurrent grade 3 colitis
Grade 4: Peritoneal signs; perforation; life threatening	Hospitalization; GI consult and colonoscopy; abdominal imaging as indicated	Discontinue treatment; corticosteroids equivalent to 1–2 mg/kg/day of prednisone; IV hydration and electrolyte repletion; consider adding infliximab 5 mg/kg or mycophenolate mofetil if no clinical improvement despite steroids; surgical intervention as needed	Permanently discontinue treatment

Tripathi A, et al. Curr Opin Urol 2016

Prompt Treatment of Colitis

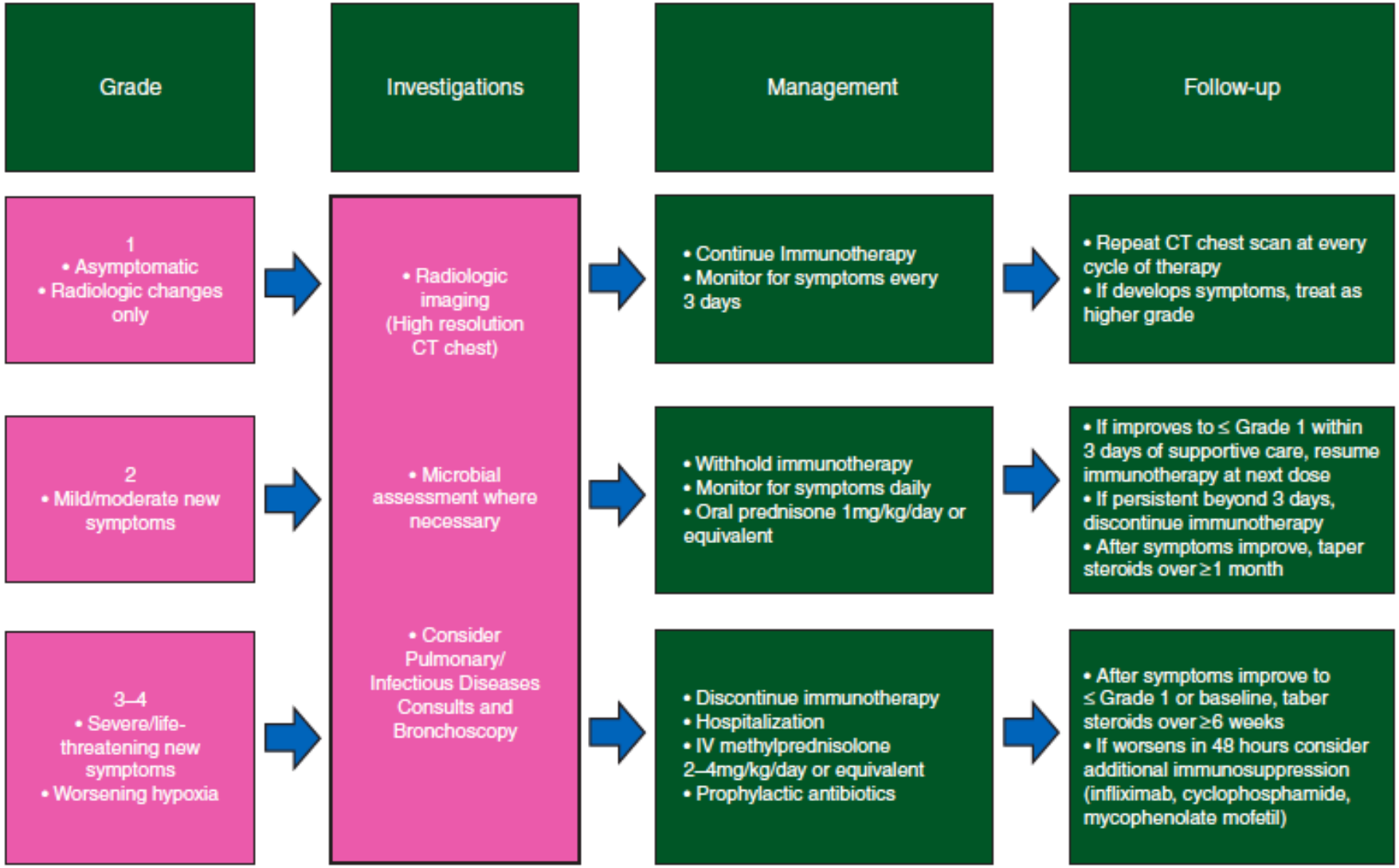
- A retrospective analysis of 836 trial pts showed that early initiation of steroid treatment for colitis led to faster resolution of symptoms than delayed steroid treatment[1]
- Several case studies support use of infliximab to further blunt immune response in steroid-refractory colitis[2,3]
- Bloody diarrhea uncommon but may indicate more severe colitis[4]
- At colonoscopy, colitis typically affects the distal colon with sparing of rectum[4]

1. O'Day S, et al. ASCO 2011. Abstract 8554. 2. Pagès C, et al. Melanoma Res 2013;23:227-230. 3. Merrill SP, et al. Ann Pharmacother. 2014;48:806-810. 4. Howell M, et al. Lung Cancer. 2015;88:117-123.

Pulmonary Toxicities related to Immunotherapy

- Several pulmonary inflammatory complications reported with ipilimumab. (sarcoidosis and organizing inflammatory pneumonia)
- Pneumonitis rarely in patients treated with PD-1 blocking agents, but with occasional fatal consequence in early trials. (< 3%)
- Symptoms of an upper respiratory infection, new cough, or SOB, pneumonitis should be considered and imaging is warranted
- In moderate to severe symptoms and/or radiographic findings, bronchoscopy should be considered to exclude infectious processes prior to starting immunosuppression.
- In severe cases, treatment with 2 mg/kg of intravenous methylprednisone and consideration of additional immunosuppression including infliximab, mycophenolate mofetil, cyclophosphamide if necessary

Management of pulmonary toxicities with immunotherapy



Naidoo J, et al. Annals of Oncology 2015; 26: 2375–2391.

Endocrine Toxicities

- Following ipilimumab therapy, incidence of hypophysitis 8% and hypothyroidism/thyroiditis 6%; primary adrenal dysfunction rare
- Combination of ipilimumab and nivolumab associated with 22% incidence of thyroiditis or hypothyroidism and 9% incidence of hypophysitis
- Symptomatic relief for hypophysitis achieved with hormone replacement, although endogenous hormone secretion rarely recovered
  - Symptoms can include: headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment
  - Events can occur within wks of beginning treatment but also have been noted to occur many mos (while still on treatment)

Ryder M, et al. Endocr Relat Cancer. 2014;21:371-381.

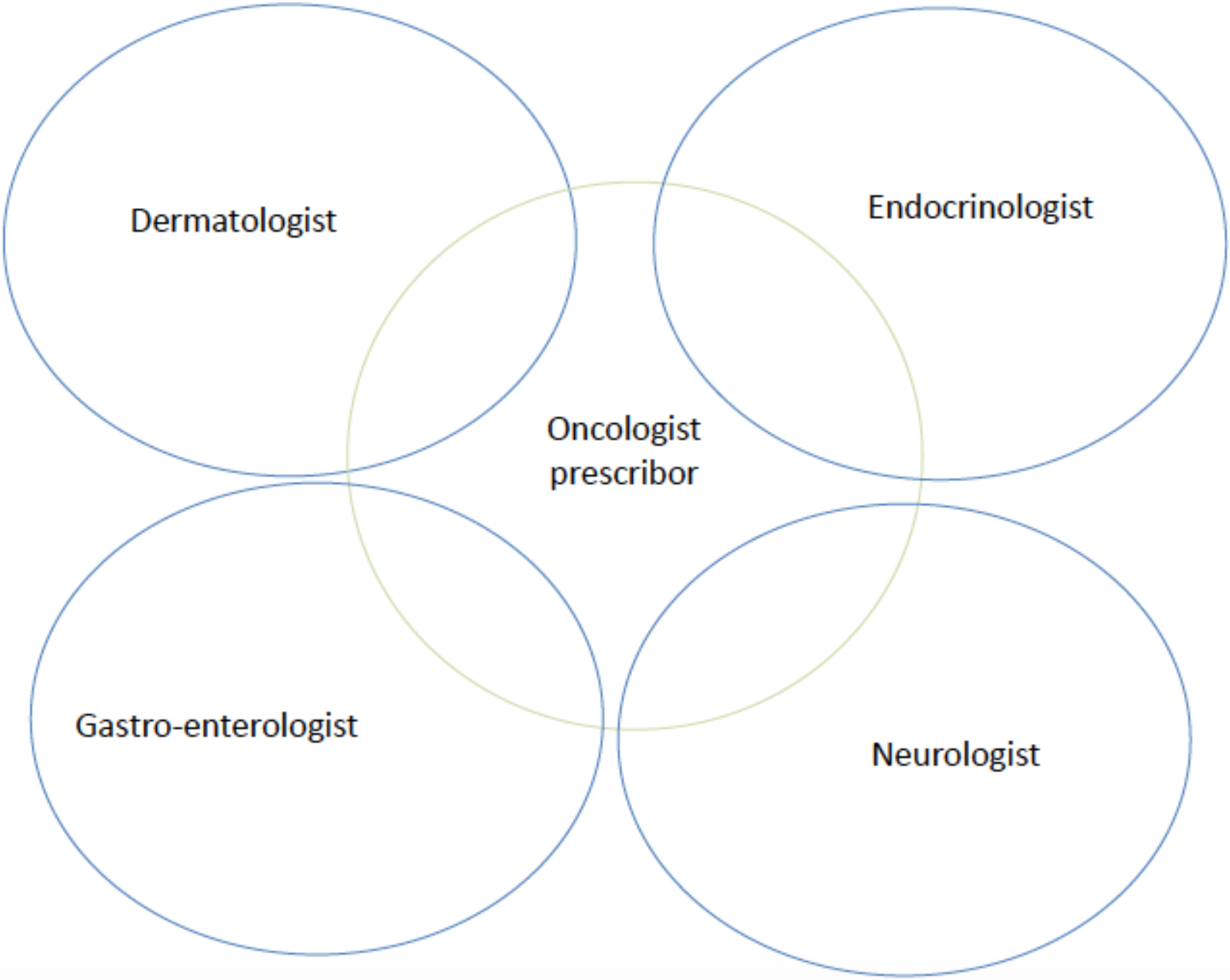
Symptom Management: Hypophysitis

- Prompt therapy ameliorates symptoms and permits continued therapy
- 25% of pts with hypophysitis have normal pituitary MRI
- Monitor ACTH and cortisol levels in pts receiving checkpoint inhibitors
- Physiologic steroid replacement may be sufficient
  - Higher-dose in symptomatic pts (headaches and vision changes)

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

Summary

- Toxicity is mostly low grade and can be managed with supportive treatment
- The majority of immunotherapy related AEs to date have been reversible and manageable by delaying study drug ± administration of corticosteroids; other immunosuppressants may also be needed
- The following categories of AEs, requiring greater vigilance and early intervention: pulmonary, hepatic, renal, GI, endocrine, neurological, skin
- A concerted effort to educate the whole multidisciplinary team needs to take place and development of accessible algorithms to ensure minimized risk with toxicity


Dermatologist
Endocrinologist
Oncologist
prescribor
Gastro-enterologist
Neurologist

Summary

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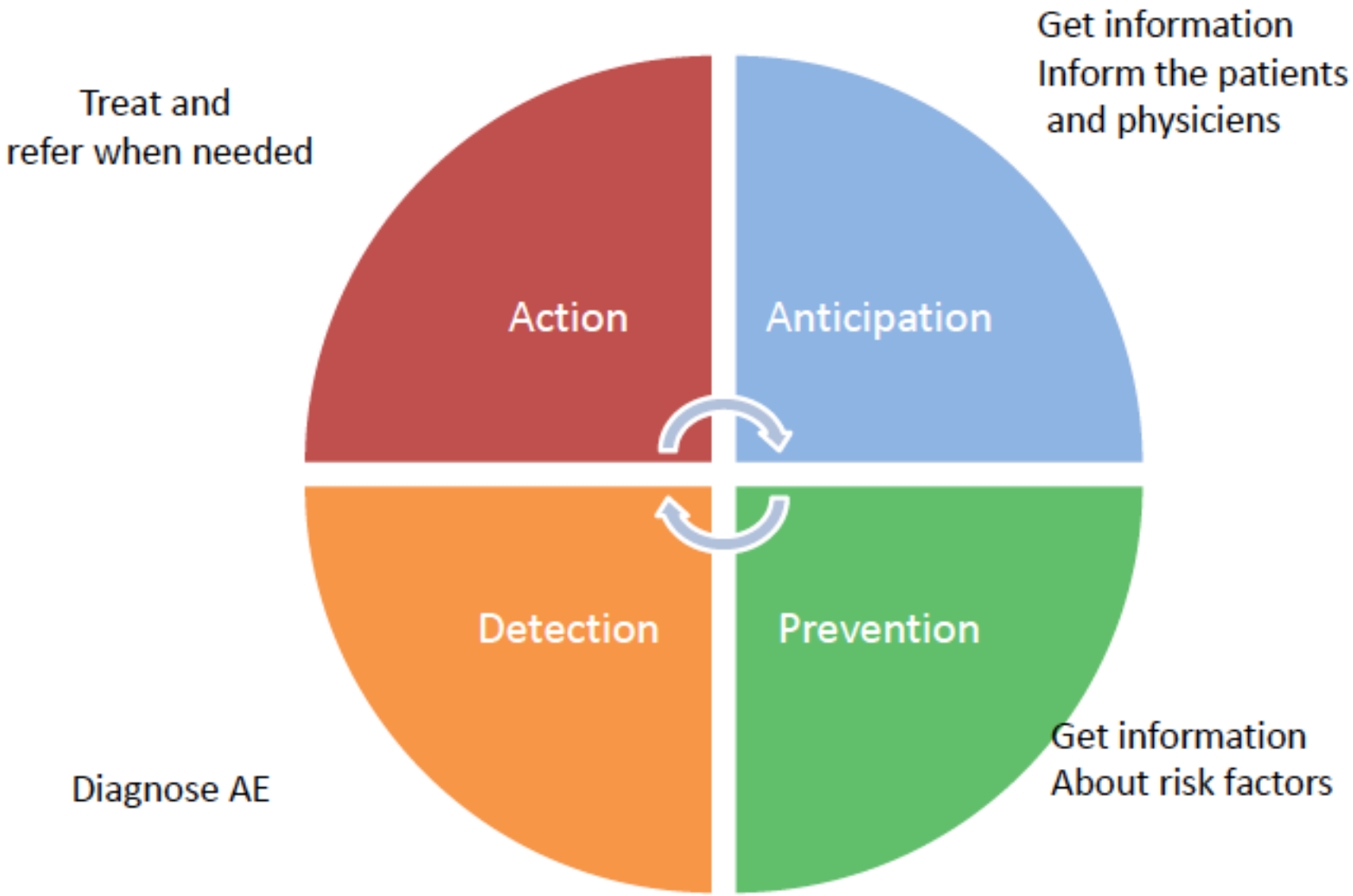
- The following categories of AEs, requiring greater vigilance and early intervention: pulmonary, hepatic, renal, GI, endocrine, neurological, skin
- A concerted effort to educate the whole multidisciplinary team needs to take place and development of accessible algorithms to ensure minimized risk with toxicity
- The key to successful management of immunotherapy toxicities is early diagnosis, high suspicion, excellent patient–provider communication, and rapid and aggressive use of corticosteroids and other immune suppressants for irAEs



Courtesy of Caroline Robert - Gustave Roussy, Paris, France

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