Con il patrocinio di:

asl napoli2nord

Associazione Italiana Donne Medico

LA GESTIONE DELLA PATOLOGIA NEOPLASTICA RENALE:

dal management sanitario alla personalizzazione delle terapie

ID ECM 256525

Pozzuoli | 11 maggio 2019

Sala Comunale | Palazzo Migliaresi | Rione Terra

I LINEA

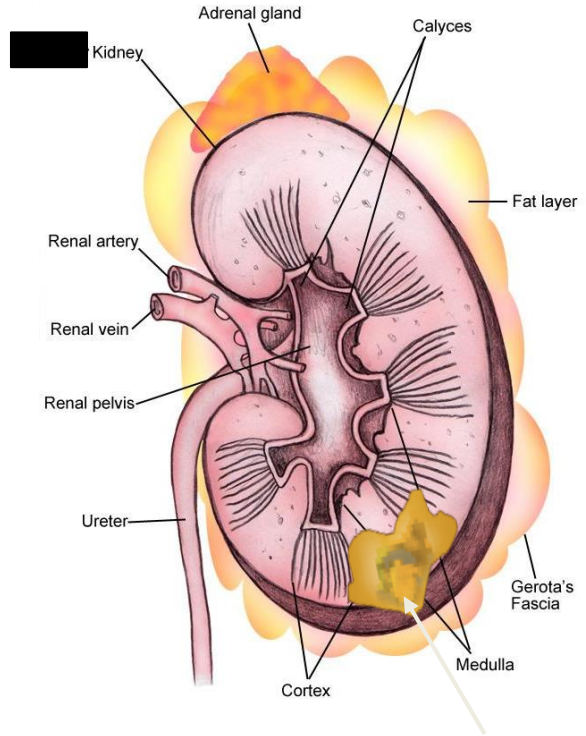
Dott.ssa Sarah Scagliarini

AORN Cardarelli

Napoli

Description of RCC

- **Approximately 90% of all kidney cancers are RCC[1]**
  - RCC typically develops in the lining of the kidney tubules[2]
    - There are 2 main histological subtypes: clear cell and non-clear cell[3]
- **The remaining 10% of kidney cancers include transitional cell carcinomas, Wilms' tumors, and renal sarcomas[1]**
- **RCC is classified as an "immunogenic" tumor based on these characteristics[4]:**
  - Incidence of spontaneous tumor regression in the absence of therapy[4]
  - High level of tumor T-cell infiltration[4]
  - Responsiveness to immunotherapies such as IL-2 and IFN-α[4]

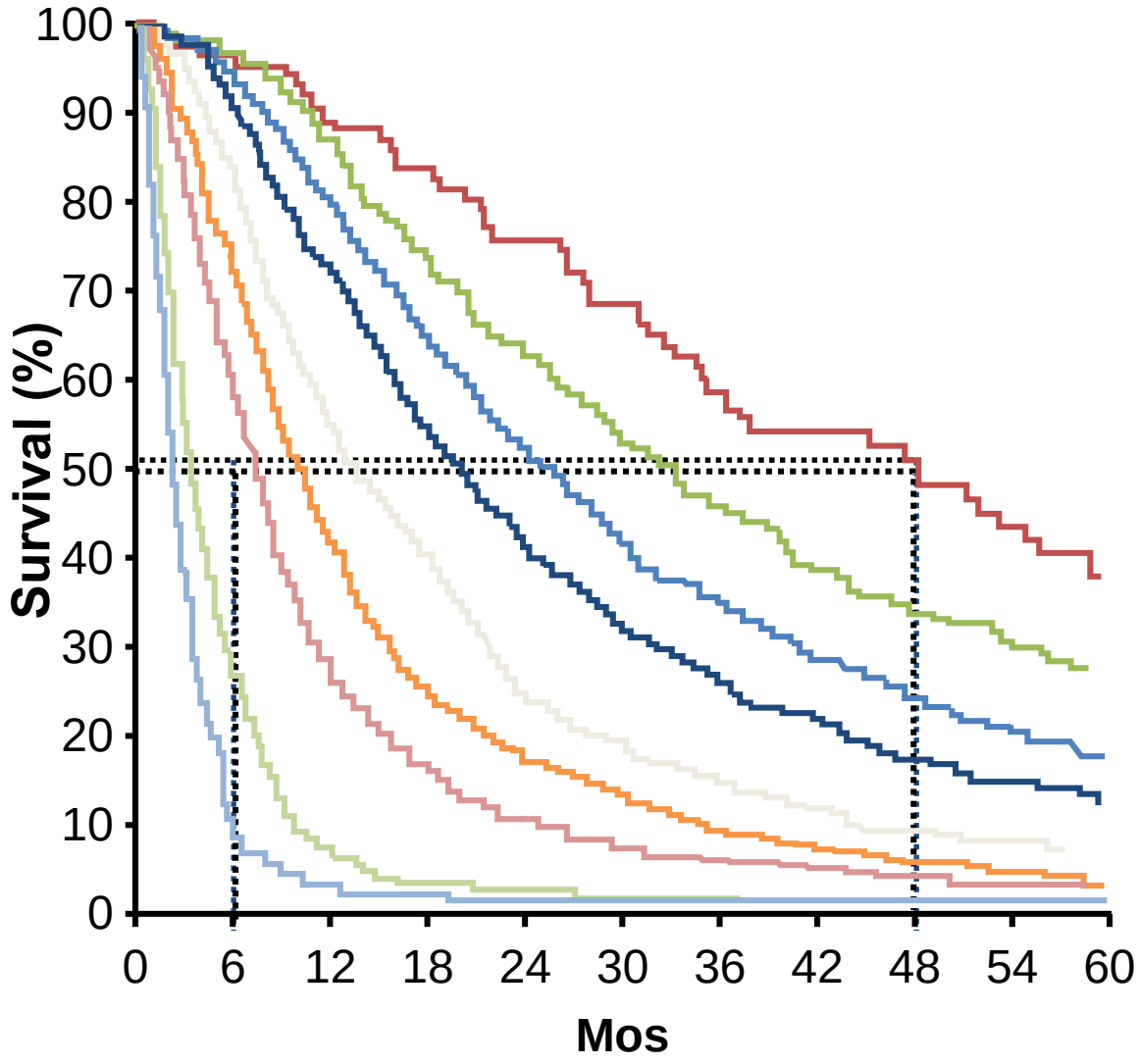


Adapted from Medscape.com.[5]

IFN-α, interferon-α; IL-2, interleukin-2; RCC, renal cell carcinoma.

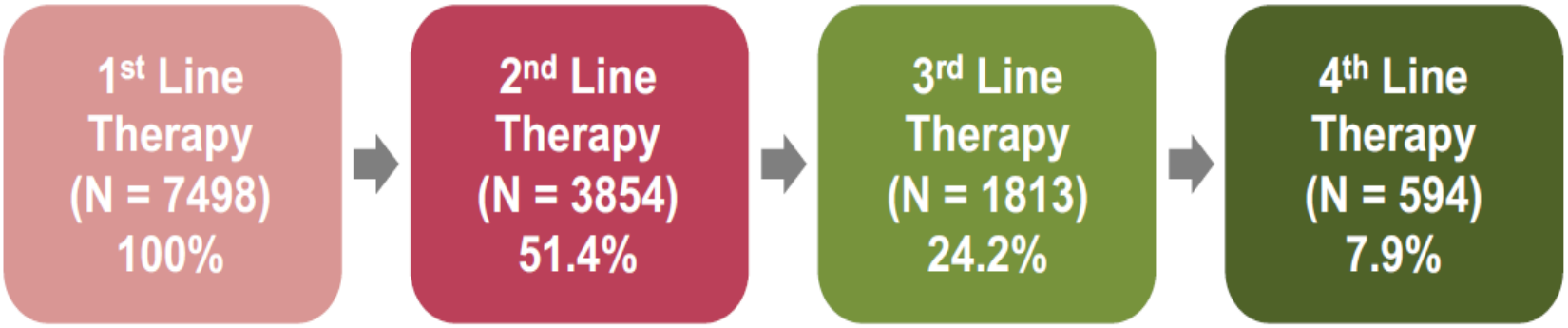
1. American Cancer Society. Kidney Cancer. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003107-pdf.pdf. Accessed October 22, 2014.
2. National Center for Biotechnology Information. Renal Cell Cancer Treatment (PDQ®): Patient Version. Available at: www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001544. Accessed June 17, 2014. 3. Xu KY, et al. *Biomark Res* 2015;3:5. 4. Itsumi M, et al. *Clin Dev Immunol* 2010;2010:284581. 5. Kidney anatomy. Available at: http://emedicine.medscape.com/article/1948775-overview. Accessed June 19, 2017.

RCC Is an Inherently Diverse Disease



Courtesy of Brian Rini, MD, FACP.

Proportion of RCC patients at each line of therapy



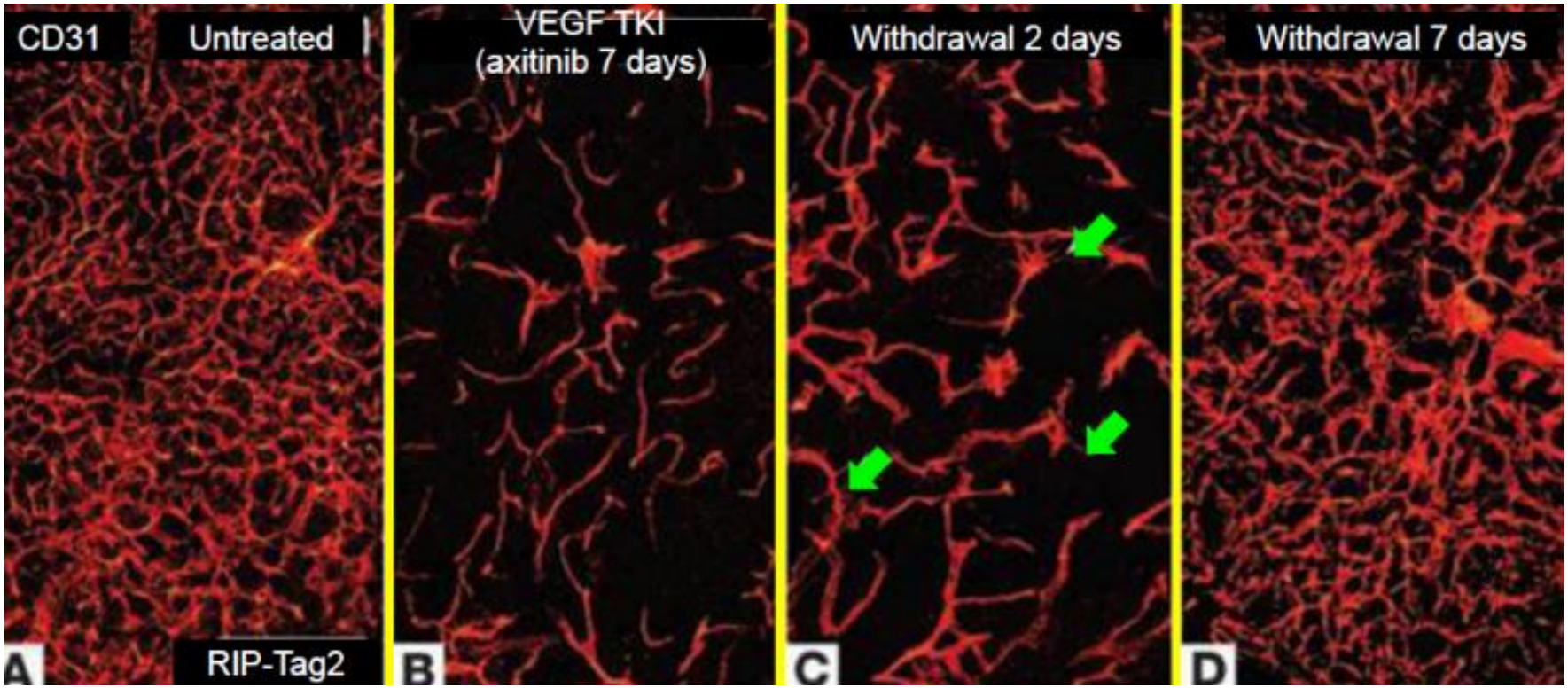
Karnofsky PS	< 80%
Tasso di emoglobinemia	< limite inferiore del *range* di normalità
Calcio corretto	> 10 mg/dl
Periodo dalla diagnosi al trattamento	< 1 anno
Conta assoluta dei neutrofili	> limite superiore del *range* di normalità
Conta piastrinica	> limite superiore del *range* di normalità

Tabella 4a - Sistema prognostico IMDC o criteri di Heng.

Prognosi	Numero di fattori	Sopravvivenza mediana	Sopravvivenza a 2 anni
Favorevole	0	NR	75%
Intermedia	1-2	27 mesi	53%
Sfavorevole	3-6	8.8 mesi	7%

Tabella 4b - Sistema prognostico Heng: categorie di rischio e relative sopravvivenze mediane.

Reversible inhibition of tumor angiogenesis by VEGFR-TKI – what is the reason of regrowth?

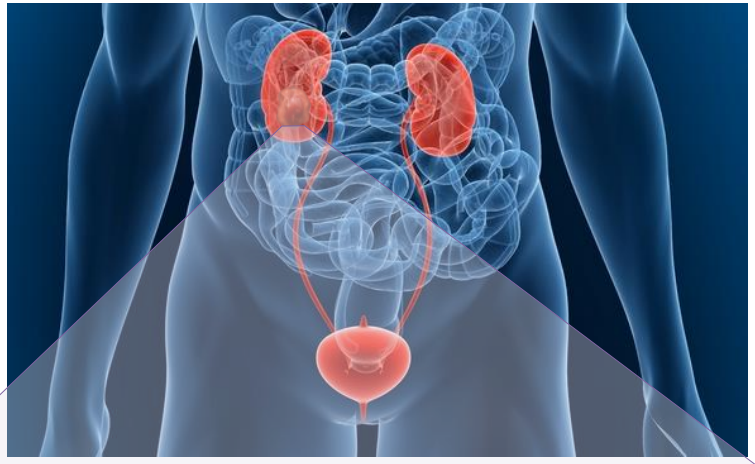


Mancuso MR et al. *J Clin Invest*. 2006.

Rationale for Immunotherapy in RCC

- **Spontaneous advanced RCC remissions attributed to the immune system have been observed[1]**
- **RCC exhibits immune cell infiltrates, and several immune escape mechanisms have been reported in RCC[2,3]**
- **Historically, the mainstay of treatment for patients with mRCC was immunotherapy with interleukin-2 or interferon-α1**
- **I-O is an evolving treatment modality encompassing agents designed to directly harness the patient's own immune system to fight cancer[7,8]**

Studies have documented alterations in various immune cell types in RCC, including[3–6]:



I-O, immuno-oncology; RCC, renal cell carcinoma; mRCC, metastatic renal cell carcinoma; Treg, regulatory T cell.

1. Escudier B. *Ann Oncol* 2012;23(Suppl 8):viii35–40 2. Noessner E et al. *OncoImmunology* 2012;1:1451–3. 3. Bockorny B et al. *Expert Opin Biol Ther* 2013;13:911–25. 4. Hotta K, et al. *Br J Cancer* 2011;105:1191–96. 5. Nakano O et al. *Cancer Res* 2001;61:5132–6. 6. Igarashi T et al. *Urol Int* 2002;69:51–6.
7. Ascierto PA et al. *J Trans Med* 2014;12:141. 8. Eggermont A et al. *OncoImmunol* 2014;3:e27560.

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-018-0053-3
Corrected: Publisher Correction

Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma

- Three biological axes:
  - Tumor angiogenesis:
    - Angio $_{\text{High}}$ / Angio $_{\text{Low}}$ → higher vascular density as evaluated by CD31
  - Pre-existing immunity
    - $T_{\text{eff High}}$ and $T_{\text{eff Low}}$ → protein expression of PD-L1 and CD8 T-cell infiltration
  - Immunosuppressive myeloid inflammation:
    - $T_{\text{eff High}}$ and $T_{\text{eff Low}}$ → expression of genes associated with myeloid inflammation

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

- Confirmed metastatic clear cell RCC / Biopsy
- ECOG – PS 0-1
- Amenable to nephrectomy
- Eligible for sunitinib
- Brain metastases absent/controlled by treatment
- No prior systemi therapy for RCC

R
1:1

Stratification:
•MSKCC risk group
•Center location

Arm A *3-6 weeks*

nephrectomy → Sunitinib 50mg QD 4 wks on / 2 wks off

Arm B

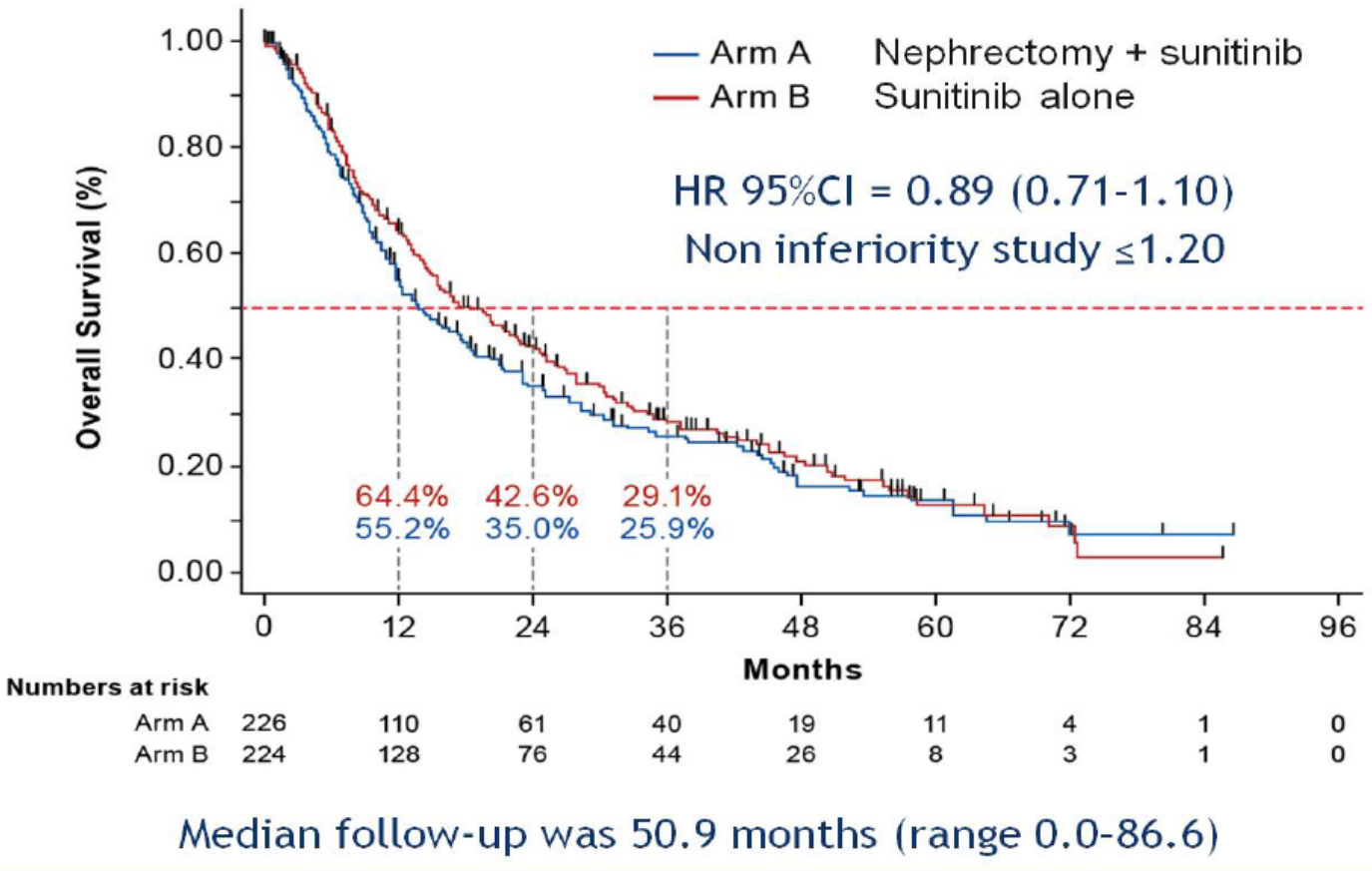
Sunitinib 50mg QD 4 wks on / 2 wks off

Primary endpoint: overall survival

Secondary endpoints: progression-free survival, objective response rate, clinical benefit, safety

LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

Overall survival (ITT)

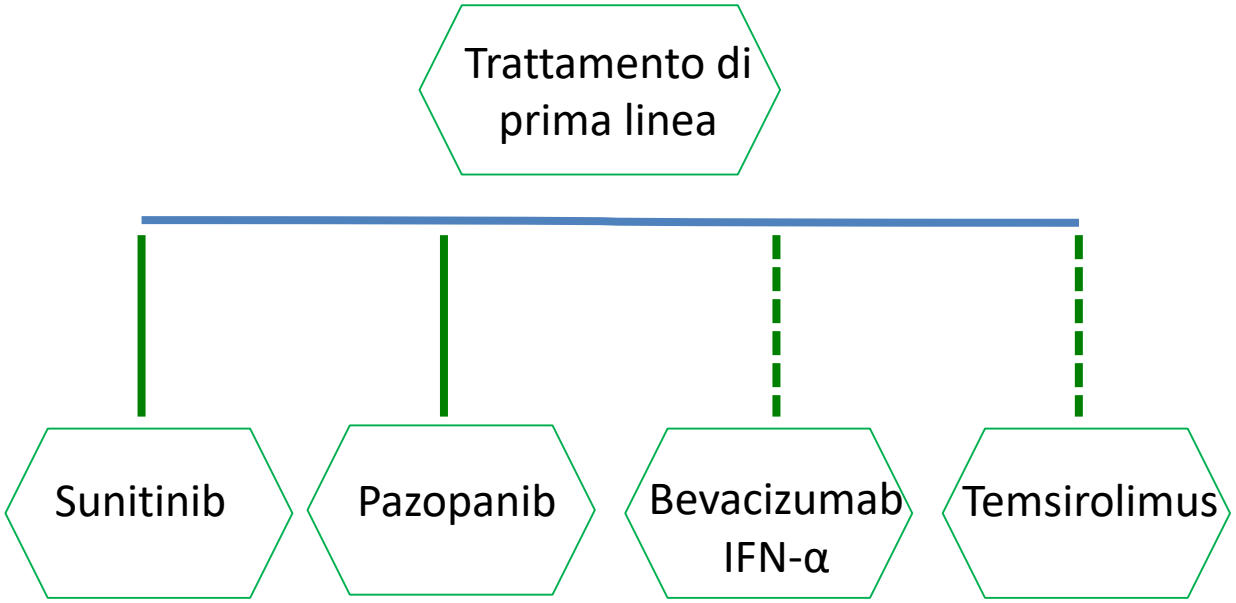


Median follow-up was 50.9 months (range 0.0-86.6)

Presented By Arnaud Mejean at 2018 ASCO Annual Meeting

Trattamento medico della malattia avanzata

Opzioni terapeutiche di prima linea



Positiva Forte

Positiva Debole

Negativa Debole

Negativa Forte

LG AIOM 2017

Personalizzazione della dose

Therapy management

Cosa ci aspettiamo dal therapy management

Minori effetti collaterali

Maggiore aderenza al trattamento

Un migliore outcome

Come si realizza il therapy management

GESTENDO LA DOSE DEL FARMACO

UTILIZZANDO UNA SCHEDULA DI SOMMINISTRAZIONE PERSONALIZZATA

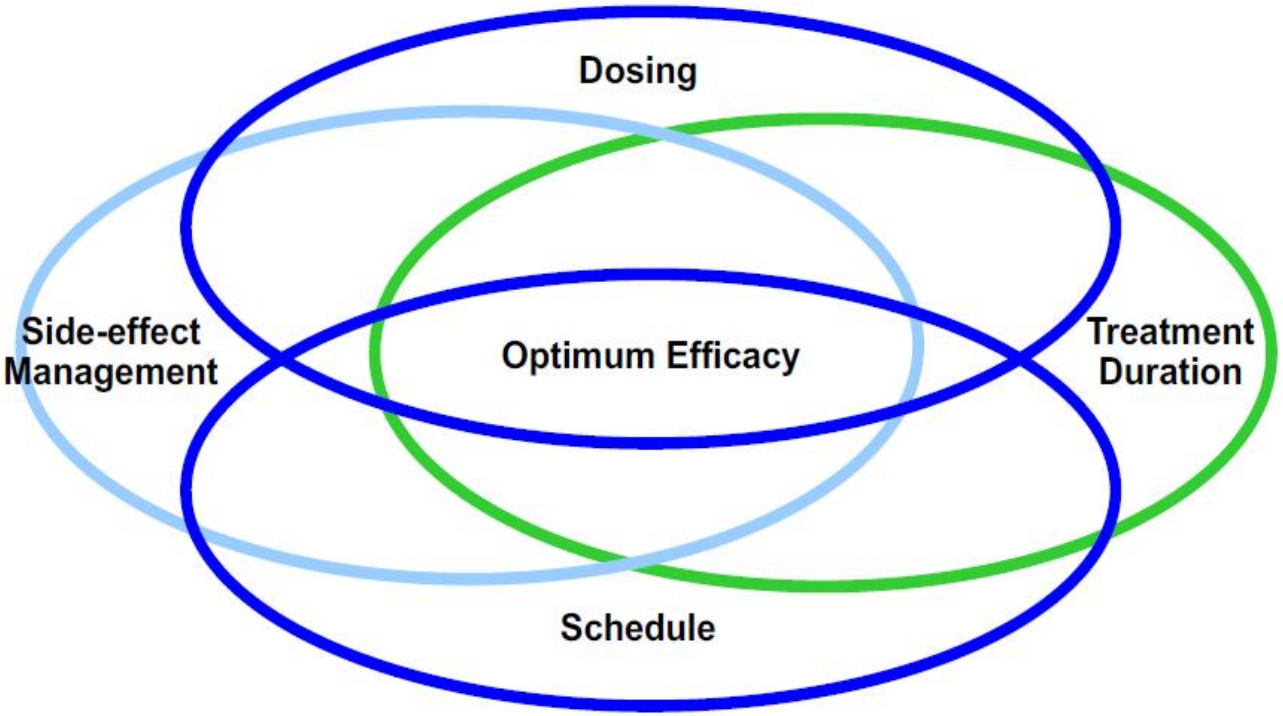
MASSIMIZZANDO LA DURATA DEL TRATTAMENTO

GESTENDO ATTIVAMENTE GLI AEs

Punti chiave del Therapy Management

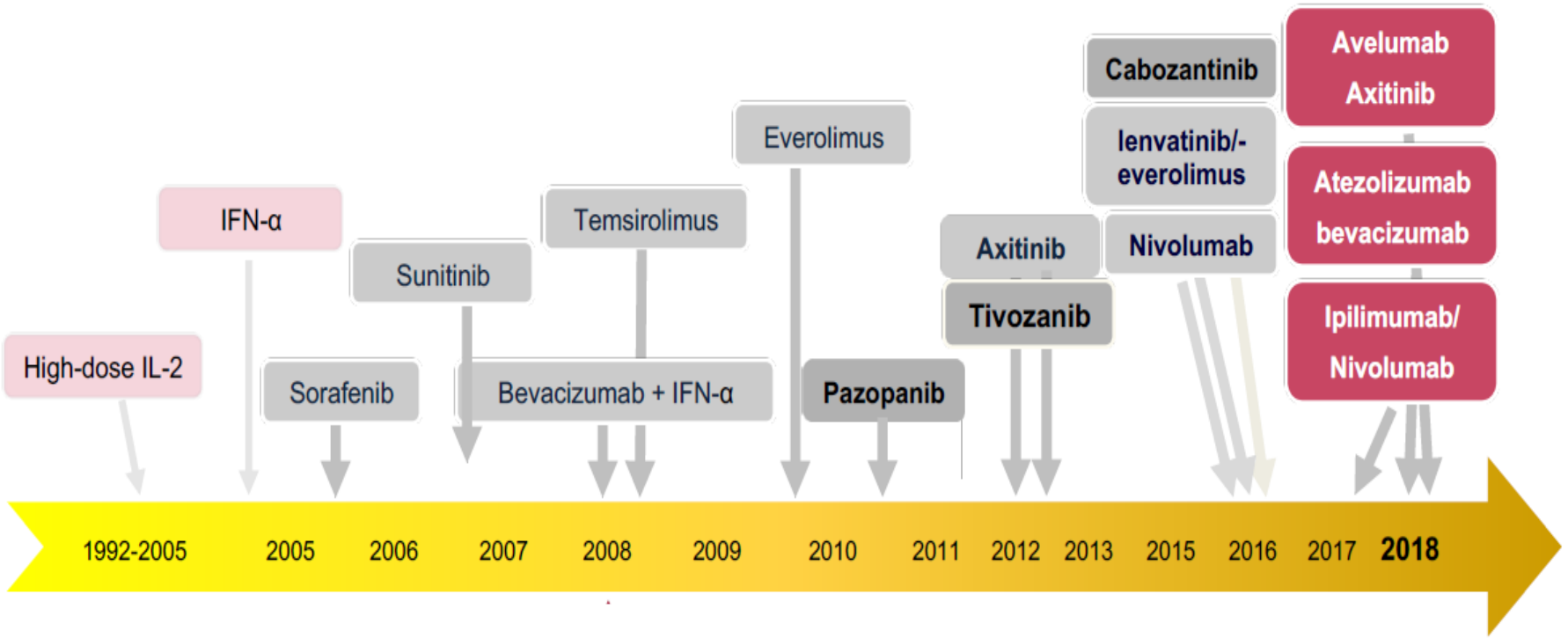
- **Importanza del rapporto dose/risposta**
- Concetto di variabilità interpersonale nella biodisponibilità dei farmaci
- Strategia per prevenire l'insorgenza della resistenza al target VEGF

Key Factors for Successful Therapy Management in mRCC



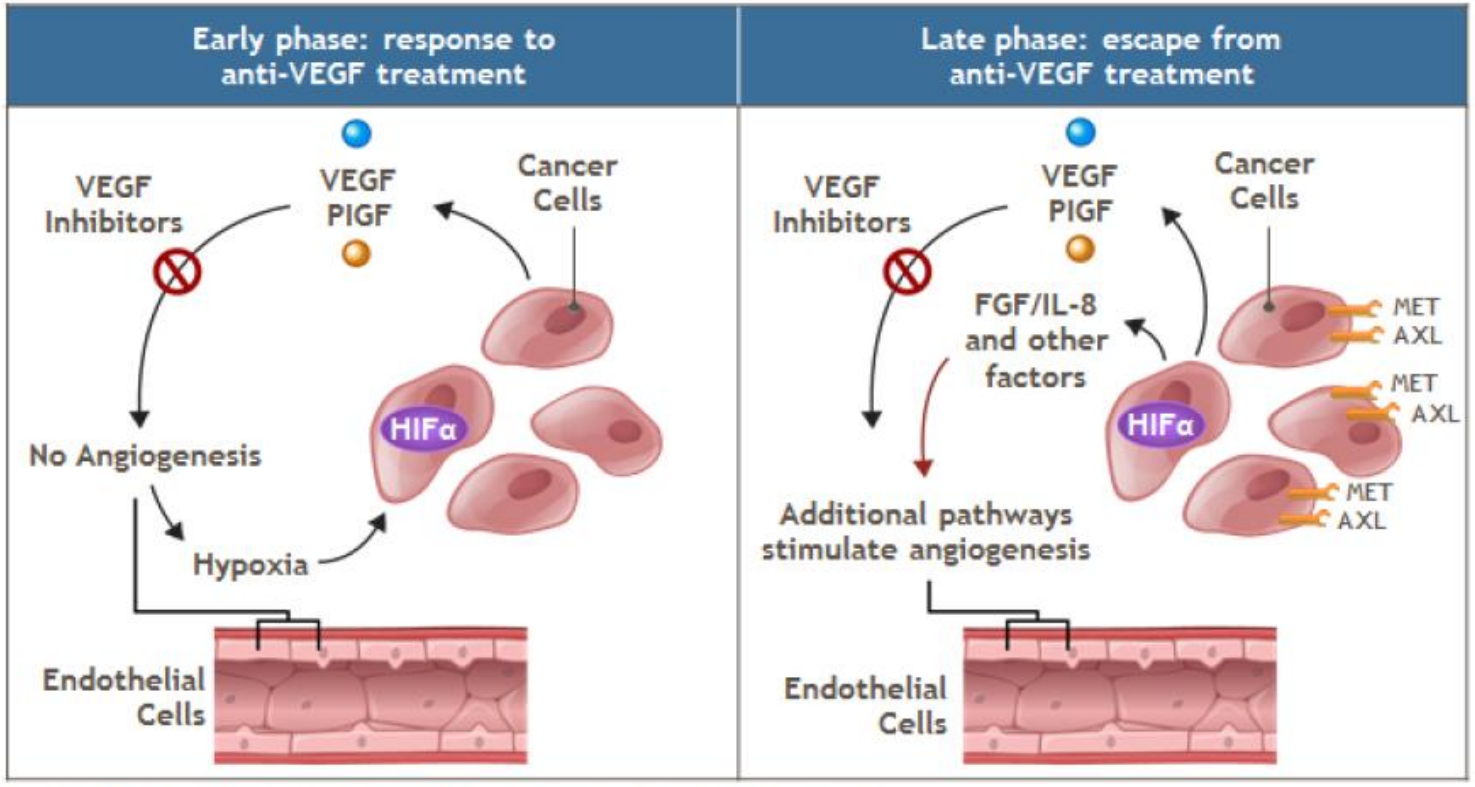
ADVERSE EVENT TKI

	Grade 1	Grade 2	Grade 3
Hypertension	• Pre-hypertension	• Stage 1 hypertension (systolic 140–159 mmHg or diastolic BP 90–99 mmHg) recurrent or persistent (≥24 hours) • Symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously WNL • Medical intervention indicated Gr 1–2: 22%	• Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg) • >1 drug or more intensive therapy than previously used indicated • Medical intervention indicated Gr 3: 15%
PPES	• Minimum skin changes or dermatitis (eg, erythema, edema, or hyperkeratosis) without pain	• Skin changes (eg, peeling, blisters, bleeding, edema, hyperkeratosis) with pain • Limiting instrumental ADL[a] Gr 1–2: 34%	• Severe skin changes (eg, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain • Limiting self-care ADL[a] Gr 3: 8%
Fatigue	• Fatigue relieved by rest	• Fatigue not relieved by rest • Limiting instrumental ADL[a] Gr 1–2: 47%	• Fatigue not relieved by rest • Limiting self-care ADL[a] Gr 3: 9%
Stomatitis	• Asymptomatic or mild symptoms; intervention not indicated	• Moderate pain; not interfering with oral intake; modified diet indicated Gr 1–2: 20%	• Severe pain; interfering with oral intake Gr 3: 2%
Diarrhea	• Increase of <4 stools over baseline	• Increase of 4–6 stools per day over baseline Gr 1–2: 63%	• Increase of ≥7 stools/day over baseline • Incontinence • Hospitalization indicated • Limiting self-care ADL[a] Gr 3: 11%
Nausea	• Loss of appetite without alteration in eating habits	• Oral intake decreased without significant weight loss, dehydration, or malnutrition Gr 1–2: 46%	• Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated Gr 3: 4%
Vomiting	• 1–2 episodes (separated by 5 minutes) in 24 hours	• 3–5 episodes (separated by 5 minutes) in 24 hours Gr 1–2: 30%	• ≥6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN, or hospitalization indicated Gr 3: 2%
Decreased appetite	• Loss of appetite without alteration in eating habits	• Oral intake decreased without significant weight loss, dehydration, or malnutrition Gr 1–2: 44%	• Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated Gr 3: 2%


High-dose IL-2
IFN-α
Sorafenib
Sunitinib
Temsirolimus
Bevacizumab + IFN-α
Everolimus
Pazopanib
Axitinib
Tivozanib
Cabozantinib
lenvatinib/-everolimus
Nivolumab
Avelumab
Axitinib
Atezolizumab
bevacizumab
Ipilimumab/
Nivolumab
1992-2005
2005
2006
2007
2008
2009
2010
2011
2012
2013
2015
2016
2017
2018

The Role of MET and AXL in Tumour Progression and Resistance to VEGF Receptor Inhibitors

- In RCC, MET and AXL are thought to function as escape pathways potentially contributing to resistance to more selective VEGFR-targeted therapy[1]

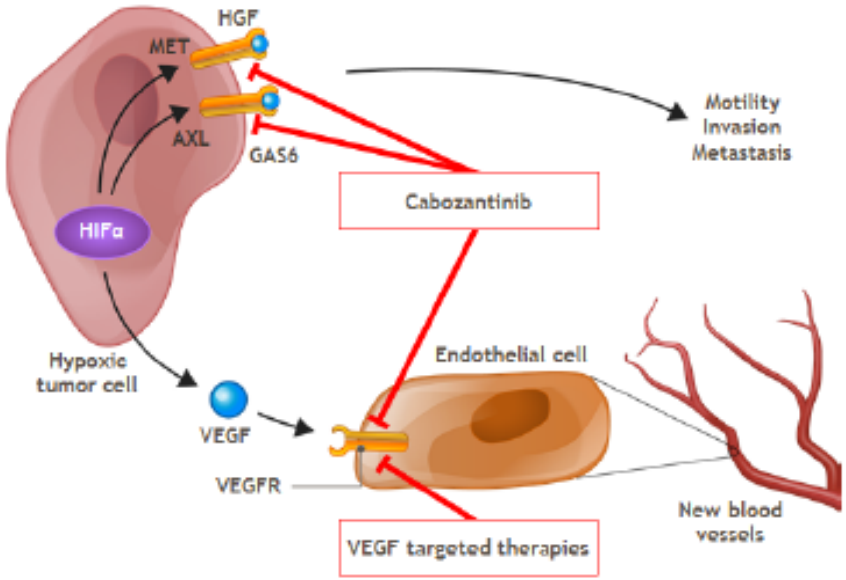


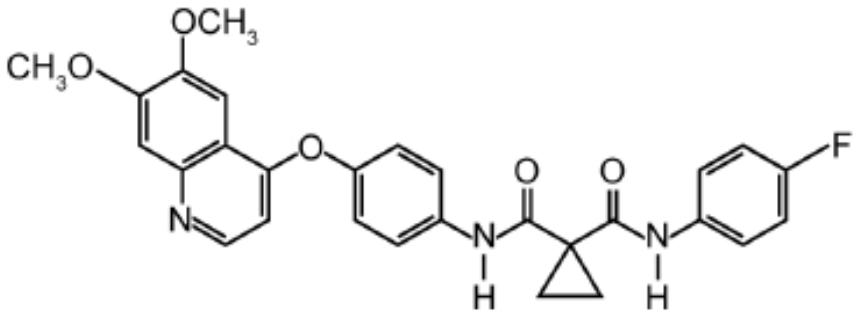
FGF, fibroblast growth factor; HIF, hypoxia-inducible factor;

1. Zhou L, et al. *Oncogene* 2016;35:2687–97.

Cabozantinib Targets Multiple Distinct Pathways

- Cabozantinib is an oral small molecule inhibitor of multiple tyrosine kinase receptors, including:
  - **MET**
  - **AXL**
  - **VEGFR-1, VEGFR-2, VEGFR-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**

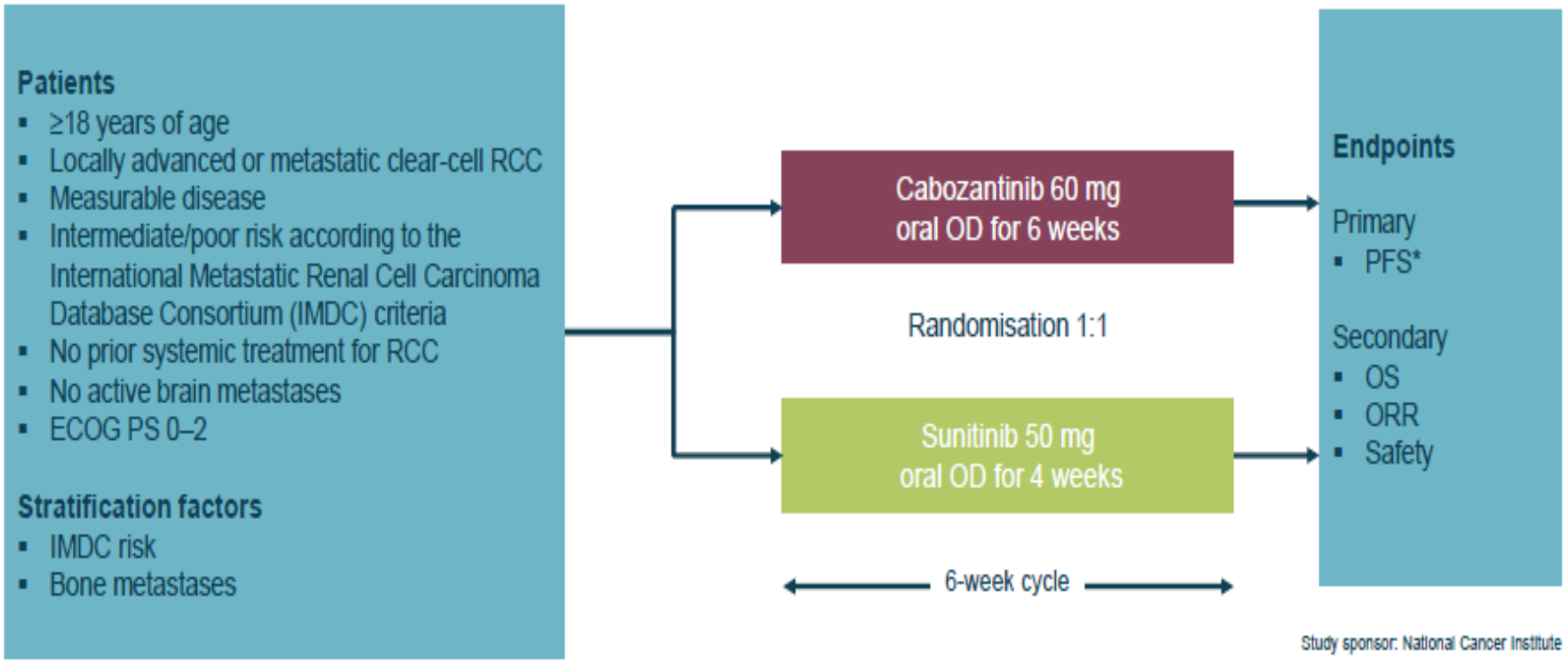




1. Yakes MF, et al. Mol Cancer Ther 2011;10:2298–2308

Cabozantinib Phase 2 Study (CABOSUN): Design

Phase 2, randomised, multicenter, open-label study to evaluate the efficacy and safety of cabozantinib vs sunitinib in patients with previously untreated local advanced or metastatic RCC



Study sponsor: National Cancer Institute

OD, daily; ECOG PS, Eastern Cooperative Oncology Group performance status. *PFS defined as time from randomisation to disease progression or death, whichever occurs first

https://clinicaltrials.gov/ct2/show/NCT01835158;
Choueiri TK, et al. *J Clin Oncol* 2017;35:591–7 ("Errata." *J Clin Oncol*, 35(32), p. 3736)

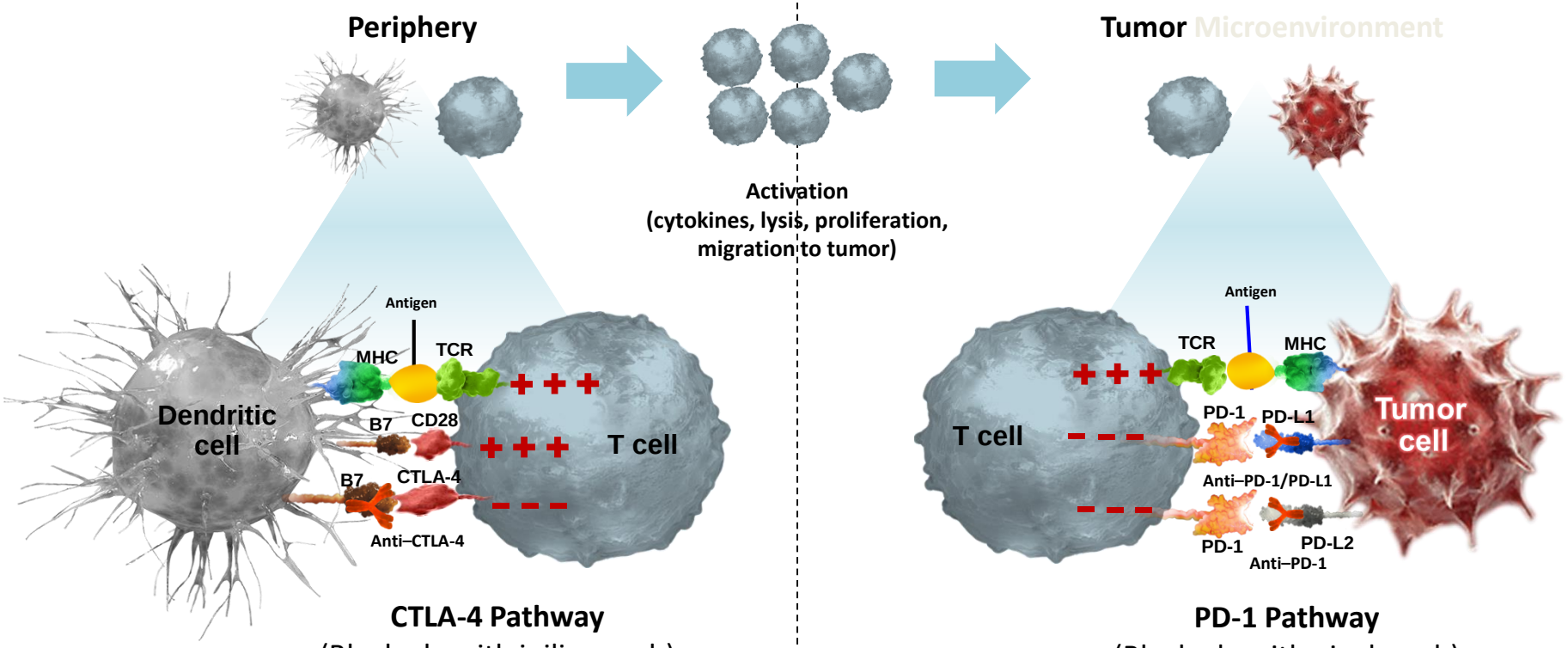
Phase 2 CABOSUN Study: Summary

- Cabozantinib significantly improved PFS compared with sunitinib in previously-untreated RCC patients of intermediate- and poor-risk IMDC categories:
  - 8.3 vs 5.4 months (HR = 0.56, P=0.0042) by investigator review (September 2016 cut-off)
  - 8.6 vs 5.3 months (HR = 0.48, P=0.0008) by independent review (September 2016 cut-off)
  - Benefit from cabozantinib was seen across subgroups
- Cabozantinib improved ORR over sunitinib
  - ORR: 33% vs 12% by investigator review (September 2016 cut-off)
  - ORR: 20% vs 9% by independent review (September 2016 cut-off)
- Trend towards improved OS with cabozantinib (the study was not powered to show an OS difference)
- The safety profile for cabozantinib was similar to sunitinib

Choueiri TK, et al. *J Clin Oncol* 2017;35:591–7 ("Errata." *J Clin Oncol*, 35(32), p. 3736); Choueiri TK, *et al. Eur J Cancer* 2016;94:115–125

Immune Checkpoint Inhibitors: Potential as Part of a Combination Regimen

Data suggest certain combinations may overcome the limitations of monotherapy[1,2]



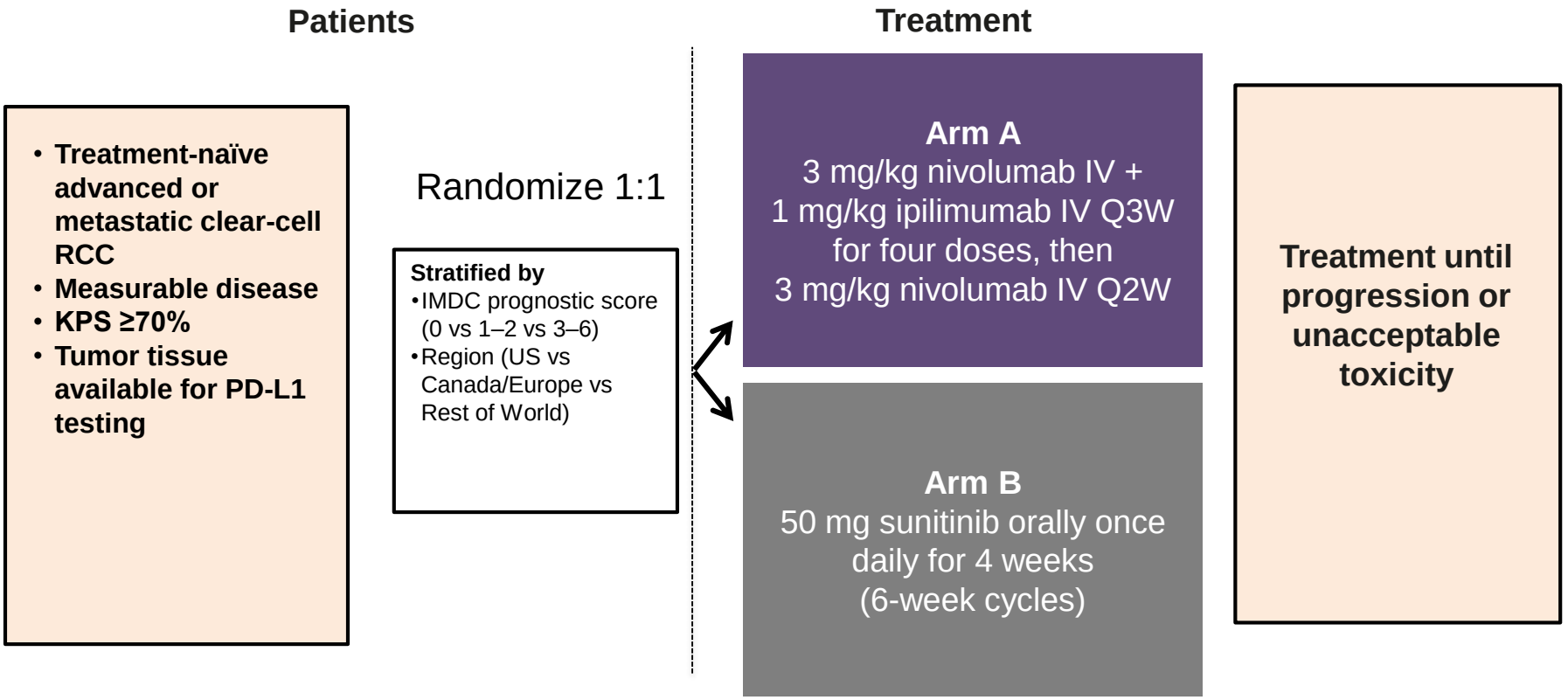
CTLA-4 Pathway
(Blockade with ipilimumab)

PD-1 Pathway
(Blockade with nivolumab)

Adapted from Pardoll DM et al. *Nat Rev Cancer* 2012.[1]

Abbreviations, references, and footnotes are listed in the speaker notes.

CheckMate 214: Study design



IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; Q2W, every 2 weeks; Q3W, every 3 weeks

IMDC risk categories for RCC

IMDC risk factors	IMDC risk categories[1]	Median OS in patients treated with anti-VEGF therapy[1]
• KPS of 70 • <1 year from diagnosis to randomization • Hemoglobin <LLN • Corrected calcium concentration >10 mg/dL • Absolute neutrophil count >ULN • Absolute platelet count >ULN	0 factors = favorable	43 months
	1–2 factors = intermediate	23 months
	3–6 = poor	8 months

1. Heng DYC et al. *Lancet Oncol* 2013; 14:141–48.

IMDC, International Metastatic RCC Database Consortium; KPS, Karnofsky performance status; LLN, lower limit of normal; ULN, upper limit of normal

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

Nizar M. Tannir,[1] Osvaldo Arén Frontera,[2] Hans J. Hammers,[3] Michael Carducci,[4] David F. McDermott,[5] Pamela Salman,[6] Bernard Escudier,[7] Benoit Beuselinck,[8] Asim Amin,[9] Camillo Porta,[10] Saby George,[11] Sergio Bracarda,[12] Scott S. Tykodi,[13] Thomas Powles,[14] Brian I. Rini,[15] Yoshihiko Tomita,[16] M. Brent McHenry,[17] Sabeen Mekan,[17] Robert J. Motzer[18]

[1]University of Texas MD Anderson Cancer Center, Houston TX, USA; [2]Centro Internacional de Estudios Clínicos, Santiago, Chile; [3]UT Southwestern, Dallas, TX, USA; [4]Johns Hopkins Medicine - The Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [5]Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [6]Fundación Arturo López Pérez, Santiago, Chile; [7]Gustave Roussy, Villejuif, France; [8]University Hospitals Leuven, Leuven, Belgium; [9]Levine Cancer Institute, Charlotte, NC, USA; [10]University of Pavia, Pavia, Italy; [11]Roswell Park Cancer Institute, Buffalo, NY, USA; [12]Ospedale San Donato, Azienda Ospedaliera S.Maria, Terni, Italy; [13]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [14]Barts Cancer Institute, London, UK; [15]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [16]Niigata University, Niigata, Japan; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Italy Mercury Number 1506IT19NP00353-01

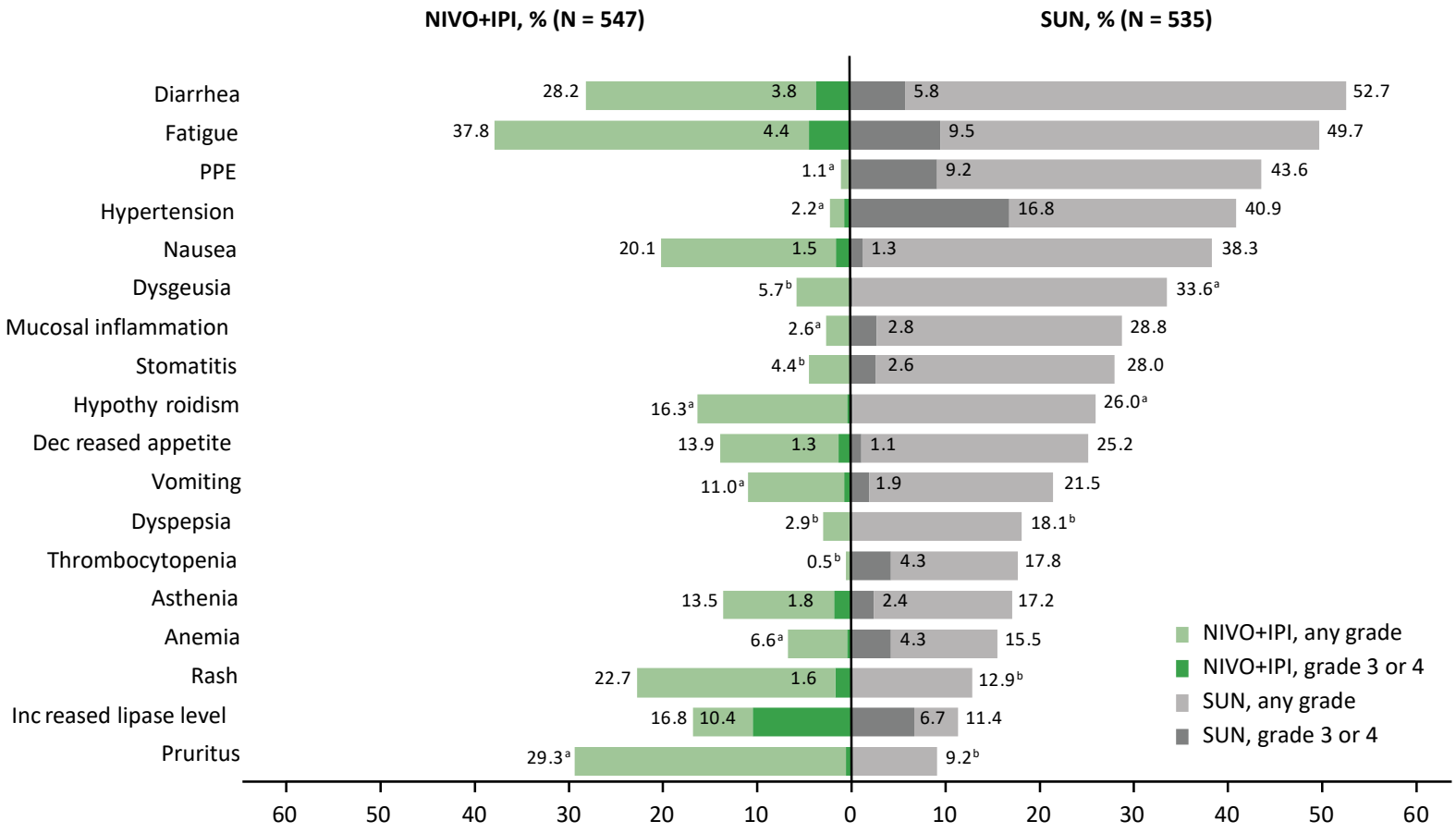
Presented at the 2019 Genitourinary Cancers Symposium; February 14–16, 2019; San Francisco, CA, USA

Table 1. Primary CheckMate 214 efficacy results: ITT, intermediate/poor-risk, and favorable-risk patients[5]

Outcome	ITT population		Intermediate/poor risk		Favorable risk	
	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (N = 425)	SUN (N = 422)	NIVO+IPI (N = 125)	SUN (N = 124)
Median OS, months	NR	32.9	NR	26.0	NR	32.9
HR for death (99.8% CI); *P* value	0.68 (0.49–0.95); <0.001		0.63 (0.44–0.89); <0.001		1.45 (0.51–4.12); 0.27	
Median PFS per IRRC, months	12.4	12.3	11.6	8.4	15.3	25.1
HR for progression/death (99.1% CI); *P* value	0.98 (0.79–1.23); 0.85		0.82 (0.64–1.05); 0.03		2.18 (1.29–3.68); <0.001	
ORR per IRRC, %	39	32	42	27	29	52
	P = 0.02		*P* < 0.001		*P* < 0.001	

CI, confidence interval; HR, hazard ratio; NR, not reached.

Figure 3. Any-grade treatment-related AEs occurring in >15% of patients in either arm: all treated patients



[a]<1% reported grade 3-4 treatment-related AE; [b]No patients reported a grade 3-4 treatment-related AE.
PPE, palmoplantar erythrodysesthesia.

Management of 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

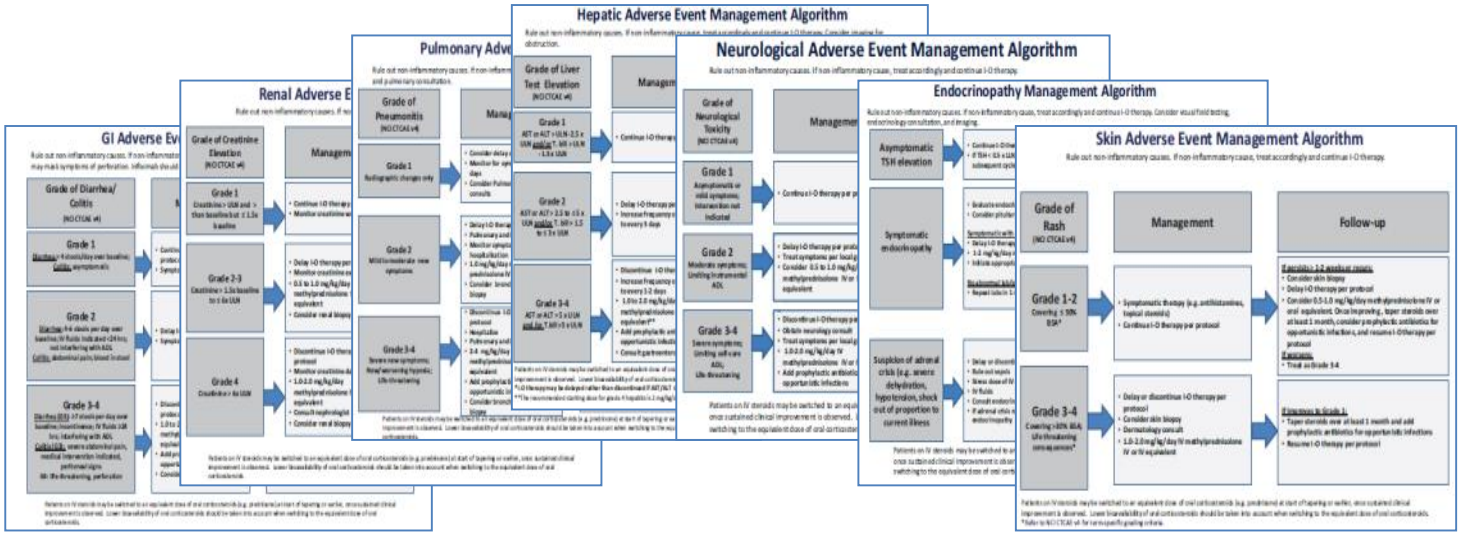
General Rules: Management of Nivolumab-Related Select AEs

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)

Select Adverse Event Categories

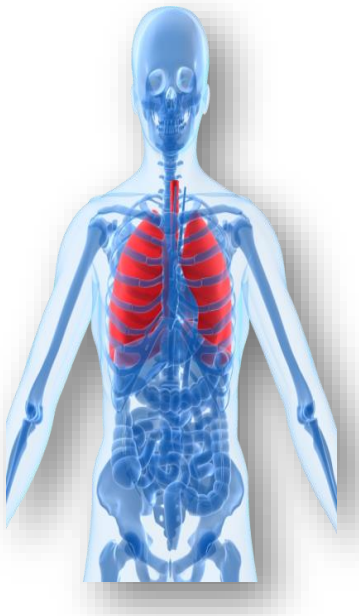
- **Potentially caused by inflammatory mechanism**
  - **Requiring more frequent monitoring**
- **Manageable with unique intervention**
  - **Steroid/ other immunosuppressants**
  - **Endocrine replacement therapy**

Refer to specific algorithms in the RMP



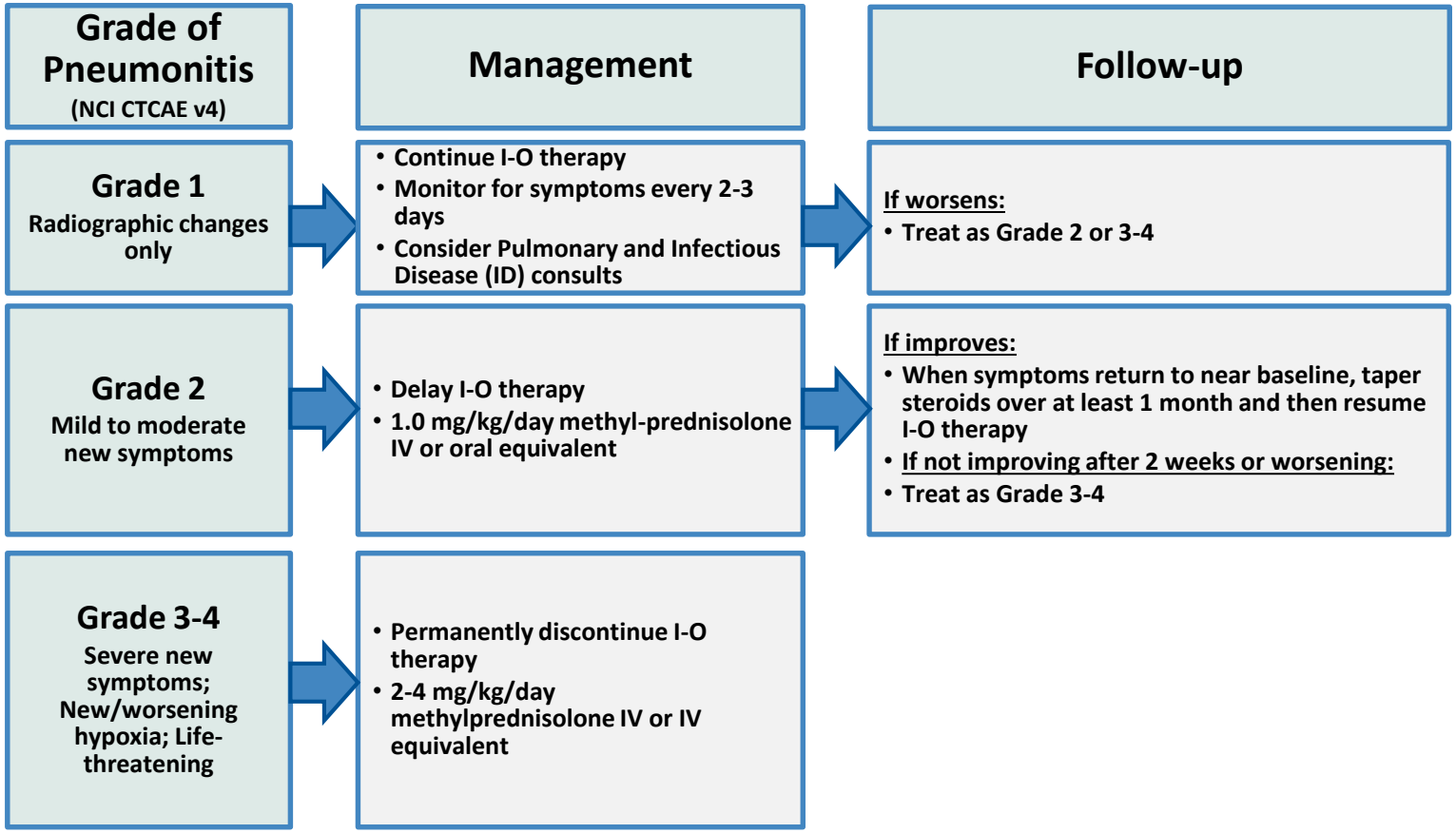
Pneumonitis

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

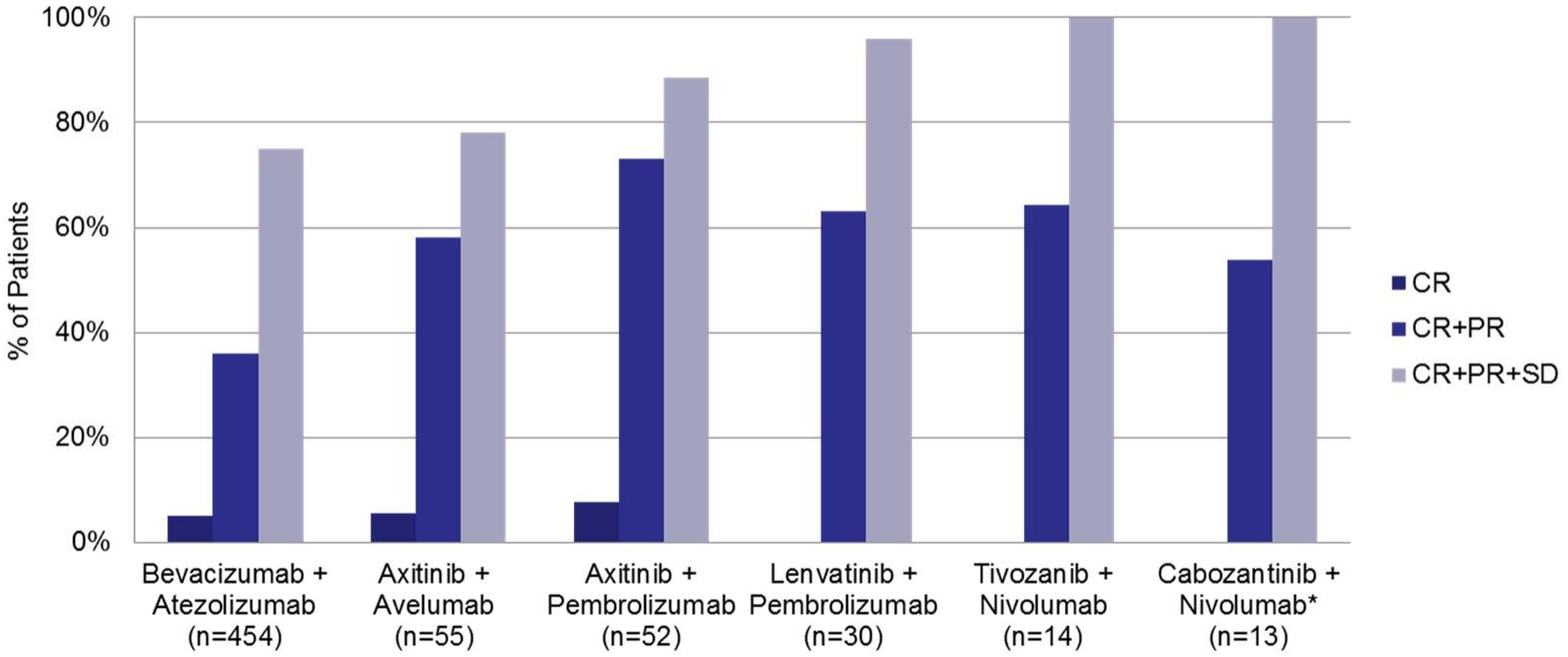
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

The current landscape …



Motzer et al ASCO GU 2018; Lee et al ESMO 2017; Choueiri et al ASCO 2017; Atkins et al ASCO GU 2018; Nadal et al ASCO GU 2018

City of Hope

Phase III Assessments of VEGF + CPI Combinations in RCC

Control	Comparator
Sunitinib	Nivolumab/Ipilimumab
Sunitinib	Bevacizumab + Atezolizumab
Sunitinib	Axitinib + Pembrolizumab
Sunitinib	Lenvatinib + Everolimus *vs* Lenvatinib/Pembrolizumab
Sunitinib	Axitinib + Avelumab
Sunitinib	Cabozantinib/Nivolumab

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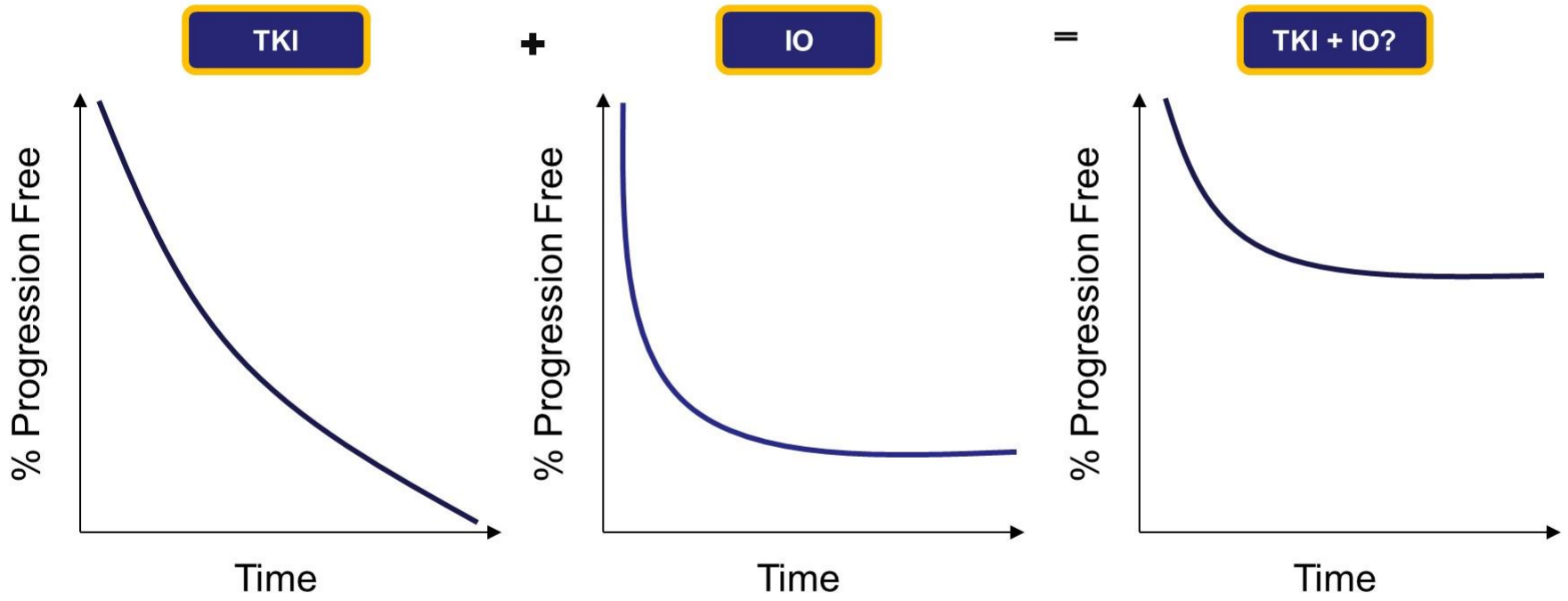
Objective of combination therapy



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Grazie dell'attenzione!!!!

GRAZIE!

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