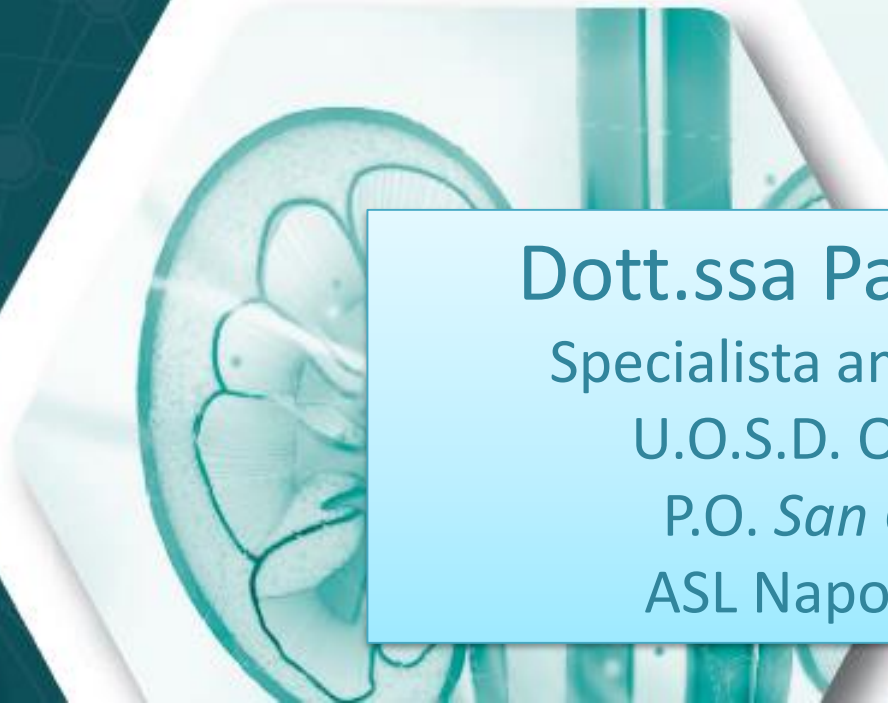
Con il patrocinio di:

Associazione Italiana Donne Medico

HERMES Centro Studi Europeo

LA GESTIONE DELLA PATOLOGIA NEOPLASTICA RENALE:

dal management sanitario alla personalizzazione delle terapie



Dott.ssa Paola Russo

Specialista ambulatoriale

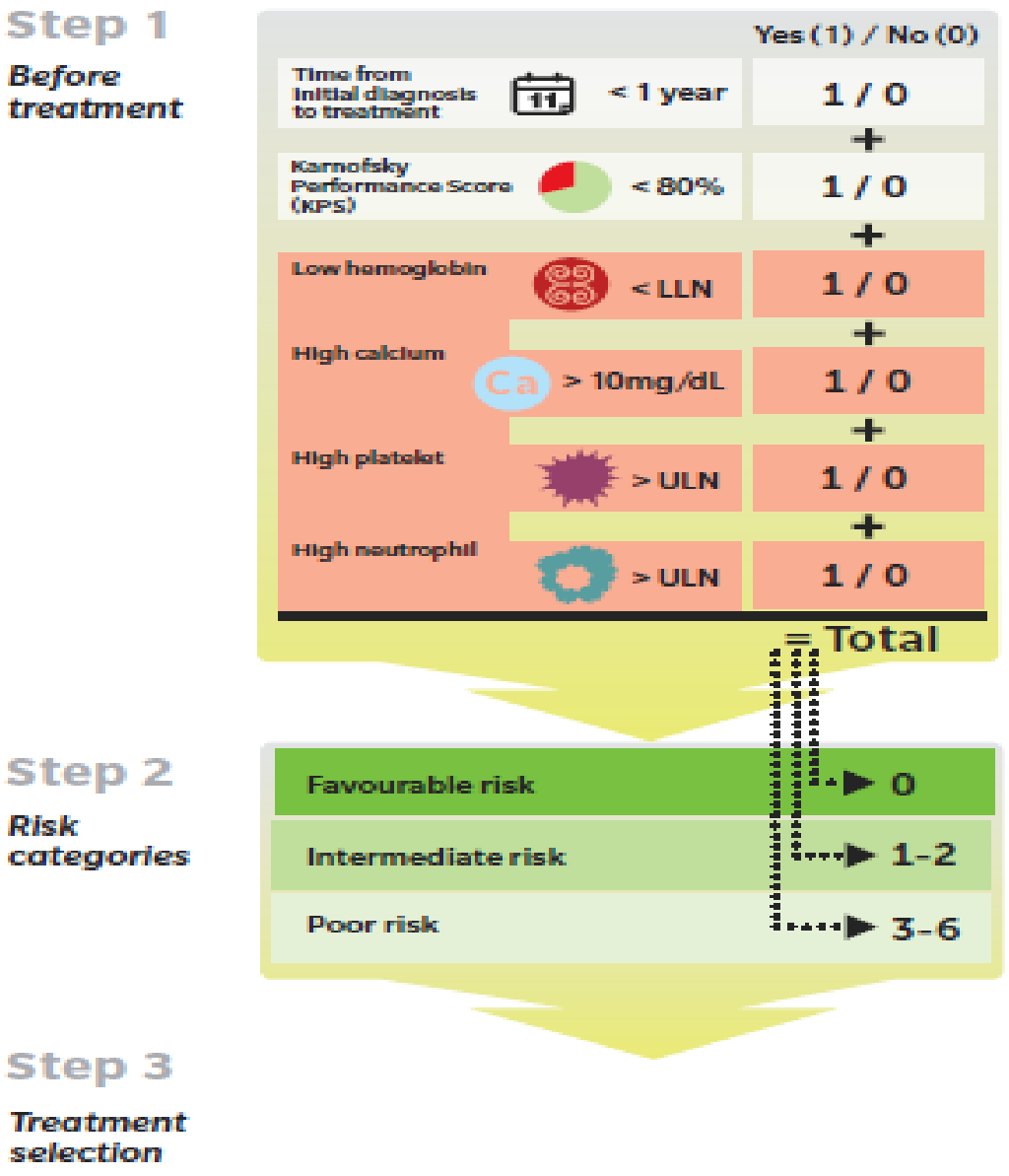
U.O.S.D. Oncologia

P.O. *San Giuliano*

ASL Napoli 2 nord

Understanding IMDC Criteria for Metastatic Renal Cell Carcinoma

(RCC; Heng criteria)

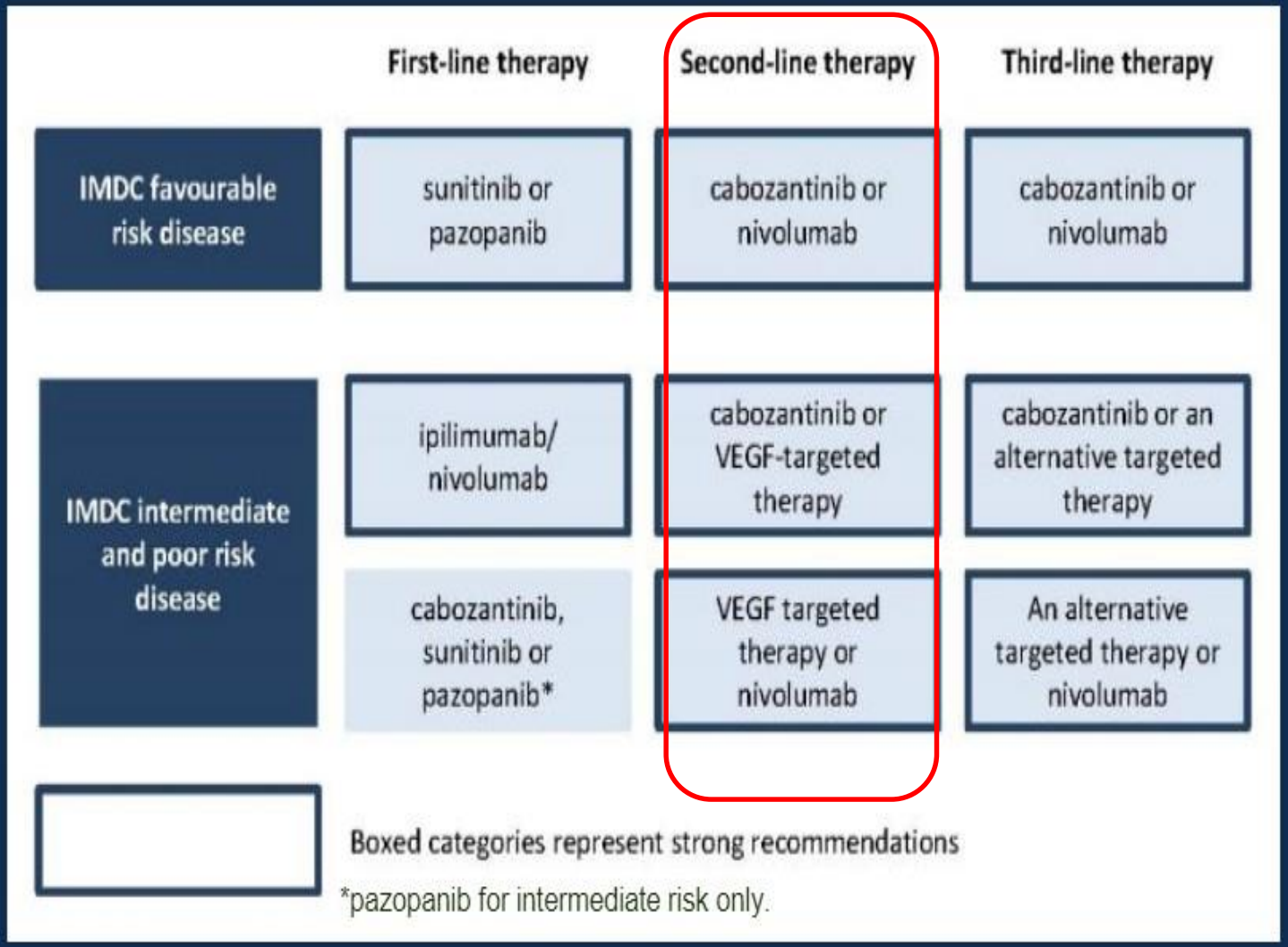


2015-2017: Introduction of New Players in 2nd-line

Trial	Phase	N	VEGF agent vs non VEGF	RR (%)	PFS (mo)	OS (mo)
TARGET trial[1]	III	903	Sorafenib vs Placebo	10 vs 2	5.5 vs 2.8	19.3 vs 15.9
RECORD 1[2]	III	410	Everolimus vs Placebo	1 vs 0	4.9 vs 1.9	14.8 vs 14.4
AXIS[3]	III	723	Axitinib vs Sorafenib	19.4 vs 9.4	6.8 vs 4.7	20.1 vs 19.2
INTORSECT[4]	III	512	Temsirolimus vs Sorafenib		4.28 vs 3.91	12.27 vs 13.55
METEOR[5]	III	658	Cabozantinib vs Everolimus	21 vs 5	7.4 vs 3.8	21.4 vs 16.5
CheckMate 025[6]	III	821	Nivolumab vs Everolimus	21.5 vs 3.9	4.6 vs 4.4	25.0 vs 19.6
HOPE[7]	II	153	Lenvatinib+Eve vs Eve vs Lenvatinib	43 vs 27 vs 6	14.6 vs 7.4 vs 5.5	25.5 vs 19.1 vs 15.4

1.Escudier B et al., New Engl J Med 2007; 2. Motzer RJ et al., J Clin Oncol 2004; 3. Rini BI et al., Lancet 2011; 4.Hutson TE et al., J Clin Oncol 20014; 5. Choueiri TK et al., New Engl J Med 2015; 6. Motzer RJ et al.,, New Engl J Med 2015; 7.Motzer RJ et al., J Clin Oncol 2013

EAU 2018 Guidelines



ESMO Guidelines 2019

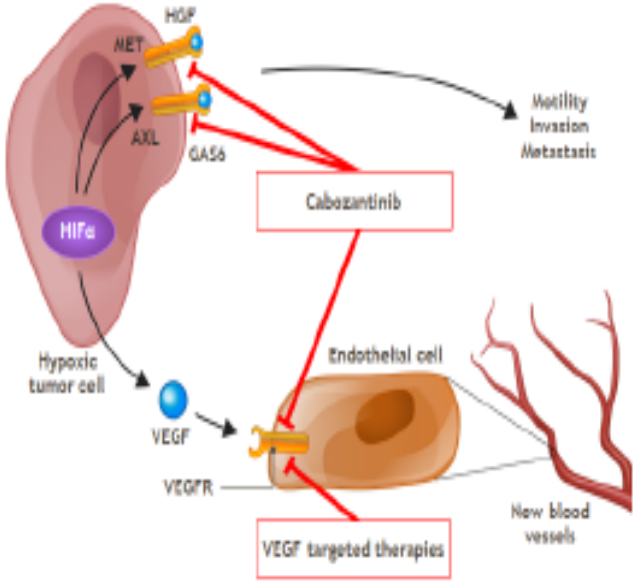
First line/ histology	Risk group/ subtype	Standard	Option
Clear cell	**Good**	Sunitinib [I, A] Pazopanib [I, A] Bevacizumab + IFN [I, A] Tivozanib [II, A]	High dose IL2 [III, B] Bevacizumab + low dose IFN [III, B]
	Intermediate	Nivolumab+ Ipilimumab [I, A]	Cabozantinib [II, A] Sunitinib [I, B] Pazopanib [I, B] Tivozanib [II, B] Bevacizumab + IFN [II, C]
	Poor	Nivolumab+ Ipilimumab [I, A]	Cabozantinib [II, B] Sunitinib [II, C] Pazopanib [II, C] Temsirolimus [I, C]

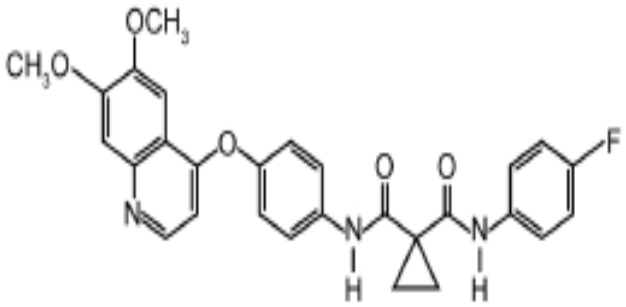
First line	Standard	Option
TKI	Nivolumab [I, A] Cabozantinib [I, A]	Axitinib [IIB] Everolimus [IIB] Lenvatinib + Everolimus [V, C]
Nivolumab + Ipilimumab		Any TKI [IV, C] Lenvatinib + Everolimus [V, C]

Escudier B, Schmidinger M et al., Ann Oncol 2019

Cabozantinib Targets Multiple Distinct Pathways[1,2]

- Cabozantinib is an oral small molecule inhibitor of multiple tyrosine kinase receptors, including:
  - MET
  - AXL
  - VEGFR-1, 2, 3
- Cabozantinib, by targeting more than just the VEGF pathway, provides a multi-targeted approach for the treatment of RCC
  - This may help to overcome resistance to VEGFR inhibition[2]

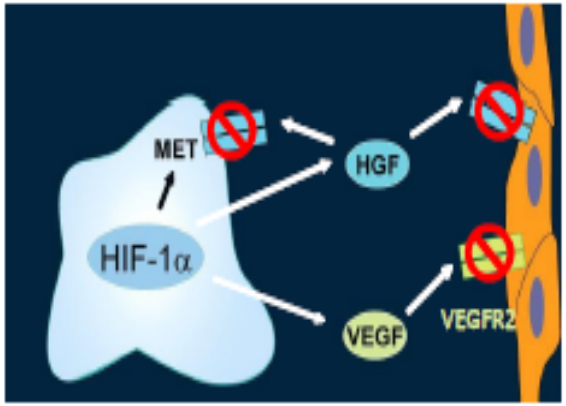




1. Elaborated from Yakes MF, et al. *Mol Cancer Ther* 2011;10:2298–308;
2. You WK, et al. *Cancer Res* 2011;71:4758–68. /Zhou

Anti-Metastatic Effects of Cabozantinib in a Preclinical Mouse Model

- In preclinical models, cabozantinib has been shown to inhibit MET, AXL, and VEGFR-1, VEGFR-2, VEGFR-3, among others, and thereby inhibit tumour angiogenesis, invasiveness, metastasis, and drug resistance[1–3]



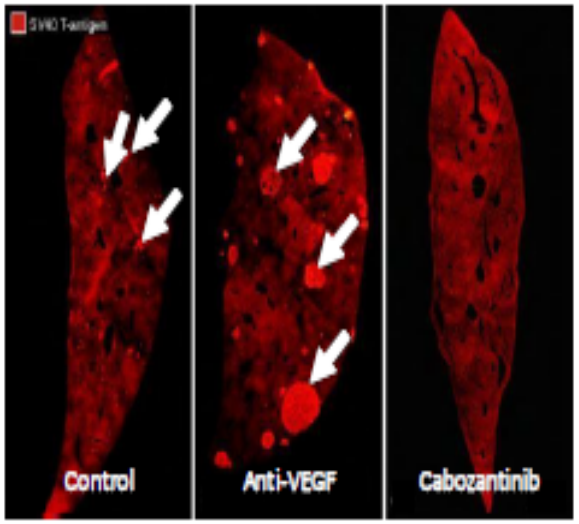
Proliferation (RAS-MAPK)
Increased invasiveness/EMT (RAS, FAK)
Inhibition of apoptosis (PI3 kinase)

GROWTH-MOTILITY-INVASION

Increased MET
Increased VEGFR2
Decrease TSP -1

ANGIOGENESIS

Anti-metastatic effect of cabozantinib in the liver[2]



RIP-Tag2 mouse model (pancreatic neuroendocrine tumour)

1. Yakes MF, et al. *Mol Cancer Ther* 2011;10:2298–308;
2. Sennino B, et al. *Mol Cancer Ther* 2009;8(12 Suppl):abstract A13;
3. Buckanovich RJ, et al. *J Clin Oncol* 2011;29(15 Suppl):abstract 5008. Presentation available at: http://meeting!brary.asco.org/content/64148?media=vm

Cabozantinib Phase 3 Study (METEOR): Design

Phase 3, randomised, multicentre, open-label study to evaluate the efficacy and safety of cabozantinib vs everolimus in patients with RCC who had progressed on prior VEGFR therapy

Patients

- ≥18 years of age
- Advanced/metastatic clear-cell RCC
- Measurable disease
- Received ≥1 prior VEGFR therapy and progressed ≤6 months after most recent dose
- Karnofsky PS ≥70
- Adequate organ and bone marrow function

Stratification factors

- Number of previous VEGFR therapies
- MSKCC criteria

Cabozantinib
60 mg oral OD

Randomisation 1:1
No crossover allowed
Tumour assessment every 8 weeks (RECIST v1.1)
Treatment until loss of clinical benefit or intolerable toxicity

Everolimus
10 mg oral OD

Endpoints

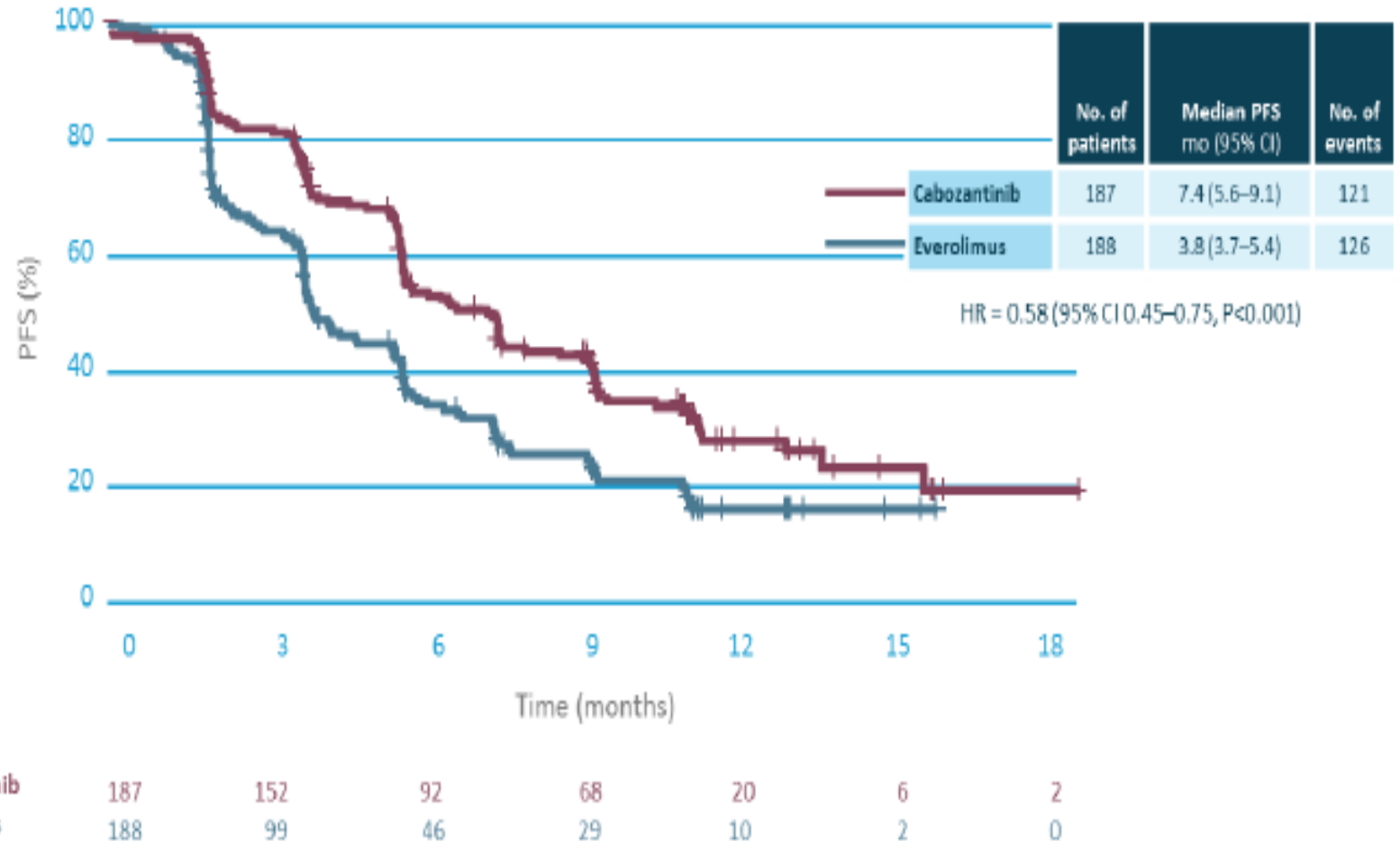
Primary
- PFS* (independent review)

Secondary
- OS
- ORR
- SAFETY

OD, daily; MSKCC, Memorial Sloan Kettering Cancer Center; PS, performance status. *PFS defined as the interval between the dates of randomisation and first documentation of disease progression or death from any cause

1. Choueiri TK, et al. *N Engl J Med* 2015;373:1814-23

Phase 3 METEOR Study: Primary Endpoint of PFS (Independent Review – PFS Population)

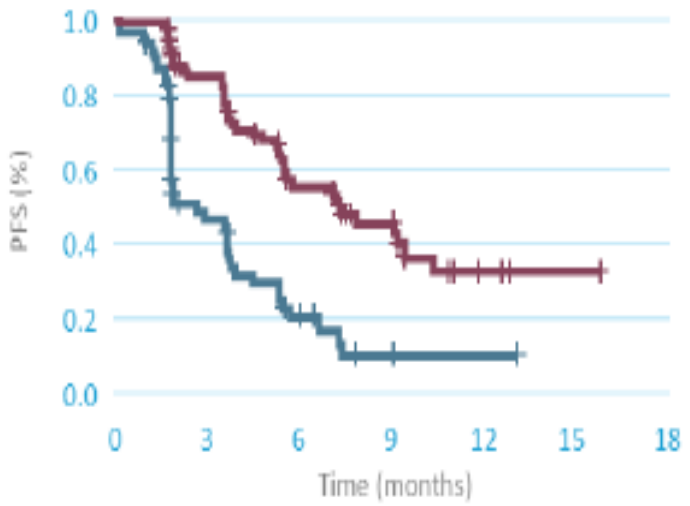


Data cut-off: 22 May 2015

1. Choueiri TK, et al. *N Engl J Med* 2015;373:1814–23

Phase 3 METEOR Study Subgroup Analyses: PFS With / Without Bone Metastases (ITT Population)

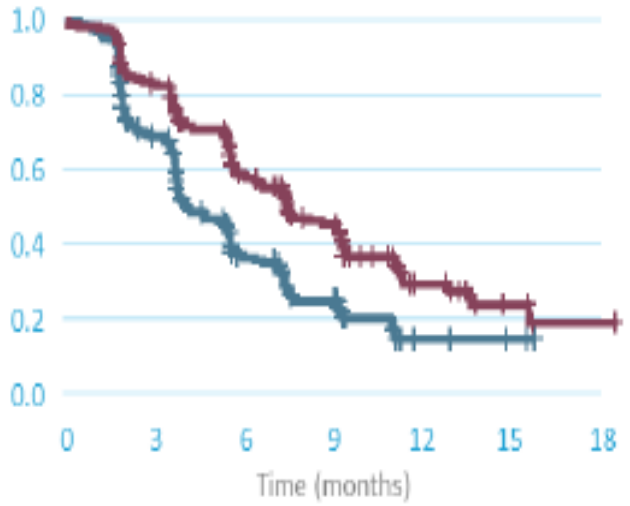
Patients With Bone Metastases



	Median, mo
Cabozantinib (n=77)	7.4
Everolimus (n=65)	2.7

HR = 0.33 (95% CI 0.21–0.54)

Patients Without Bone Metastases



	Median, mo
Cabozantinib (n=253)	7.4
Everolimus (n=263)	4.2

HR = 0.57 (95% CI 0.45–0.71)

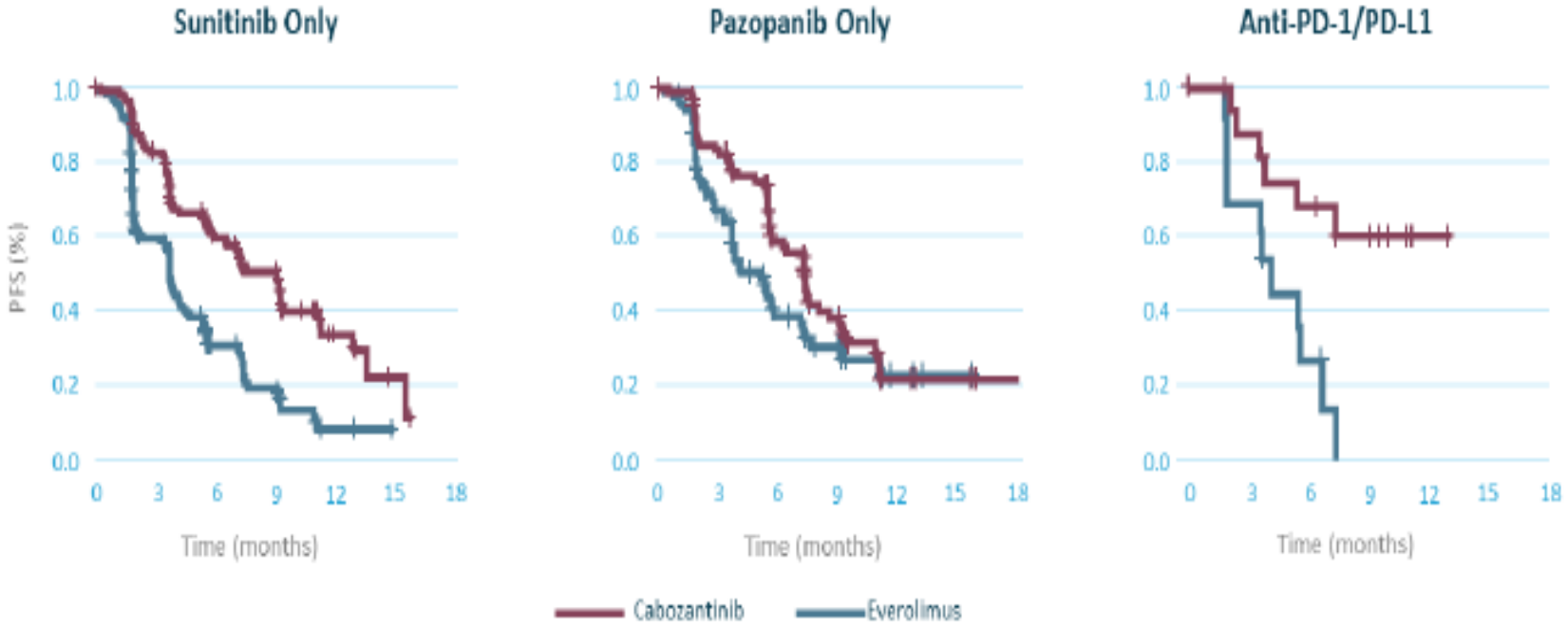
Cabozantinib — Everolimus

Bone metastases status was based on the presence of bone metastases by CT or MRI per IRC at baseline

Data cut-off: 22 May 2015

1. Escudier BJ, et al. *J Clin Oncol* 2016;34(2 Suppl):abstract 499. Poster available at http://meetinglibrary.asco.org/content/158003-172;
2. Choueiri TK, et al. *Lancet Oncol* 2016;17:917-27

Phase 3 METEOR Study Subgroup Analyses: PFS by Selected Prior Therapy (ITT Population)



	Median, mo
Cabozantinib (n=135)	9.1
Everolimus (n=132)	3.7

HR = 0.43 (95% CI 0.32–0.59)

	Median, mo
Cabozantinib (n=88)	7.4
Everolimus (n=83)	5.1

HR = 0.67 (95% CI 0.45–0.99)

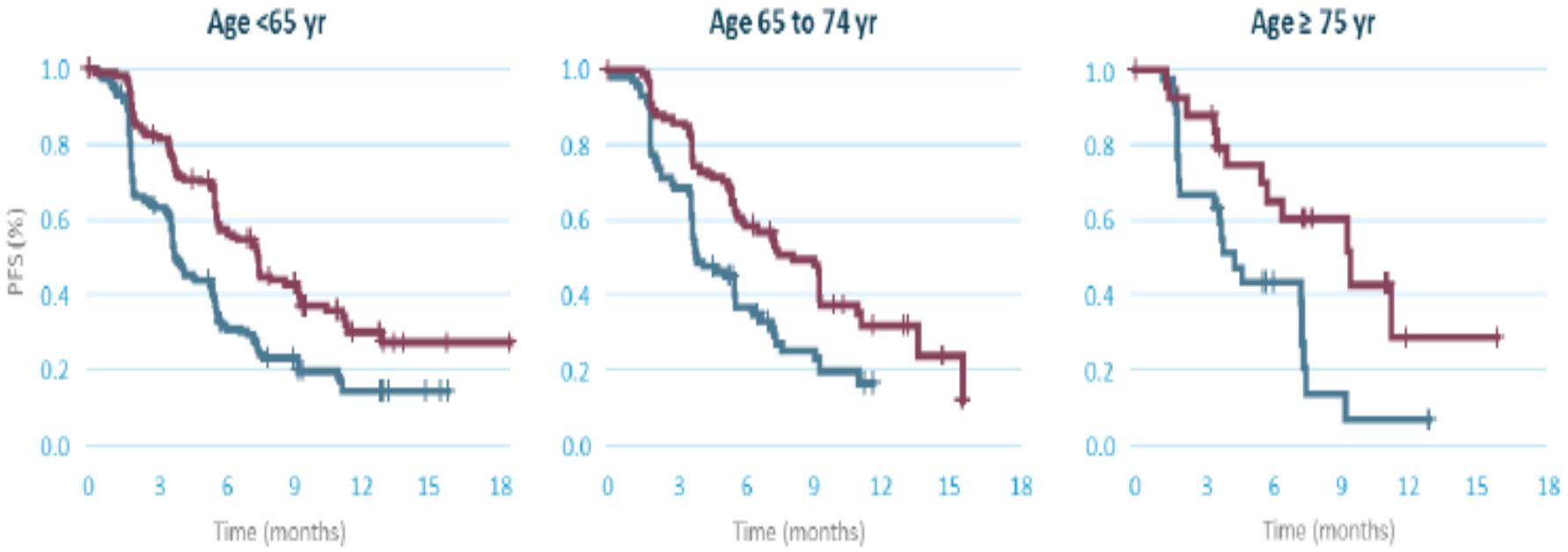
	Median, mo
Cabozantinib (n=18)	NE
Everolimus (n=14)	4.1

HR = 0.22 (95% CI 0.07–0.65)

NE: not estimable
Data cut-off: 22 May 2015

1. Powles T, et al. *J Clin Oncol* 2016;34(Suppl):abstract 4557;
2. Choueiri TK, et al. *Lancet Oncol* 2016;17:917–27

Phase 3 METEOR Study Subgroup Analyses: PFS by Age (ITT Population)



	Median, mo
Cabozantinib (n=96)	7.4
Everolimus (n=98)	3.8

HR = 0.53 (95% CI, 0.41–0.68)

	Median, mo
Cabozantinib (n=07)	8.1
Everolimus (n=94)	3.9

HR = 0.53 (95% CI, 0.37–0.77)

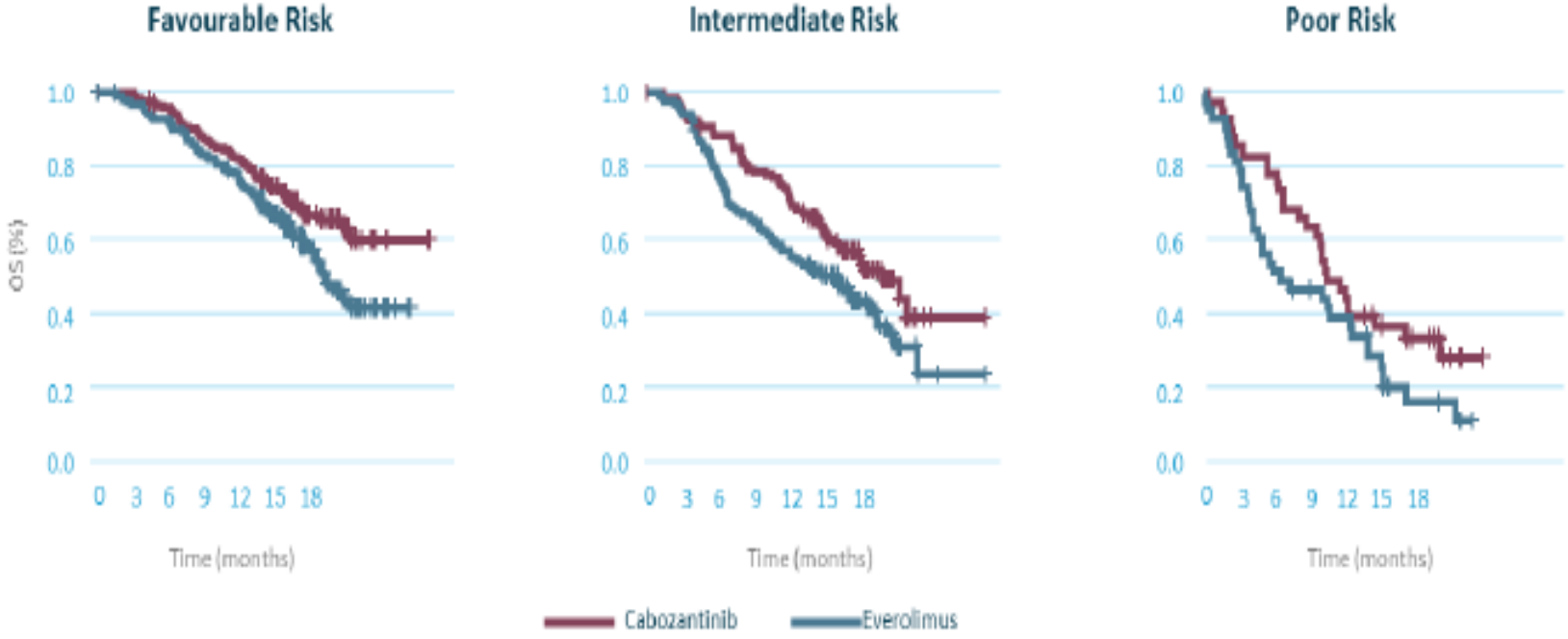
	Median, mo
Cabozantinib (n=27)	9.4
Everolimus (n=36)	4.4

HR = 0.38 (95% CI, 0.18–0.79)

Data cut-off: 22 May 2015

1. Donskov F, et al. J Clin Oncol 2017;35(Suppl):abstract 4578

Phase 3 METEOR Study Subgroup Analyses: OS by MSKCC Risk Group (ITT Population)



	Median, mo
Cabozantinib (n=150)	NE
Everolimus (n=150)	19.3

HR = 0.66 (95% CI, 0.64–0.96)

	Median, mo
Cabozantinib (n=139)	19.9
Everolimus (n=135)	14.9

HR = 0.67 (95% CI, 0.48–0.94)

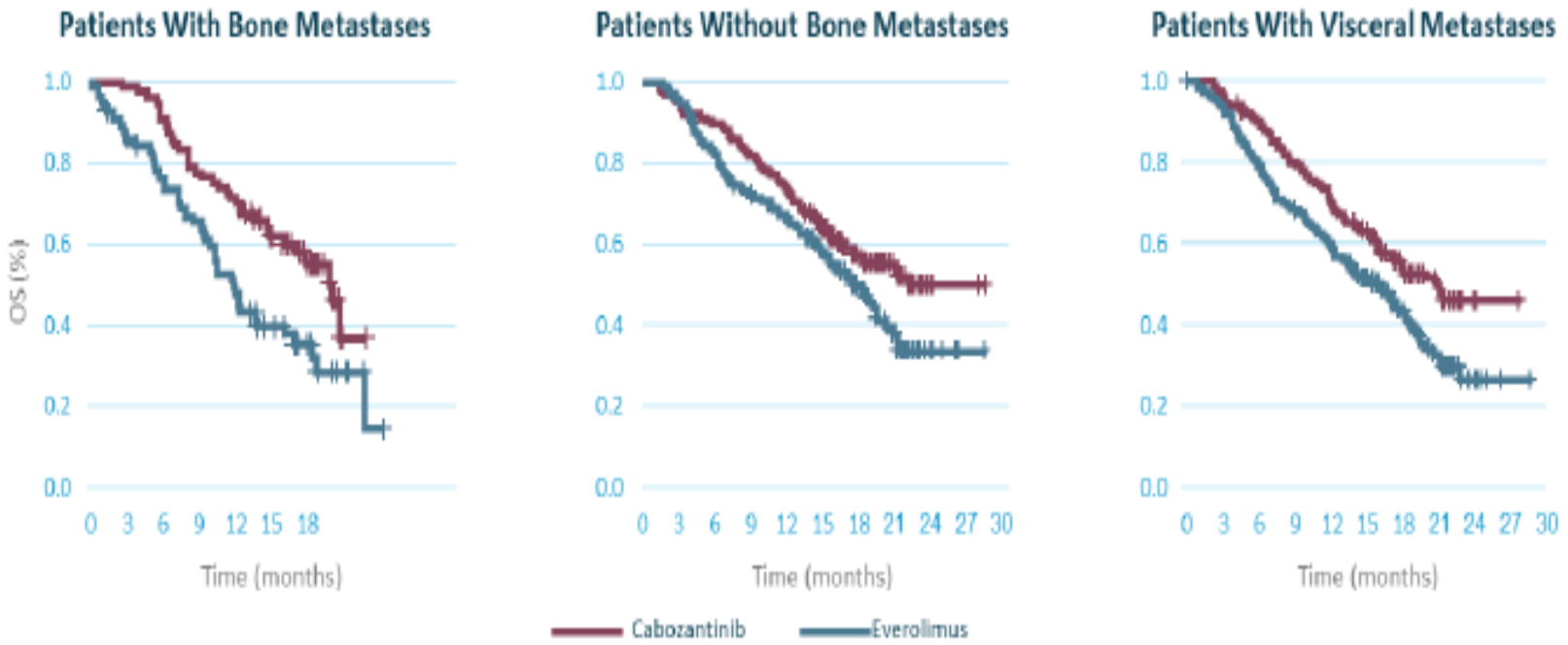
	Median, mo
Cabozantinib (n=41)	10.5
Everolimus (n=43)	6.5

HR = 0.65 (95% CI 0.39–1.07)

NE: not estimable
Data cut-off: 31 Dec 2015

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 Subgroup Analyses: OS by Metastatic Site (ITT Population)



	Median, mo
Cabozantinib (n=77)	20.1
Everolimus (n=65)	12.1

HR = 0.54 (95% CI 0.34–0.84)

	Median, mo
Cabozantinib (n=253)	NE
Everolimus (n=263)	17.5

HR = 0.71 (95% CI 0.55–0.91)

	Median, mo
Cabozantinib (n=241)	21.3
Everolimus (n=245)	16.1

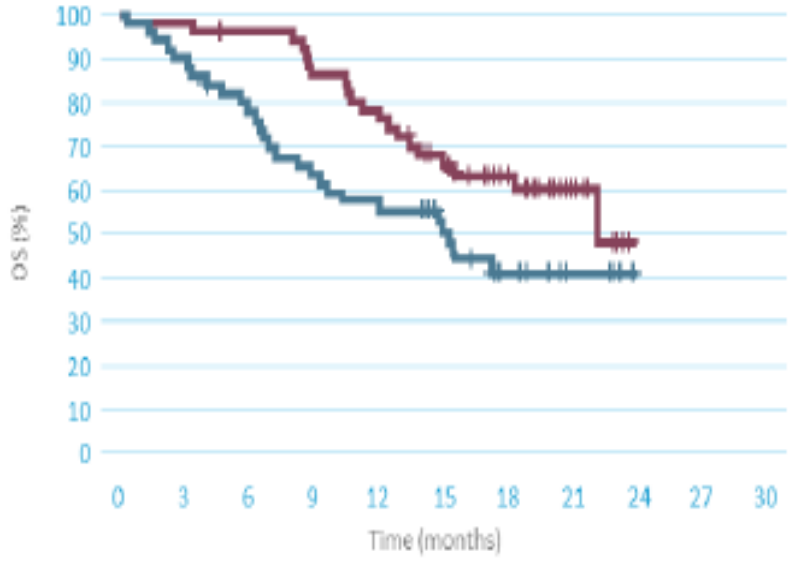
HR = 0.66 (95% CI 0.21–0.85)

Bone metastases status was based on the presence of bone metastases by CT or MRI per IRC at baseline.
NE, not estimable

1. Escudier BJ, et al. *J Clin Oncol* 2016;34(Suppl;abstract 4558;
2. Choueiri TK, et al. *Lancet Oncol* 2016;17:917–27;
3. Powles T, et al. ESMO 2016; Poster 814P

Phase 3 METEOR Study Subgroup Analyses: OS by Tumour MET Expression (ITT Population)

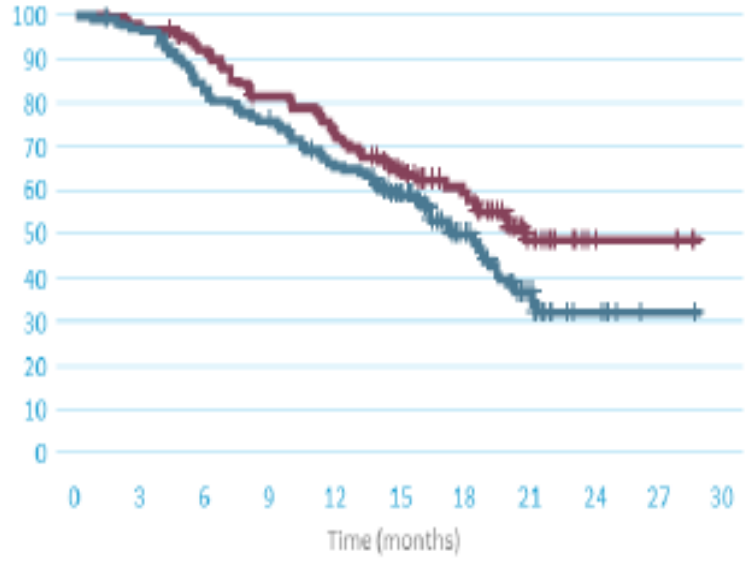
High MET Expression



	No. of patients	Median OS mo (95% CI)	No. of deaths
Cabozantinib	51	22.0 (15.4–NE)	20
Everolimus	50	15.2 (8.7–NE)	27

HR = **0.55** (95% CI, 0.31–**0.99**)

Low MET Expression



	No. of patients	Median OS mo (95% CI)	No. of deaths
Cabozantinib	150	20.8 (18.1–NE)	63
Everolimus	162	18.4 (15.9–19.6)	87

HR = **0.72** (95% CI, **0.52–1.00**)

NE: not estimable
Data cut-off: 31 Dec 2015

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

Phase 3 METEOR Study: Overall Survival Rates at Selected Timepoints

- Proportion of patients alive at 6, 12, 18, and 24 months in the cabozantinib group compared with the everolimus group

Timepoint	Estimate of Patients Alive: % (95% CI)	
	Cabozantinib N=330	Everolimus N=328
6 months	91 (87, 93)	81 (76, 85)
12 months	73 (68, 79)	63 (58, 78)
18 months	58 (53, 64)	47 (41, 52)
24 months	48 (39, 55)	31 (23, 39)

Data cut-off: 31 Dec 2015

1. Choueiri TK, et al. *N Engl J Med* 2015;373:1814–23;
2. Choueiri TK, et al. *Lancet Oncol* 2016;17:917–27

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 Age

Grade 3/4 adverse event, %	Age < 65 yr		Age 65 to 74 yr		Age ≥75 yr	
	Cabozantinib (n=197)	Everolimus (n=193)	Cabozantinib (n=107)	Everolimus (n=93)	Cabozantinib (n=27)	Everolimus (n=36)
Any AE	68	60	75	60	78	58
Diarrhoea	14	2	12	2	11	3
Hypertension	13	2	15	6	26	8
Fatigue	8	7	11	10	30	6
PPE syndrome	8	0	10	3	0	0
Anaemia	5	15	7	18	7	22
Hyperglycaemia	0	5	3	5	0	6
Hyponatraemia	2	1	6	3	19	8
Asthenia	3	2	5	3	15	3

PPE, palmar-plantar erythrodysaesthesia

1. Donskov F, et al. J Clin Oncol 2017;35(Suppl):abstract 4578

Phase 3 METEOR Study: Summary

- Treatment with cabozantinib significantly increased OS, delayed disease progression, and improved the objective response compared with everolimus in patients with advanced RCC post-VEGFR TKI therapy
- Consistent PFS, OS and ORR benefit associated with cabozantinib was observed across all patient subgroups included in the Phase 3 study
  - The observed survival benefit was applicable to patients in all MSKCC risk categories and irrespective of the extent of tumour burden and number of previous VERGFR TKIs
    - The most common previous treatments were sunitinib and pazopanib, consistent with standard clinical practice
- Cabozantinib maintains QoL over time in patients with advanced RCC to a similar extent to everolimus
- The safety profile of cabozantinib was acceptable and tolerability was similar to other VEGFR TKIs used in this patient population
  - The most common Grade 3/4 adverse events reported following treatment with cabozantinib were hypertension (15%), diarrhoea (11%) and fatigue (9%)

ESMO Guidelines 2019

First line/ histology	Risk group/ subtype	Standard	Option
Clear cell	**Good**	Sunitinib [I, A] Pazopanib [I, A] Bevacizumab + IFN [I, A] Tivozanib [II, A]	High dose IL2 [III, B] Bevacizumab + low dose IFN [III, B]
	Intermediate	Nivolumab+ Ipilimumab [I, A]	Cabozantinib [II, A] Sunitinib [I, B] Pazopanib [I, B] Tivozanib [II, B] Bevacizumab + IFN [II, C]
	Poor	Nivolumab+ Ipilimumab [I, A]	Cabozantinib [II, B] Sunitinib [II, C] Pazopanib [II, C] Temsirolimus [I, C]

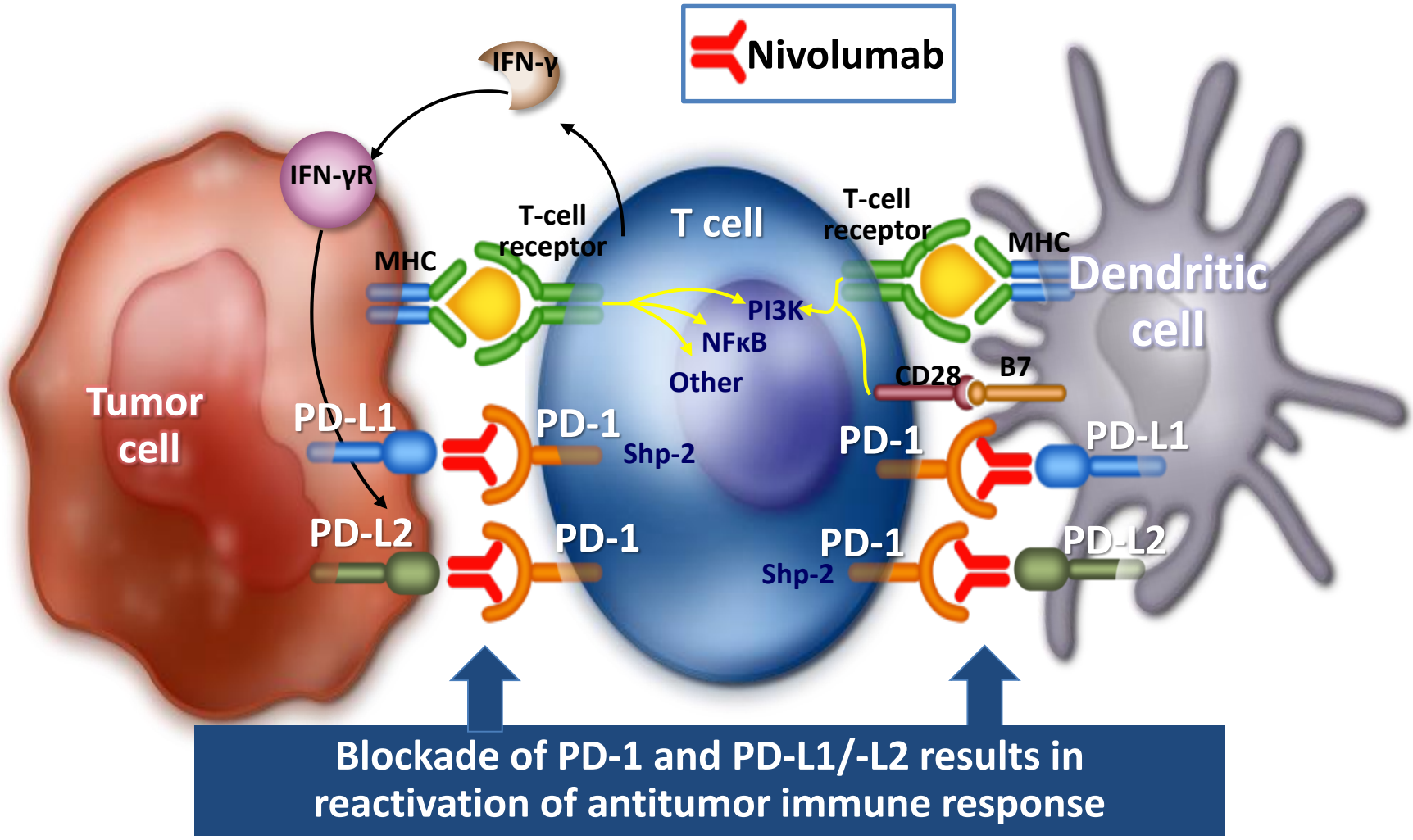
First line	Standard	Option
TKI	Nivolumab [I, A] Cabozantinib [I, A]	Axitinib [IIB] Everolimus [IIB] Lenvatinib + Everolimus [V, C]
Nivolumab + Ipilimumab		Any TKI [IV, C] Lenvatinib + Everolimus [V, C]

Escudier B, Schmidinger M et al., Ann Oncol 2019

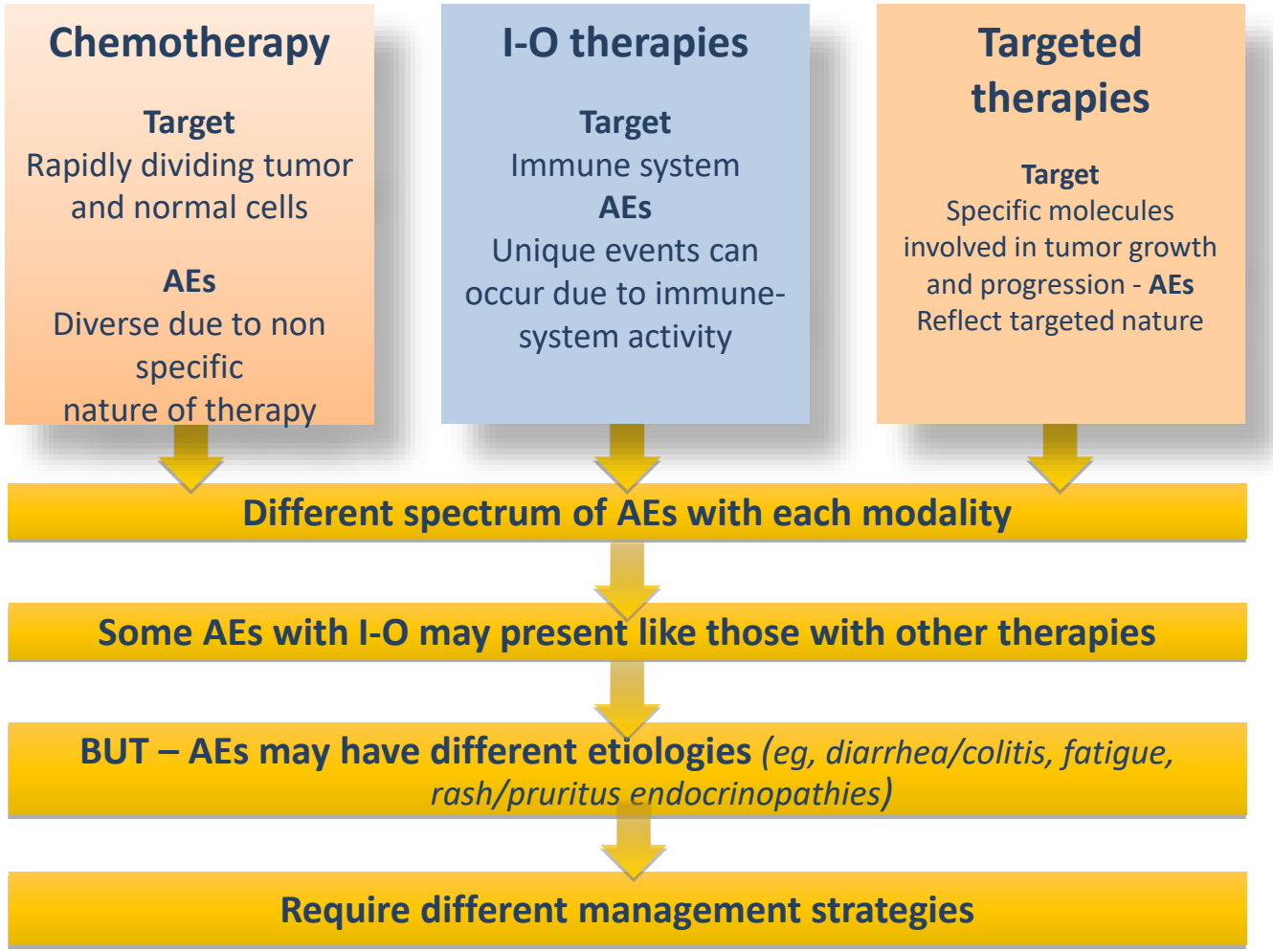
Nivolumab

fully human IgG4 programmed death-1 (PD-1) antibody that blocks PD-1 interaction with its ligands, PD-L1 and PD-L2, releasing inhibition of the antitumor immune response

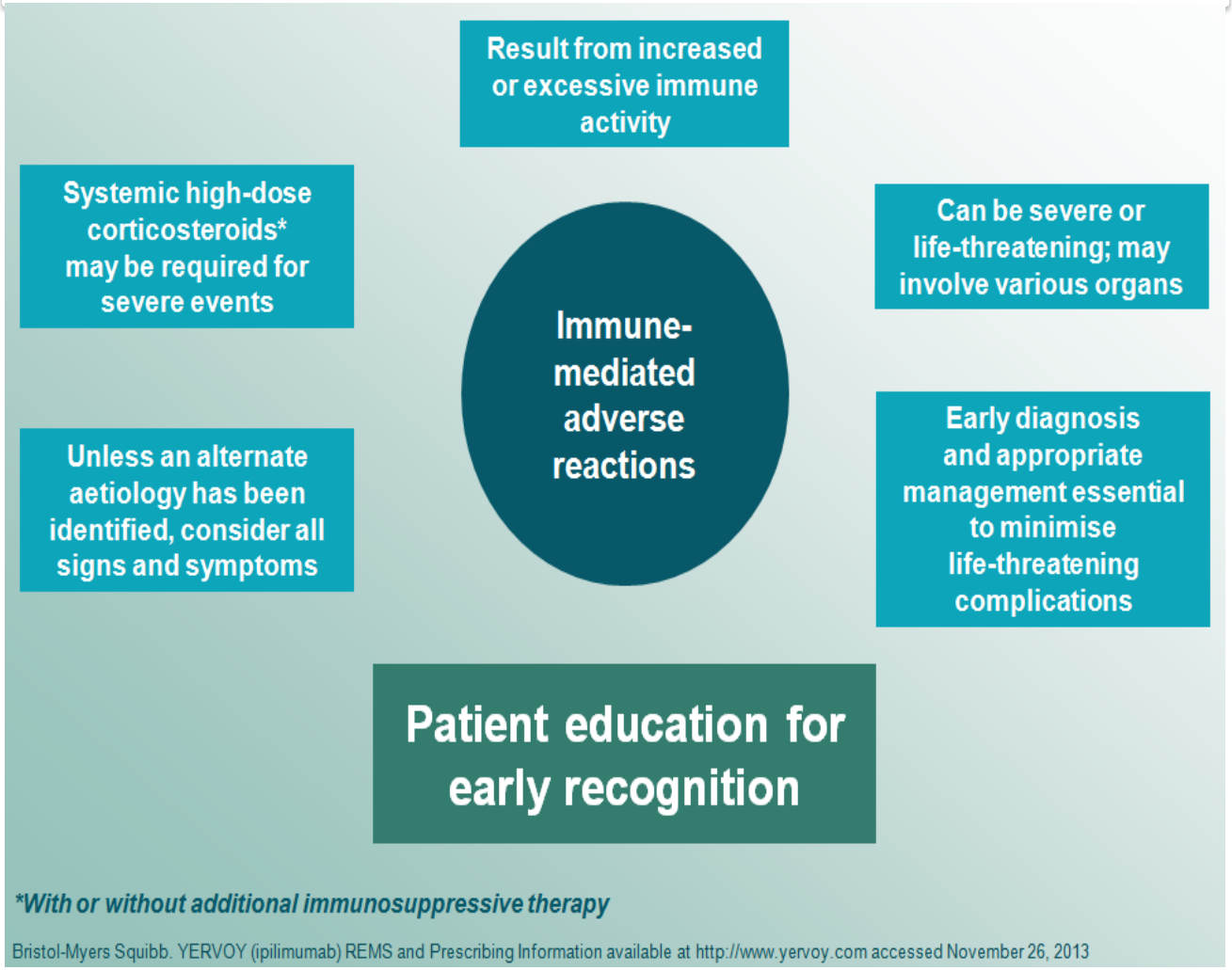
Nivolumab Mechanism of Action



Tolerability of I-O therapies



Different toxicity

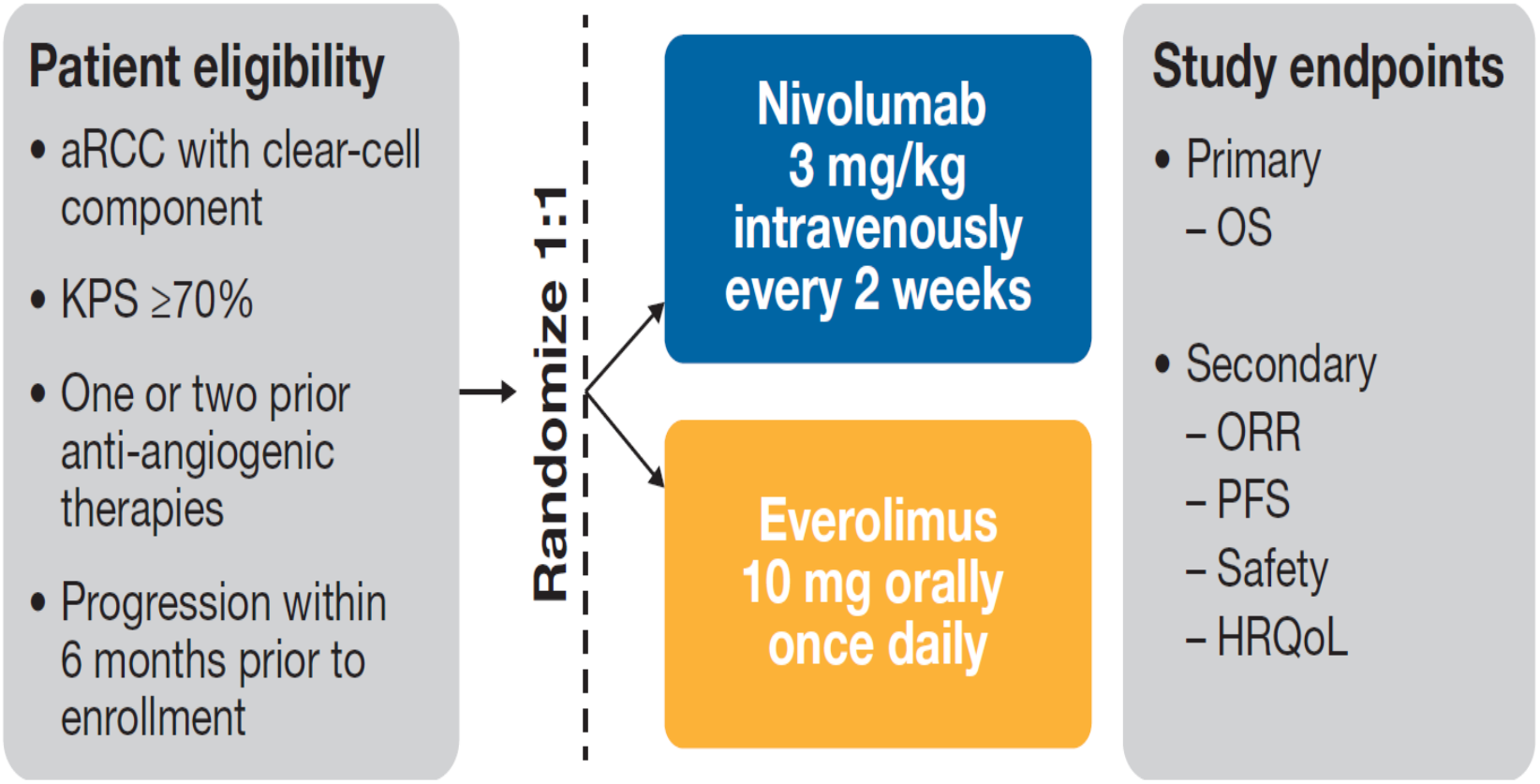


Bristol-Myers Squibb. YERVOY (ipilimumab) REMS and Prescribing Information available at http://www.yervoy.com accessed November 26, 2013

Quality of Life and Overall Survival in Patients With Advanced Clear-Cell Renal Cell Carcinoma Treated With Nivolumab Versus Everolimus in the Phase III CheckMate 025 Study

David Cella,[1] Viktor Grünwald,[2] Paul Nathan,[3] Justin Doan,[4] Homa Dastani,[4] Fiona Taylor,[5] Bryan Bennett,[6] Michael DeRosa,[5]
Scott Berry,[7] Kristine Broglio,[7] Elmer Berghorn,[4] Robert J. Motzer,[8]

Figure 1. CheckMate 025 Study Design[1]



KPS = Karnofsky performance status; ORR = objective response rate; PFS = progression-free survival

Introduction

- In the phase III CheckMate 025 study in previously treated patients with advanced renal cell carcinoma (aRCC), nivolumab demonstrated an overall survival (OS) benefit and an improvement in quality of life versus everolimus
  - Median OS (95% confidence interval [CI]): 25.0 months versus 19.6 months
  - Median change from baseline scores on the Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms (FKSI-DRS) questionnaire was significantly improved ($P < 0.05$) with nivolumab versus everolimus through week 104

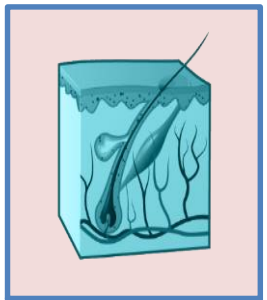
HRQoL Assessment

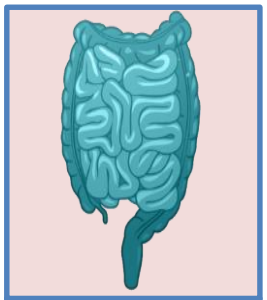
- HRQoL was assessed with FKSI-DRS[2] in the phase III CheckMate 025 trial
  - HRQoL assessments with FKSI-DRS were done at baseline, on day 1 of each cycle, beginning with cycle 2, and at the first two follow-up visits
  - FKSI-DRS is a disease-related kidney cancer questionnaire consisting of nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fever, and hematuria
  - Higher scores indicate better health state
  - The HRQoL questionnaire was completed before treatment dosing or any procedures

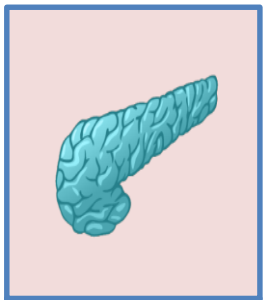
Summary and Conclusions

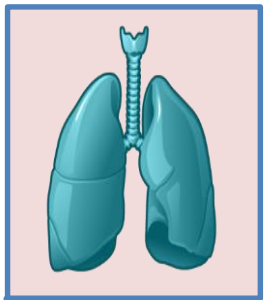
- In the phase III CheckMate 025 study, HRQoL change from baseline FKSI-DRS scores were significantly better for the nivolumab versus everolimus treatment arm by both descriptive and mixed-model analyses
- More patients experienced a clinically meaningful improvement and a shorter time to improvement in HRQoL when treated with nivolumab versus everolimus
- There was a positive association between baseline HRQoL scores and OS, suggesting the potential for baseline HRQoL to be considered as a prognostic indicator of clinical outcomes

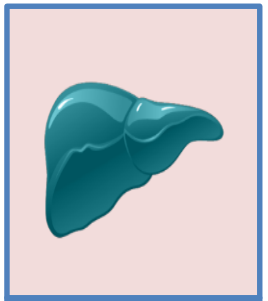
Immune-Mediated Adverse Reactions

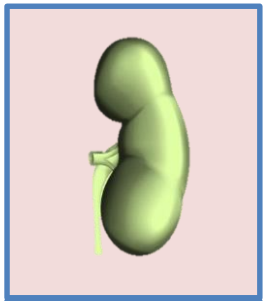

Skin[1,2,4]

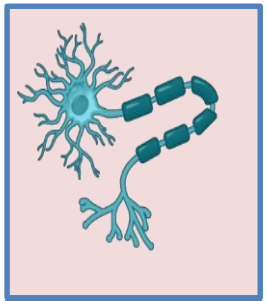

Gastrointestinal tract[1-4]

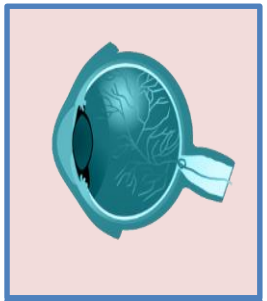

Endocrine system[2,4]


Respiratory system[1,2]


Liver[2,4]


kidneys

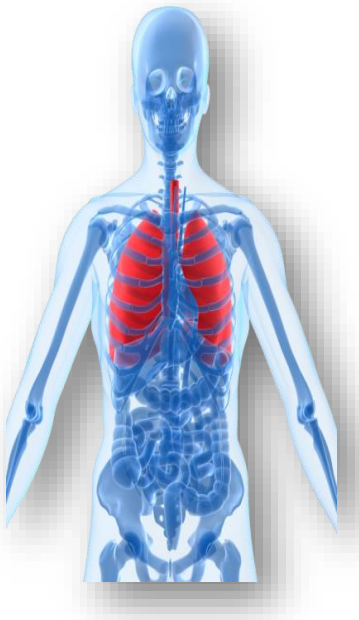

Nervous system[2]


Eyes[1,3]

Immune activation, as a result of modulating T-cell activity, may lead to
immune-mediated adverse reactions that affect certain organ systems

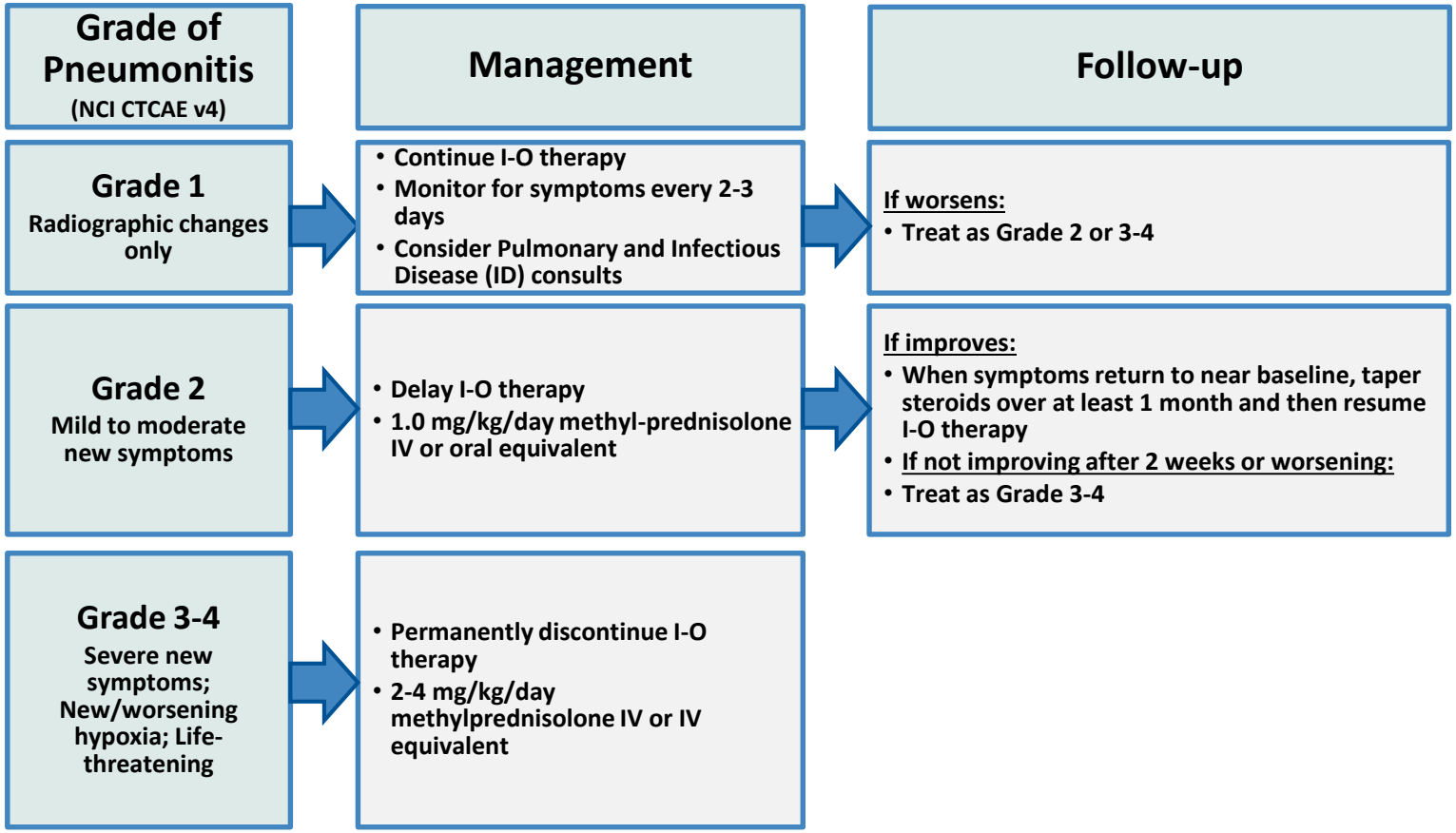
Pneumonitis

Incidence	• Pneumonitis (including interstitial lung disease) • All grades: 3,2% Grades 3: 0,8% Grades 4: <0,1% • No grade 5 reported
Risk factor	• No underlying factor identified to date • No apparent relationship to tumor type → Cases observed in multiple tumor types (Melanoma, RCC, NSCLC, etc)
Symptom	• Cough, SOB/Dyspnea (rest or exertion), Fever • Asymptomatic radiographic changes
Onset	• Median time to onset 3.6 months (range: 0.4-19.6)
Assessment	• Pulse oximetry (rest and exertion) • CXR or CT
Management	• Delay Nivolumab dosing • Corticosteroids • ⇒ if not improving 48 hrs or worsening, add immunosuppressants • Call BMS Medical



Algorithm for Pulmonary Adverse Event

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Antibiotics + Antiinfectives

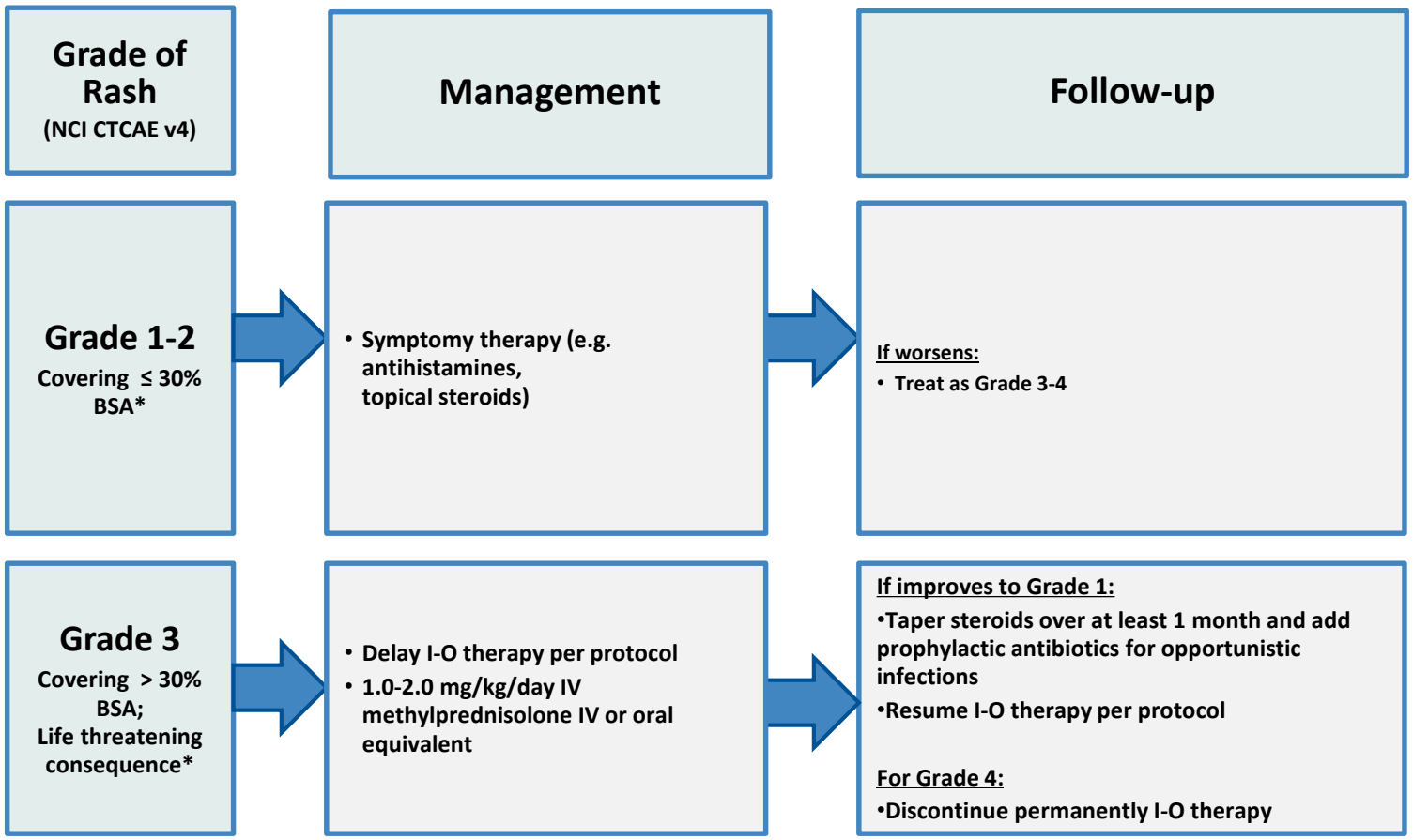
Skin Toxicity

Incidence	• Rash All grades: 28,0% Grade 3: 1,0% • No Grade 4 reported
Manifestations	• Rash typically focal with a maculopapular appearance occurring on the trunk, back, or extremities • Pruritus • Erythema • Rash–maculopapular • Skin exfoliation • Urticaria • Ulcer • Vitiligo
Onset	• Median time to onset 1.4 months (range:0.0-17.2)

Management	• Symptomatic management
	  • Topical corticosteroids for rashes
	  • Anti-histamines for pruritus

Note	• Some skin reactions occurred in the context of infusion related reaction

Skin Toxicity Management Algorithm



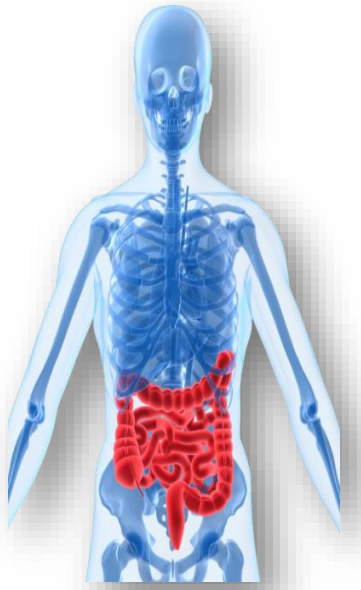
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

Antibiotics = Anti-infectives

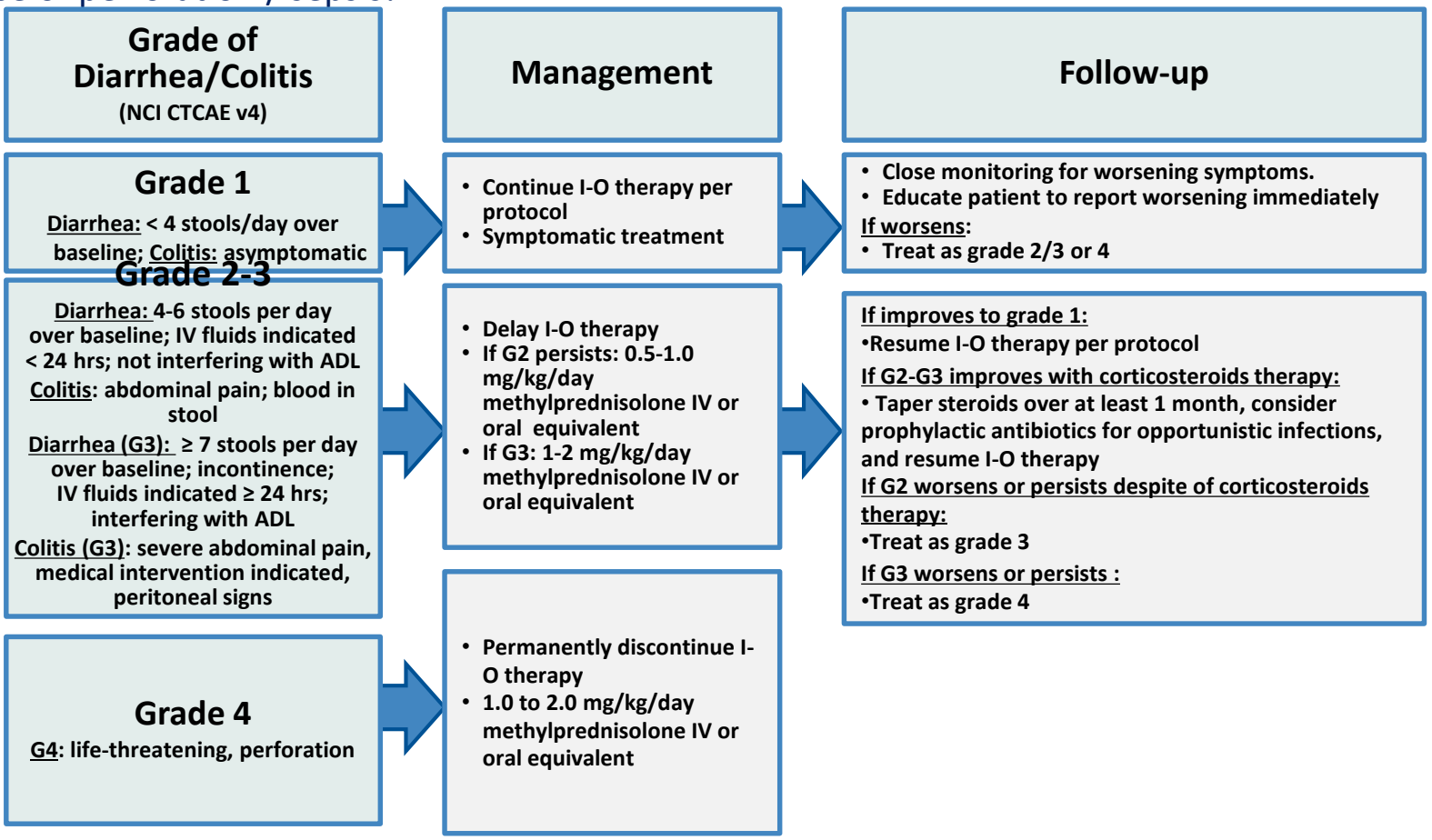
Gastrointestinal Toxicity

Incidence	• Diarrhea or colitis All grades: 13,6% Grades 3: 1,6% • No grade 4 reported • Most cases of diarrhea were low grade • Colitis occurs less frequently than diarrhea
Onset	• Median time to onset 1.8 months (range:0.0-20.9)
Assessment	• Use results of diagnostic evaluation to guide management • A negative diagnostic evaluation may need to be repeated
Treatment	• Initiate treatment early • Low grade diarrhea → managed symptomatically ± dose delay • High grade cases of diarrhea/colitis → managed with corticosteroids (If steroids are begun, taper slowly) • All cases of high grade diarrhea/colitis have resolved



Algorithm for Suspected GI Toxicity

Infectious causes to be ruled out! Opiates / narcotics may mask symptoms of perforation! No infliximab in case of perforation / sepsis!



Antibiotics = Anti-infectives

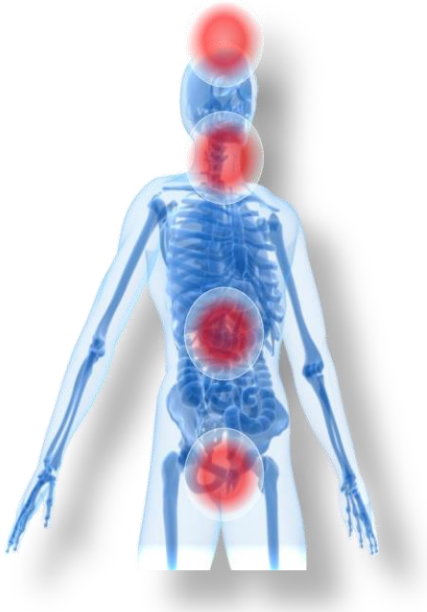
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Endocrinopathies

Incidence	• Thyroid abnormalities All grades: 8,6% Grades 3: 0,1% No Grade 4 • More than one endocrine organ may be involved
Manifestations	• Thyroid disorders • Adrenal disorders • Diabetes • Pituitary disorders

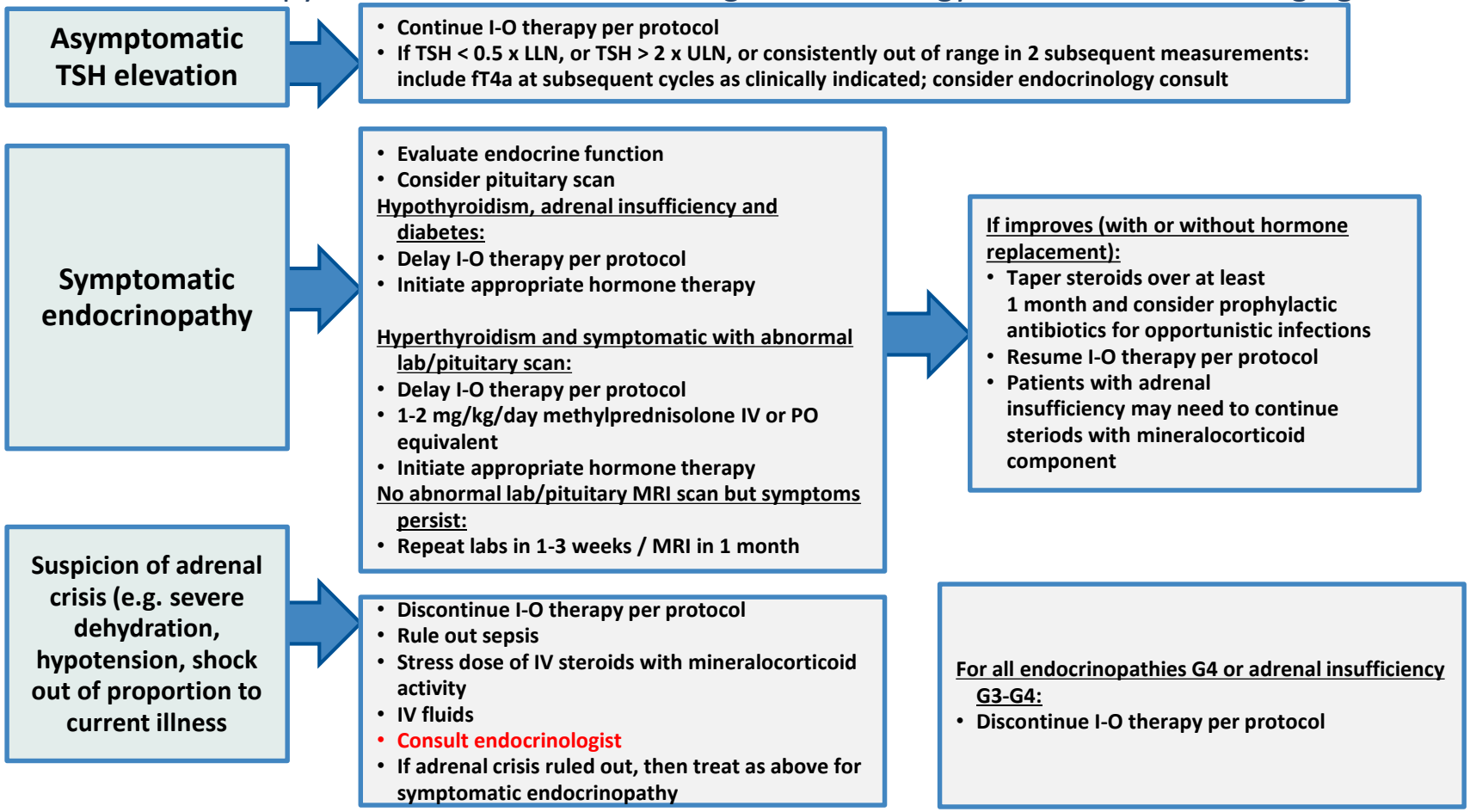
Onset	• Median time to onset 2.8 months (range: 0.0-14.0)
	• Within weeks ~may occur many months
	  • Typically identified through routine periodic monitoring or
	  • Part of work up of associated symptoms

Symptom	• Non-specific symptoms • Headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment • When encountering non-specific symptoms, think of endocrinopathies
Management	• Nivolumab may be continued once appropriate hormone replacement initiated • Subjects with endocrinopathy may require replacement dose steroids rather than high-dose steroids



Algorithm for Endocrinopathy

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation and imaging

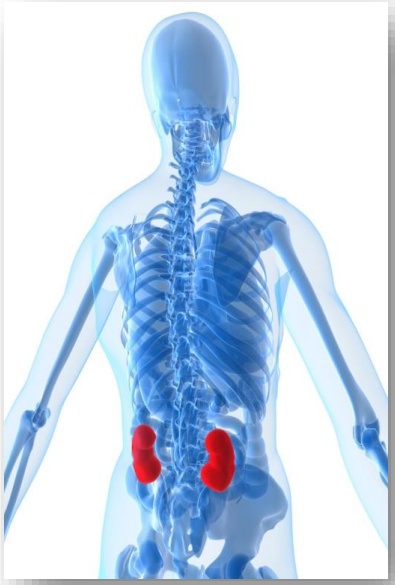


Antibiotics = Anti-infectives

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

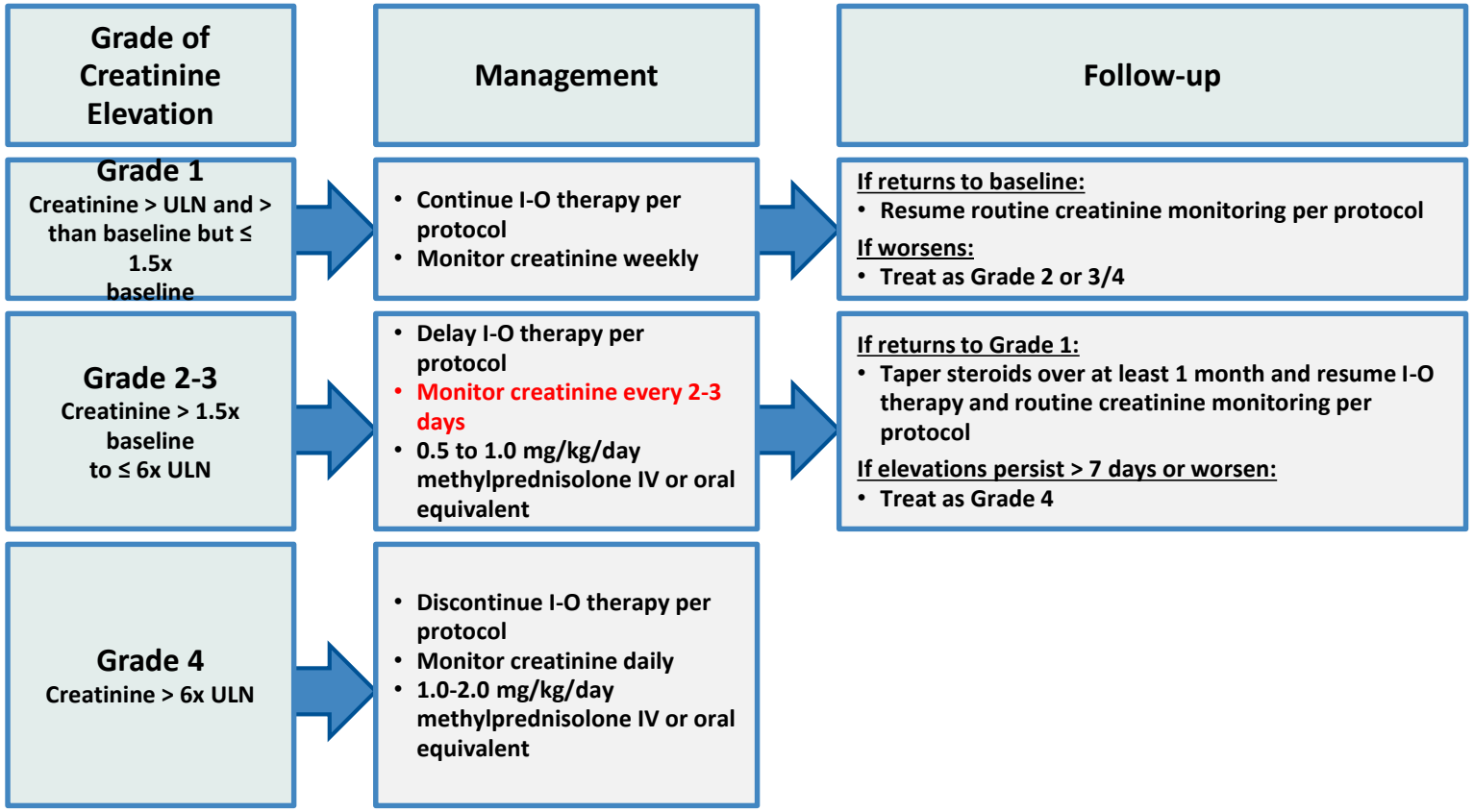
Renal Toxicity

Incidence	•Nephritis and renal dysfunction All grades: 3,2% Grade 3: 0,5% Grades 4: < 0,1% •No grade 5 reported
Onset	• Median time to onset 2.3 months (range: 0.0-18.2) • Most commonly present with elevations in serum creatinine
Management	• Steroids generally lead to clinical improvement/resolution
Renal biopsy	• May help distinguish inflammatory versus non-inflammatory etiologies



Renal Toxicity Management Algorithm

Rule out non-inflammatory causes! If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Antibiotics = Anti-infectives

General Rules: Management of Nivolumab-Related Select AEs

Grade	Management	Continue the drug?
Low	Delay the dose	Resume Nivolumab when AEs resolve to grade ≤ 1 or baseline
Moderate ~ High	Administer Corticosteroids ± Immunosuppressants (anti-TNF, mycophenolate, etc)	Discontinue Nivolumab permanently (Delay in some situations)

Lessons Learned from ~1,570 Subjects enrolled in Nivolumab trials

The majority of treatment-related AEs are manageable with drug interruption ± corticosteroid and reversible

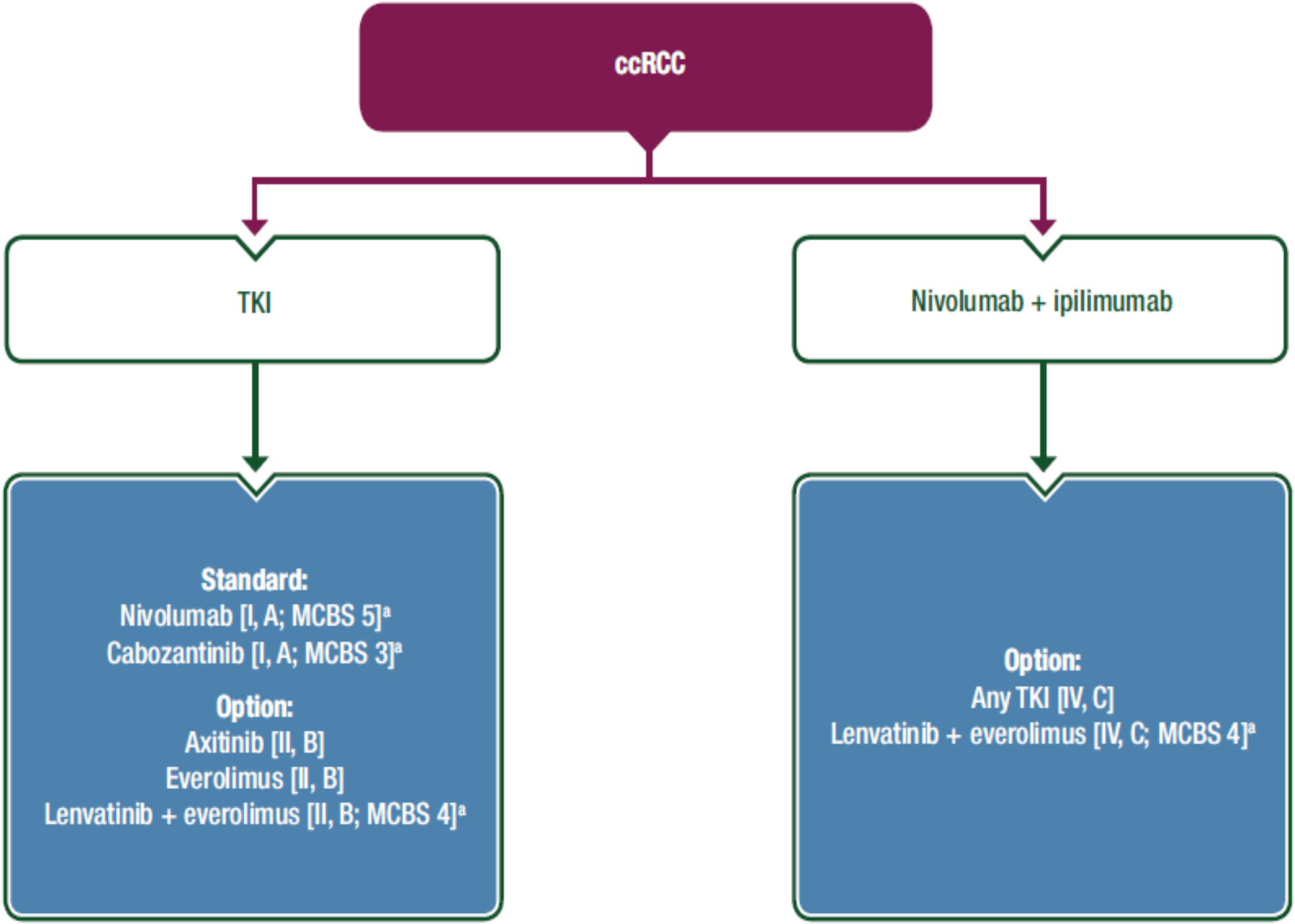
Remember These Things!
1. Early recognition and consideration may mitigate severe toxicity ⇒ **Patient education**
2. Refer to specific algorithms (RMP) • Endocrinopathy • Renal Toxicity • Hepatic Toxicity • Pulmonary Toxicity • GI Toxicity • Skin Toxicity • Neurological Toxicity

Awareness is Key

- Effective management of treatment related AEs is based on:
  1. Early recognition
  2. Frequent monitoring
  3. Use of corticosteroids (and/or other immunosuppressive therapies) combined with either delaying or discontinuing Nivolumab
- Patient Education
  1. Note how they feel prior to starting treatment, any change advise patient to call
  2. Best to treat early, may help you remain on therapy

Management of nivolumab irAEs: general considerations

- Consistent with randomized phase 3 trials, most treatment-related AEs were of low grade and manageable with established guidelines
- Delaying the use of corticosteroids or other immunosuppressive therapy may allow the development of severe irAEs and/or life threatening complications
- irAE treatment is dependent upon severity:
  - Grade 1–2 irAEs: dose delays and observation
  - Grade 3–4 irAEs: immunosuppression with corticosteroids
- After irAE improvement, corticosteroids should be tapered over 4–6 weeks (depending on the severity of the AE)
- Good compliance with irAE management algorithms is essential
- Patients on IV steroids may be switched to oral corticosteroid at an equivalent dose at start of tapering or earlier, once sustained clinical improvement observed. Lower bioavailabilty of oral corticosteroids should be considered when switching.


ccRCC
TKI
Nivolumab + ipilimumab
Standard:
Nivolumab [I, A; MCBS 5]a
Cabozantinib [I, A; MCBS 3]a
Option:
Axitinib [II, B]
Everolimus [II, B]
Lenvatinib + everolimus [II, B; MCBS 4]a
Option:
Any TKI [IV, C]
Lenvatinib + everolimus [IV, C; MCBS 4]a

30-Month Follow-Up of the Phase 3 CheckMate 214 Trial of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma

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PRESENTED AT: 2019 Genitourinary Cancers Symposium | #GU19

Introduction

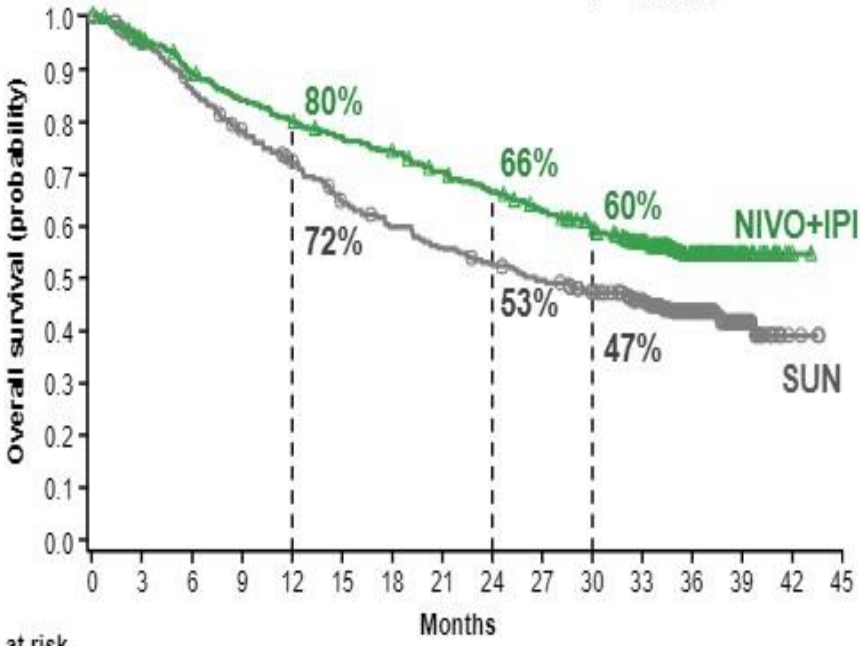
- NIVO+IPI is approved for first-line treatment of intermediate/poor-risk aRCC, based on superior OS and ORR over SUN in the randomized, phase 3 CheckMate 214 trial[1–3]
  - At a minimum follow up of 17.5 months, OS was superior with NIVO+IPI vs SUN (median OS not reached vs 26.0 months; HR, 0.63; $P < 0.001$)[1]
  - Confirmed ORR per IRRC with NIVO+IPI vs SUN was 42% vs 27% ($P < 0.001$), with complete responses in 9% vs 1% ($P < 0.001$)[1]
  - Median PFS per IRRC was 11.6 months with NIVO+IPI vs 8.4 months with SUN, but the difference did not reach statistical significance[1]

Overall Survival: by IMDC Risk

Intermediate/poor risk

Median OS, months (95% CI)	
NIVO+IPI	NR (35.6–NE)
SUN	26.6 (22.1–33.4)

HR (95% CI), 0.66 (0.54–0.80)
P < 0.0001

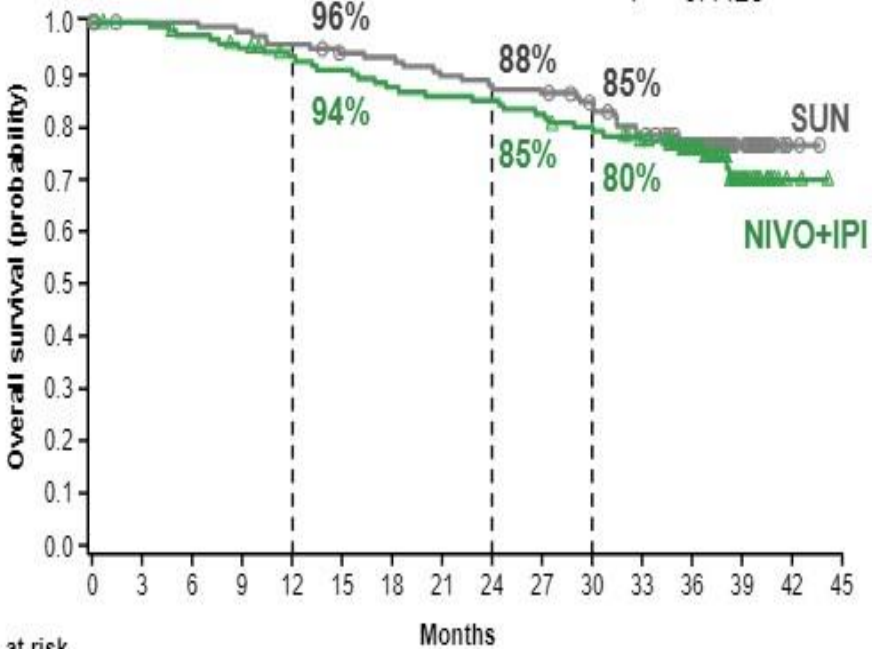


No. at risk																
NIVO+IPI	425	399	372	348	332	317	306	287	270	253	233	183	90	34	2	0
SUN	422	388	353	318	290	257	236	220	207	194	179	144	75	29	3	0

Favorable risk

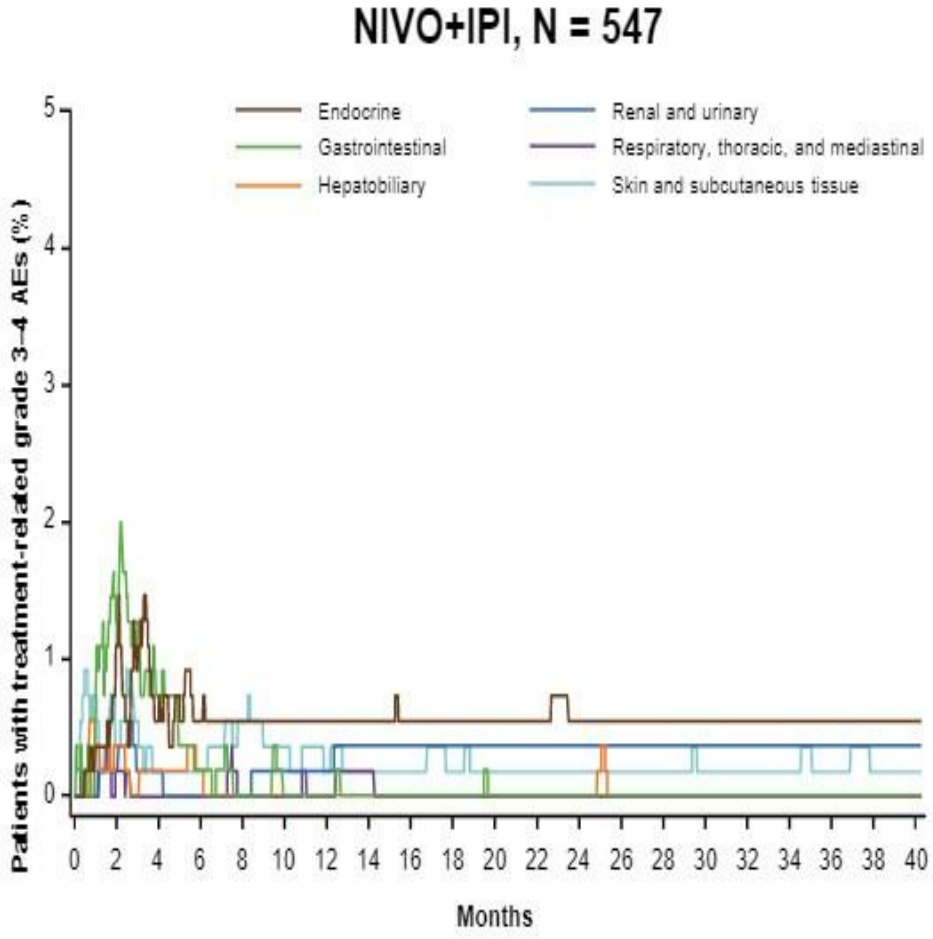
Median OS, months (95% CI)	
NIVO+IPI	NR (NE)
SUN	NR (NE)

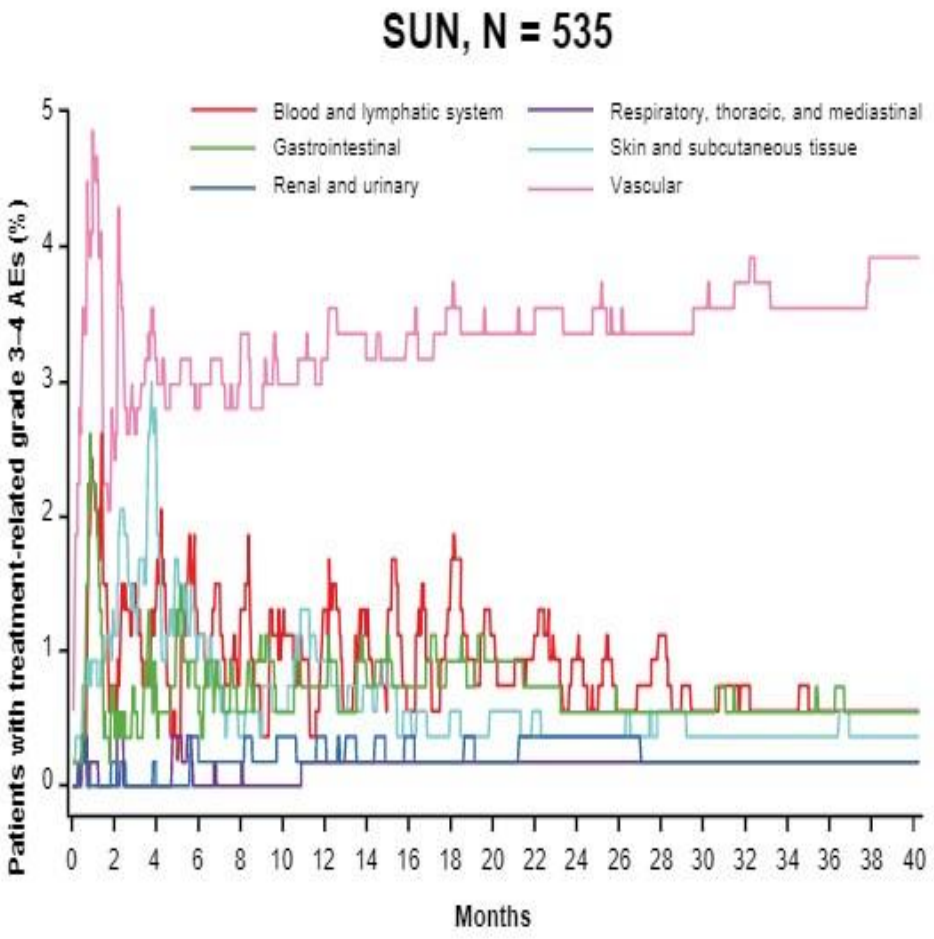
HR (95% CI), 1.22 (0.73–2.04)
P = 0.4426



No. at risk																
NIVO+IPI	125	124	120	116	111	108	104	102	101	98	94	88	71	24	2	0
SUN	124	119	119	117	114	110	109	105	103	101	96	88	70	26	2	0

Treatment-Related AEs Over Time by Most Common System Organ Class (All Treated Patients)





- In the NIVO+IPI arm, 35% of patients received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent) for select treatment-related AE management
- No additional treatment-related deaths occurred