

Incontri
di aggiornamento
del Dipartimento
Oncologico



mRCC: walking through the first line

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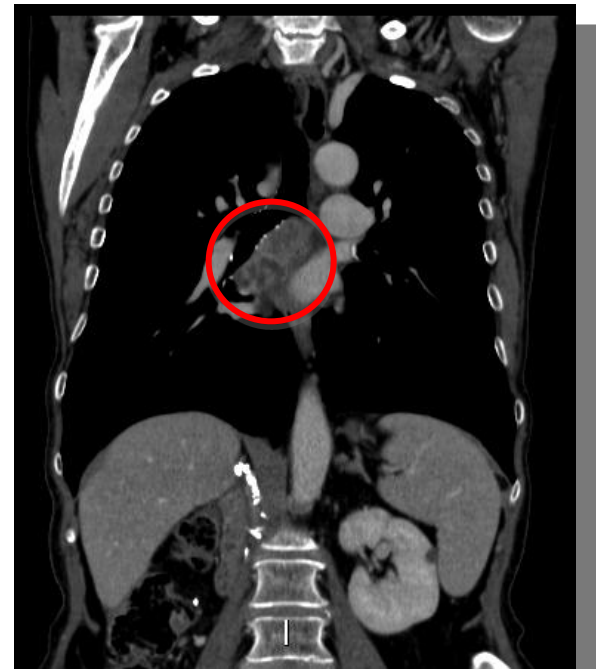
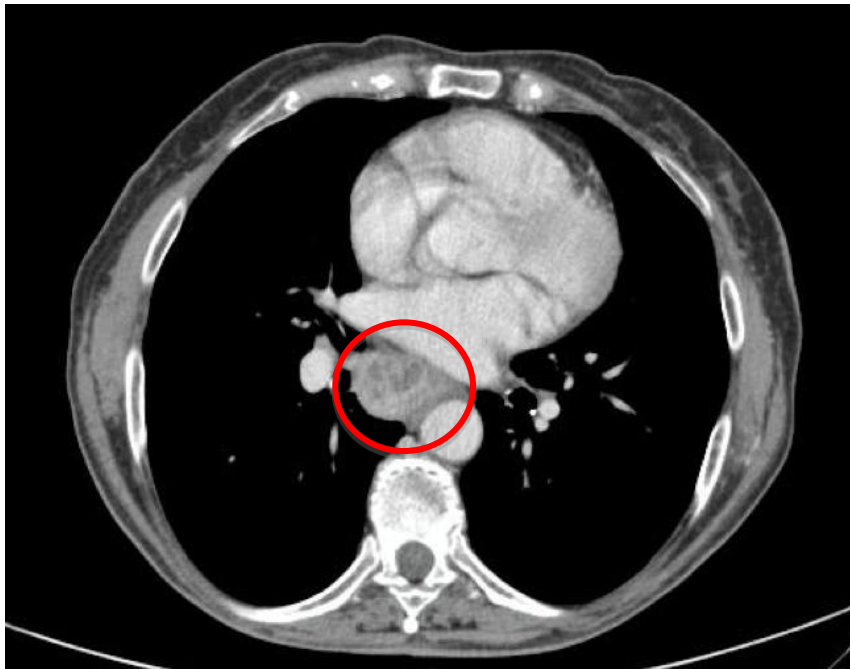


CLINICAL PRESENTATION

- Woman, **67 years old** at diagnosis, ECOG PS 0, no comorbidities

Which treatment in first-line?

- March 2012: on CT-scan appearance of **mediastinal lymph nodes**
- **Biopsy: metastasis of clear cell renal cell carcinoma**



mRCC: AIOM GUIDELINES



Risk Criteria for VEGFR-targeted therapy (Prognostic factors for poor OS)

KPS <80

Diagnosis to therapy <1 year

Anaemia

Hypercalcaemia

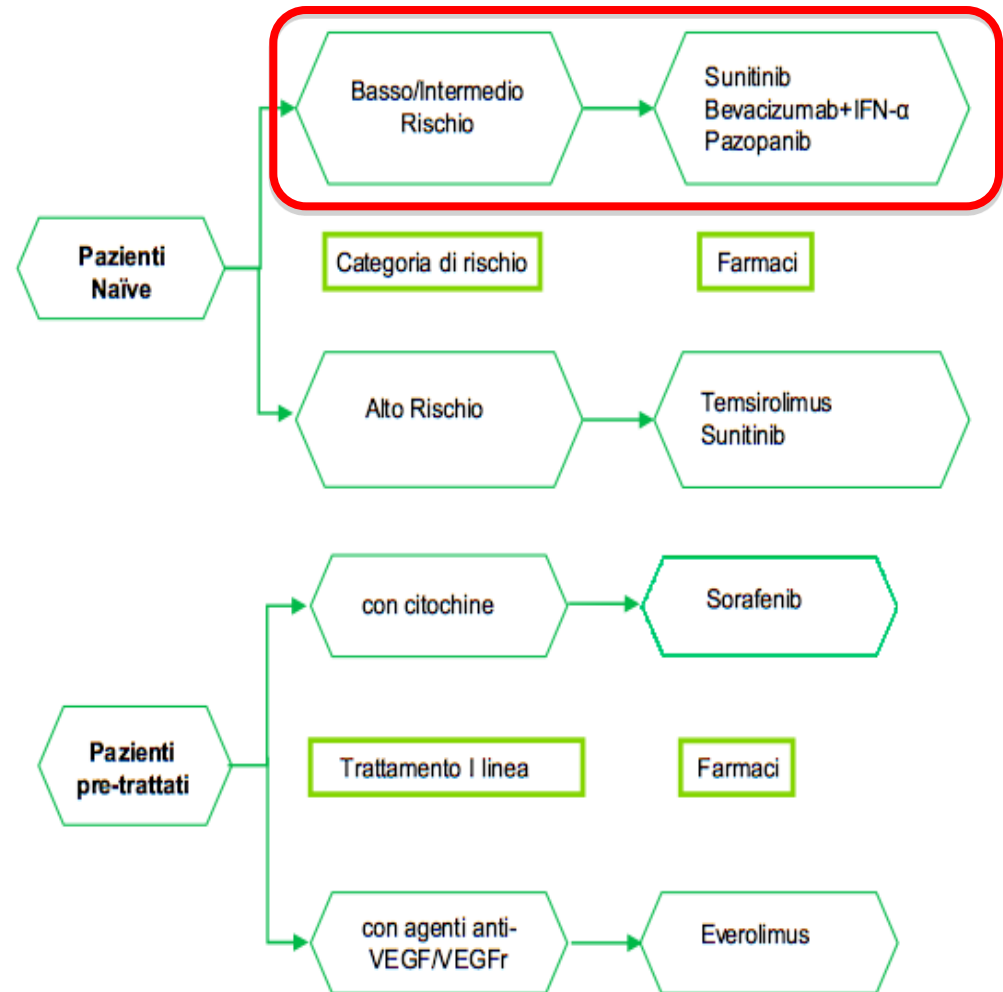
Neutrophilia

Elevated LDH

0 factors: Favourable risk

1-2 factors: Intermediate risk

≥3 factors: Poor risk



HOW TO CHOOSE THE FIRST-LINE TREATMENT IN mRCC?



QUALITY OF LIFE

COMORBIDITIES

TOLERABILITY PROFILE

TOXICITY RISK FACTORS

MSKCC RISK CLASSIFICATION

**NEED OF TUMOR
SHRINKAGE?**

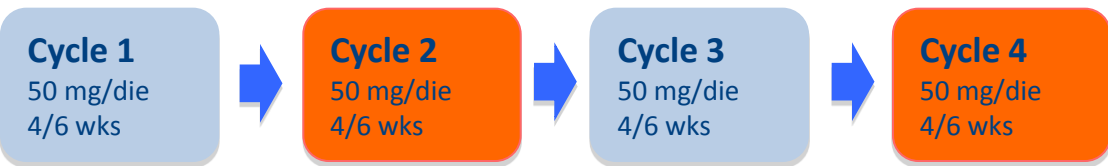
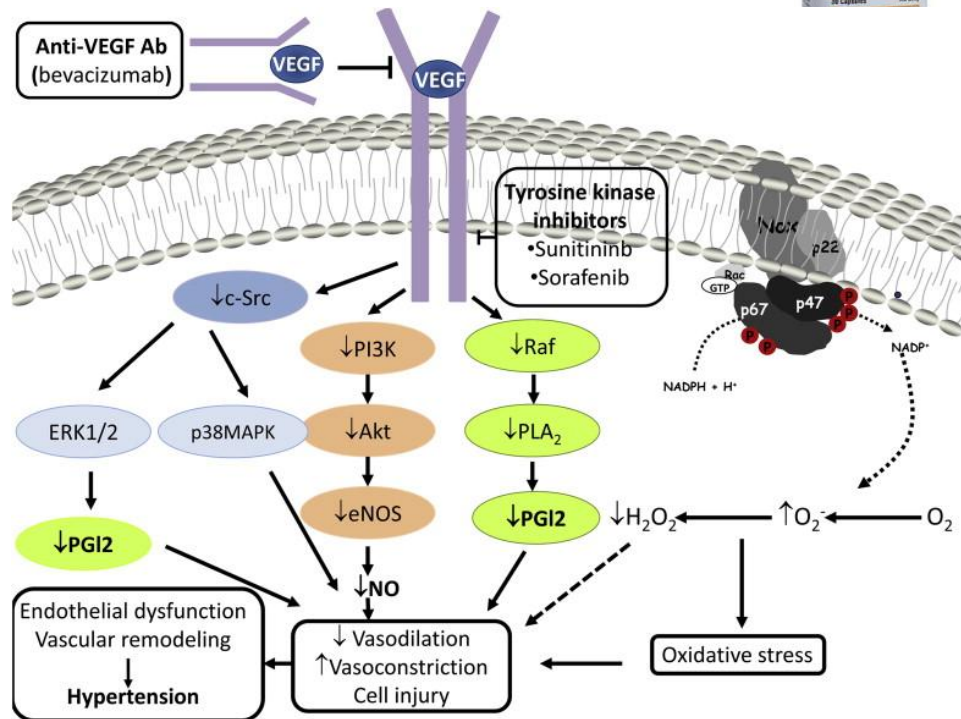
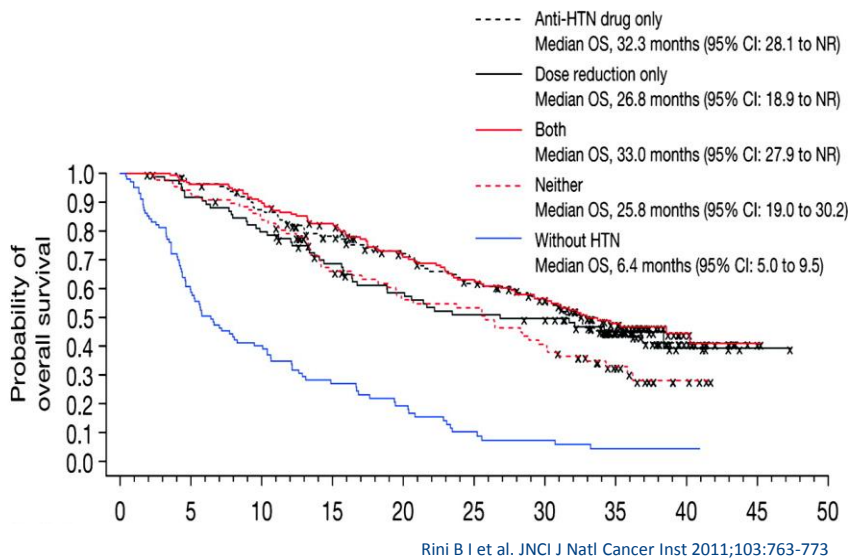
**QUALITY OF
EVIDENCE**

RANDOMIZED CLINICAL TRIALS' RESULTS

First-line treatment: SUNITINIB



Hypertension as a potential biomarker of sunitinib-related efficacy



HYPERTENSION HAND-FOOT SYNDROME G3

FATIGUE G2

First-line treatment: SUNITINIB



Alternative scheduling

- Retrospective review of 21 pts at CCF on Sutent 4/2 changed to 2/1 schedule due to toxicity (Najjar et al. abstract #406).

	4/2 Schedule		2/1 Schedule		No. w/ less tox on 2/1 ¹	P ²
	All grade	Grade 3+	All grade	Grade 3+		
Fatigue	11 (53%)	7 (33%)	10 (48%)	3 (14%)	7 (33%)	.04
Diarrhea	7 (34%)	3 (15%)	9 (43%)	1 (5%)	5 (24%)	.75
Hand-foot	7 (34%)	6 (29%)	3 (14%)	-0-	7 (33%)	.04
Thrombocytopenia	4 (20%)	2 (10%)	1 (5%)	-0-	4 (19%)	0.12
Worst grade	21 (100%)	20 (95%)	21 (100%)	7 (33%)	14 (67%)	.001

¹ Refers to any grade change in toxicity

² Wilcoxon signed-rank test comparing significance of increased or decreased any grade toxicity on 2/1 vs. 4/2 regimen

- Median overall treatment duration on the 4/2 schedule was 13.5 months and median overall treatment duration on the 2/1 schedule was 24.4 months.

Brian I. Rini, ASCO GU 2013

Retrospective Observational Study of Sunitinib administered in a 2/1-2/1 Schedule (2 weeks on-1 week off for an overall cycle length of 6 weeks) in patients with metastatic Renal Cell Carcinoma (mRCC): **RAINBOW Study.**

54 Retrospective observational study of sunitinib administered on schedule 2/1 in patients with metastatic renal cell carcinoma (mRCC): the RAINBOW study

Background: Sunitinib is a standard of care in first line mRCC. However, an increasing percentage of treatment-related adverse events are observed in the last 2 treatment weeks (w) of the standard schedule 4/2 (8-w-on/2-w-off). In a multicenter retrospective study, we evaluated the efficacy and safety of a modified 2/1 schedule (2-w-on/2-w-off), largely used in Italy based on a favorable initial experience.

Aims of the study: The primary objective of the RAINBOW study was to collect data regarding safety and the efficacy profile of sunitinib with a modified schedule 2/1. Adverse events are graded using RECIST-CR4, version 4.0.2. Efficacy is evaluated in terms of Progression Free Survival (PFS) and Treatment Duration.

Methods: Data from all consecutive patients (pts) treated in 24 Italian centers with sunitinib on schedule 2/1 were analyzed according to the following groups:
 - Group A, pts moved to schedule 2/1 because of treatment-related toxicities during initial therapy using schedule 4/2.
 - Group B, pts treated up into with schedule 2/1, mainly because of poorer clinical conditions.
 - Group C, a small group of pts treated with schedule 4/2 used as a control.

Results: 236 consecutive pts treated from Nov 2005 to Aug 2013 were analyzed, including 249 treated with schedule 2/1. Number of pts in Group A was 208, in Group B was 41. Baseline characteristics were:

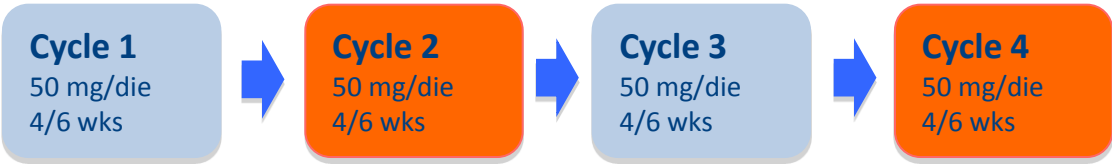
Efficacy: In Group A, median PFS was 13.5m and median OS was 24.4m. In Group B, median PFS was 13.5m and median OS was 24.4m. In Group C, median PFS was 13.5m and median OS was 24.4m.

Safety: In Group A, maximum toxicity grade (G3) was significantly reduced on schedule 2/1 compared with the initial schedule 4/2 (8-w-on/2-w-off), table 1. Specific toxicities such as fatigue and hypertension were also reduced respectively (9% vs 20%, p=0.02 and 26% vs 9%, p<0.01, table 2). The maximum toxicity grade G3 was significantly reduced also in pts of group A who did not reduce the dose of sunitinib (n=188) moving to schedule 2/1 from the initial schedule 4/2 (7% vs 43%, respectively, table 3).

Conclusions: Patients moved to a modified schedule 2/1 because of treatment-related toxicities during initial therapy using standard schedule 4/2 were to be:
 - as improved safety profile with a reduction of overall grade 3-4 toxicities and of specific toxicities such as fatigue and hypertension.
 - the improved safety profile was also maintained in the subgroup of pts who did not reduce the dose of sunitinib.
 - a potential improvement of PFS, to be confirmed in a prospective trial.
 - results observed in the group A should be evaluated taking into account the poorer characteristics of pts.

Take home message: In our experience, sunitinib on a modified schedule 2/1 has an improved safety profile and possible increased efficacy compared with schedule 4/2. Prospective evaluation of this schedule is warranted.

References: 1) Motzer et al. J Clin Oncol. 2002; 20:1537-42. 2) Motzer et al. J Clin Oncol. 2002; 20:1537-42. 3) Motzer et al. J Clin Oncol. 2002; 20:1537-42.



HAND-FOOT SYNDROME G3

FATIGUE G2

April 2012

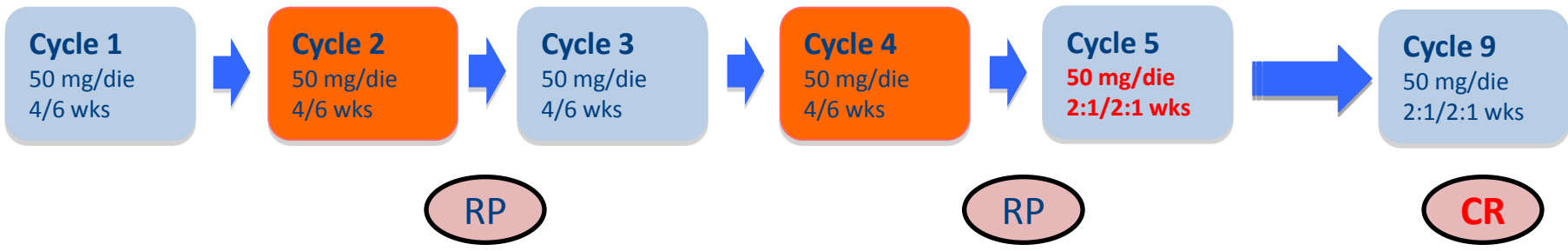
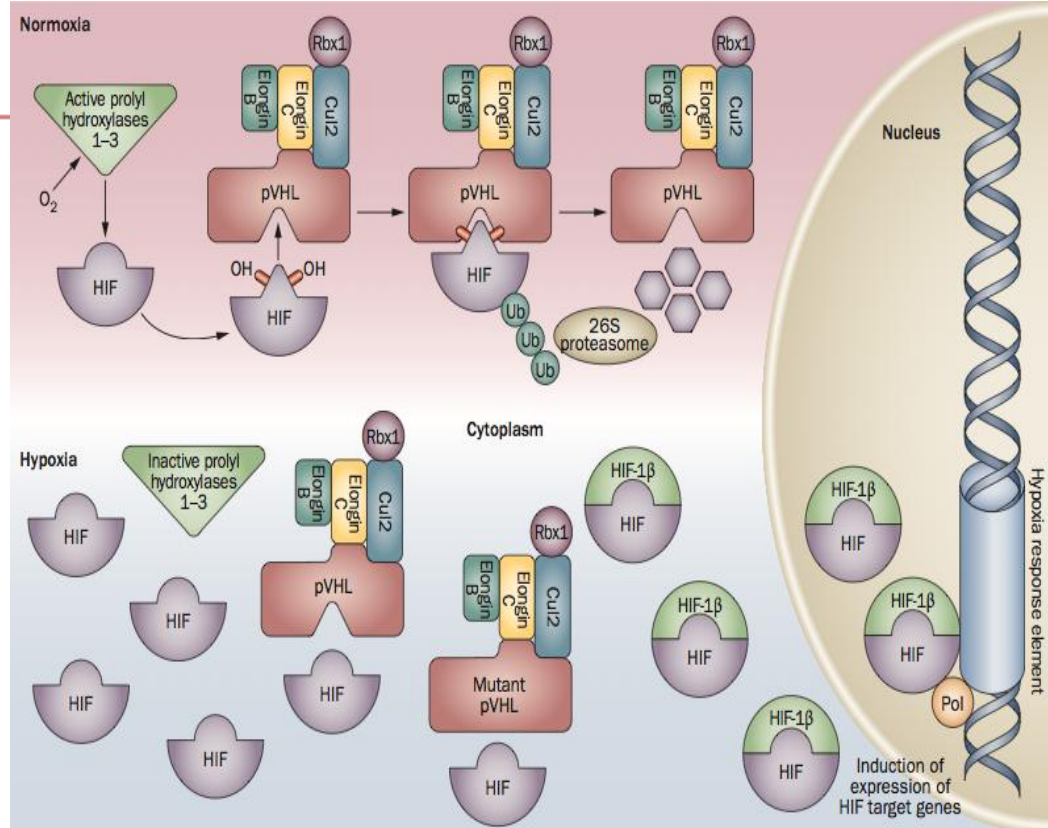
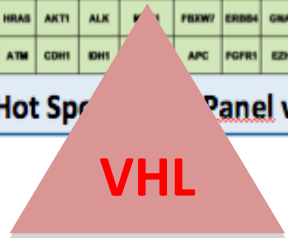
COMPLETE REMISSION

Materials and Methods



KRAS	BRAP	EGFR	TP53	PK3CA	CSF1R	JAK2
NRAS	PTPN11	ERBB2	SRC	FGFR3	NPM1	CDKN2A
RET	SHF1A	SMAD4	GNAS	PDGFRA	MPL	ABL1
PTEN	FLT3	STR11	SMARCB1	KIT	MET	NOTCH1
FGFR2	RB1	JAK3	VHL	KDR	BMO	ERK2
HRAS	AKT1	ALK		FBXW7	ERBB4	GNAS
ATM	CDH1	EDH1		APC	FGFR1	EDHD

Hot Spot Panel v2

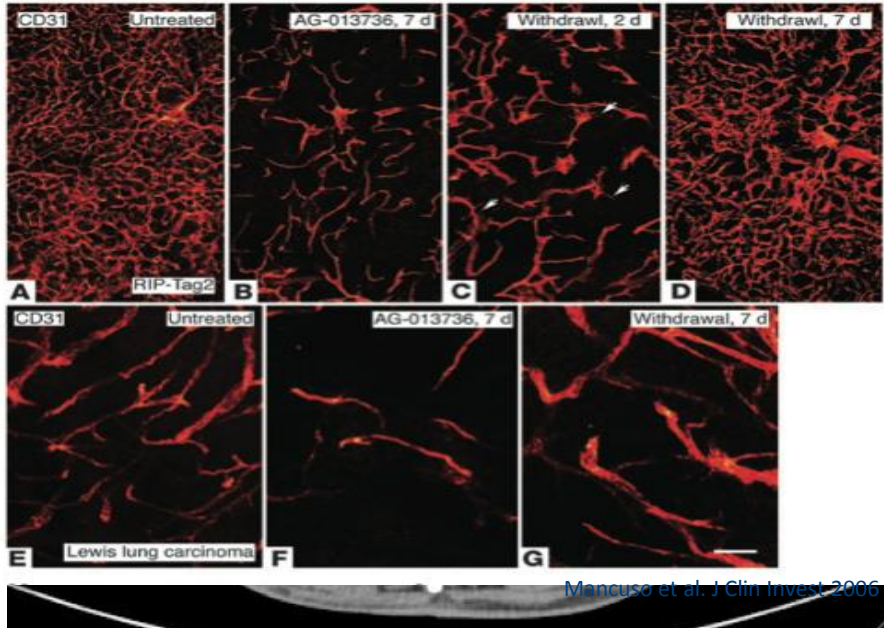


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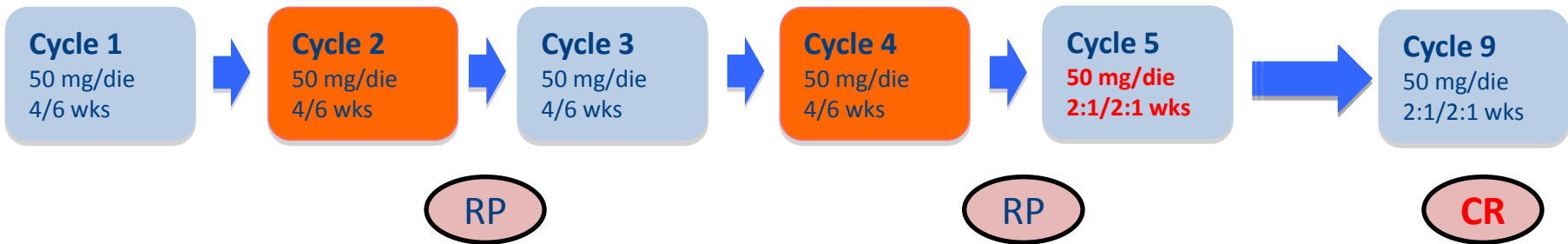
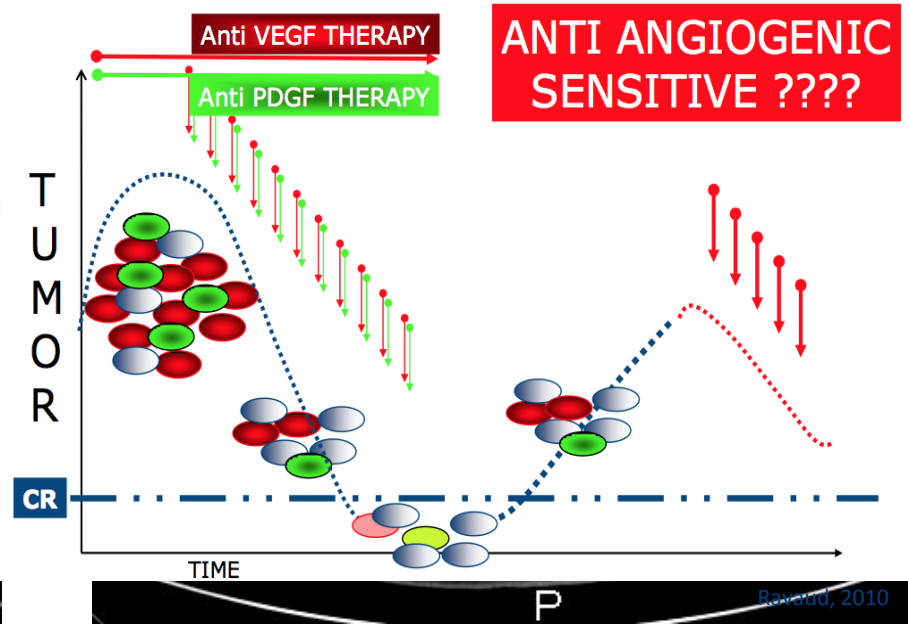
July 2013

COMPLETE REMISSION

Rapid vascular regrowth in tumors after reversal of VEGF inhibition



Maintenance after CR: development of VEGF-resistance



April 2012

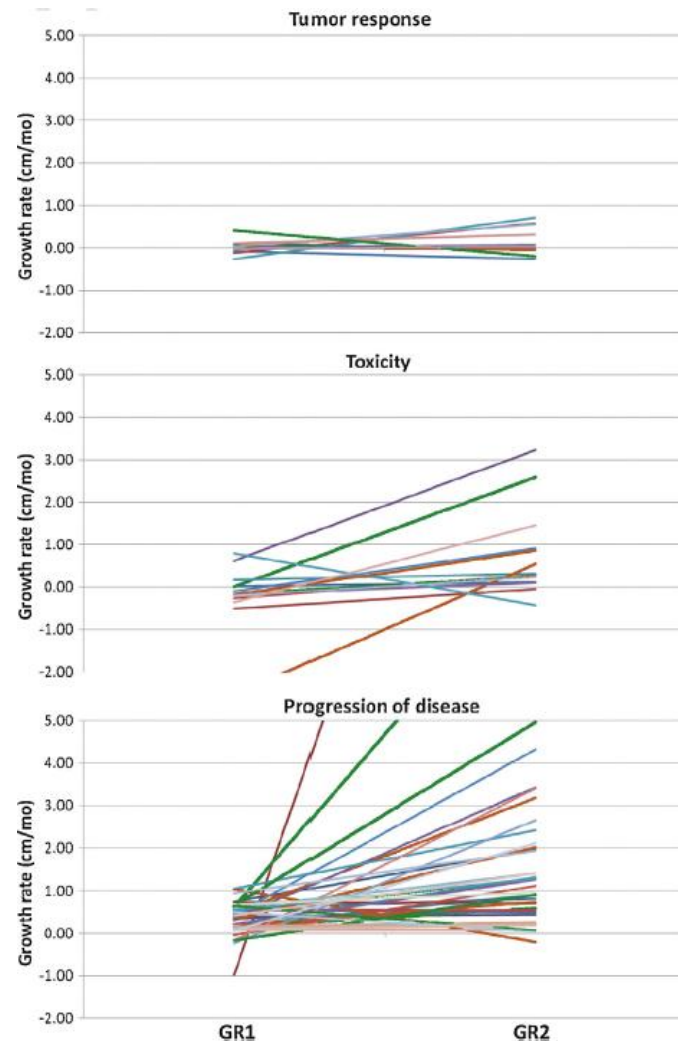
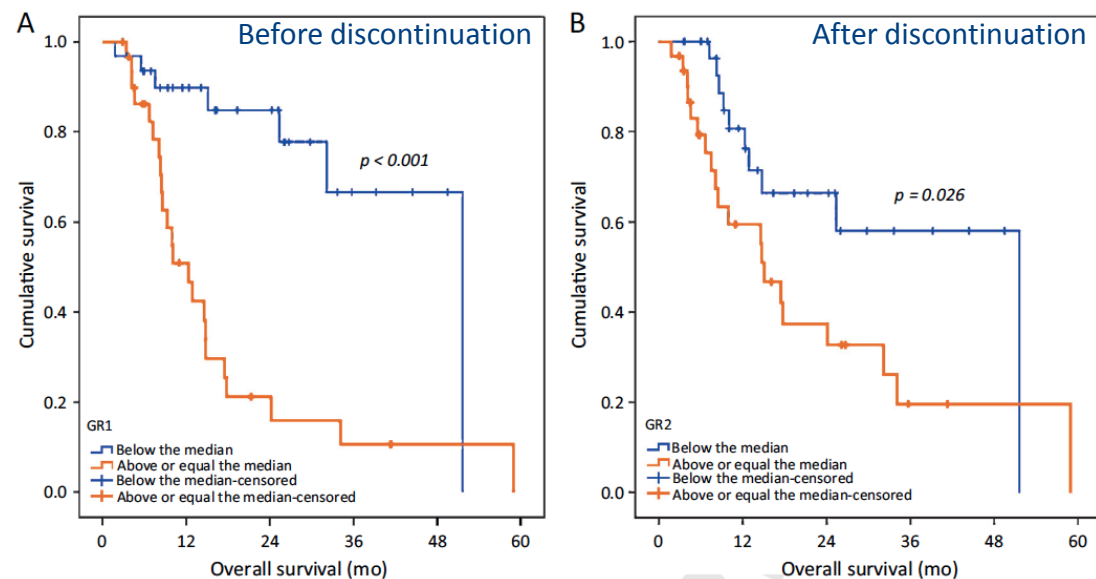
July 2013

Platinum Priority – Kidney Cancer
Editorial by XXX on pp. x–y of this issue

Evidence and Clinical Relevance of Tumor Flare in Patients Who Discontinue Tyrosine Kinase Inhibitors for Treatment of Metastatic Renal Cell Carcinoma

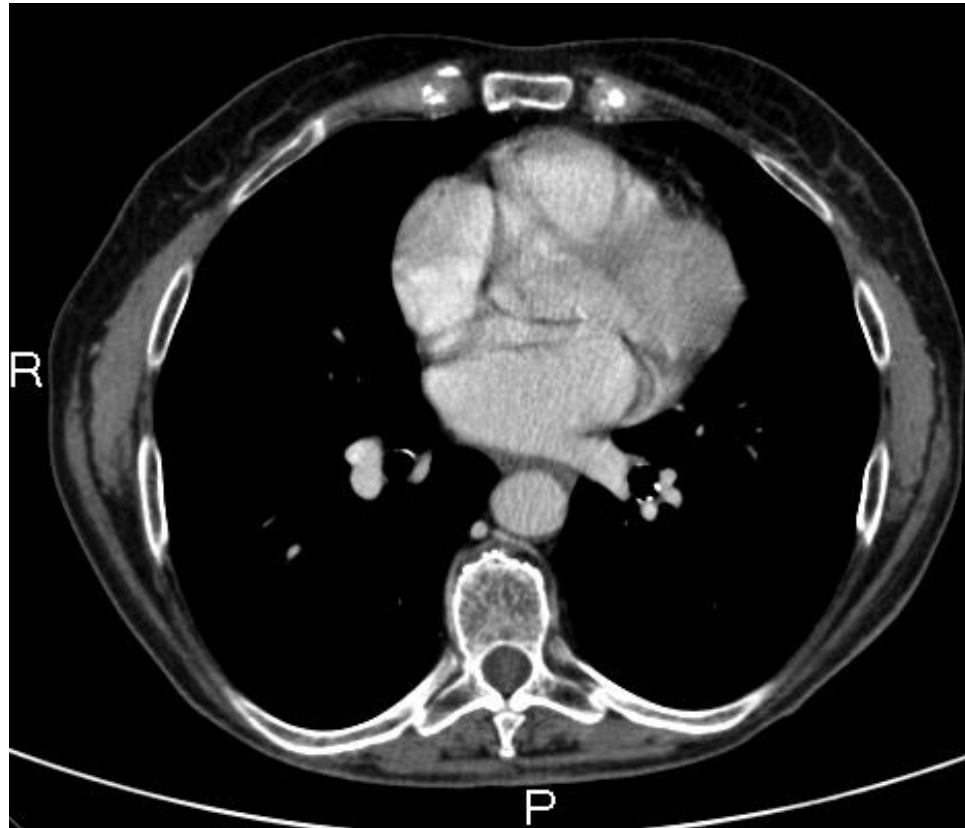
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TKI discontinuation results in acceleration of tumor GR and induces TF, which can negatively affect the prognosis of mRCC patients.

AFTER ONE YEAR...



Cycle 9
50 mg/die
2:1/2:1 wks

CR

FOLLOW UP

CR

July 2013

November 2014



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