TiNivo
A Phase Ib Dose Escalation Trial of Tivozanib and Nivolumab in Renal Cell Carcinoma

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Sixteenth International Kidney Cancer Symposium

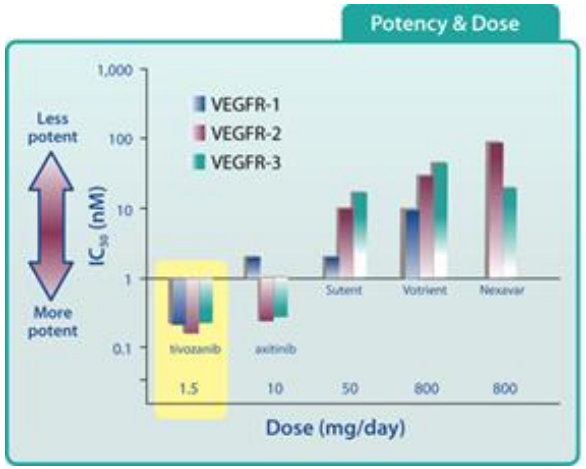
November 3-4, 2017
National Doral, Miami, Florida

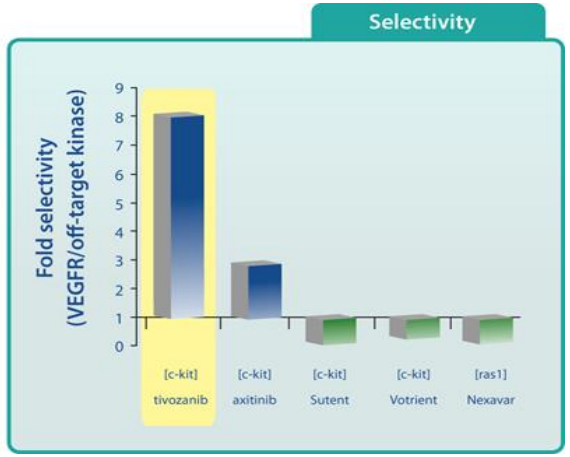
KidneyCancer.org

www.kidneycancersymposium.com

Study Rationale (I)

- Tivozanib is a VEGFR-TKI with high specificity and a favorable AE profile compared to other members of the class





- Tivozanib has been approved by EMA in first line setting of metastatic RCC

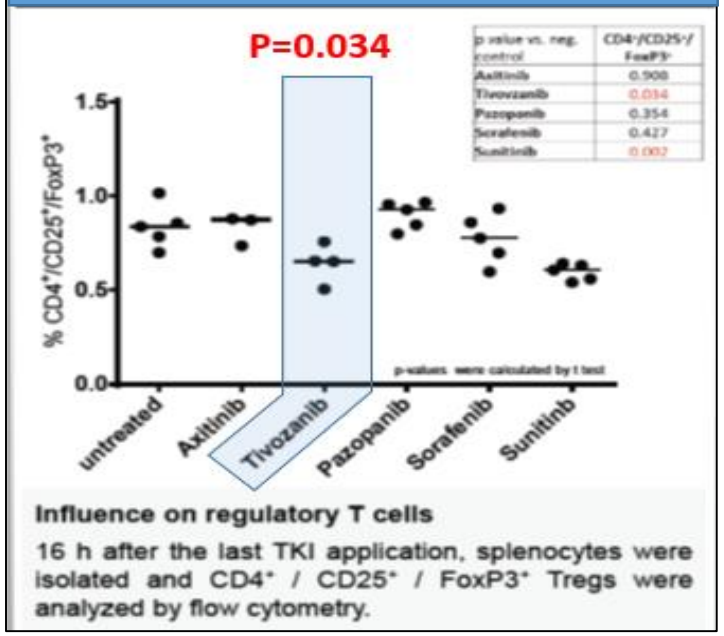
1. Eskens FALM, et al. In: *Proceedings of the 99th Annual Meeting of the AACR*. San Diego, CA: AACR; 2008. Abstract LB-201.
2. Chow LQM, Eckhardt SG. *J Clin Oncol.* 2007;25(7):884-896.

Study Rationale (II)

- Combinations of checkpoint inhibitors and VEGFR-TKIs suggest strong activity in phase I/II in metastatic RCC

Down Regulation of Tregs Contributes to Checkpoint Inhibition

Tivozanib significantly reduces T cells

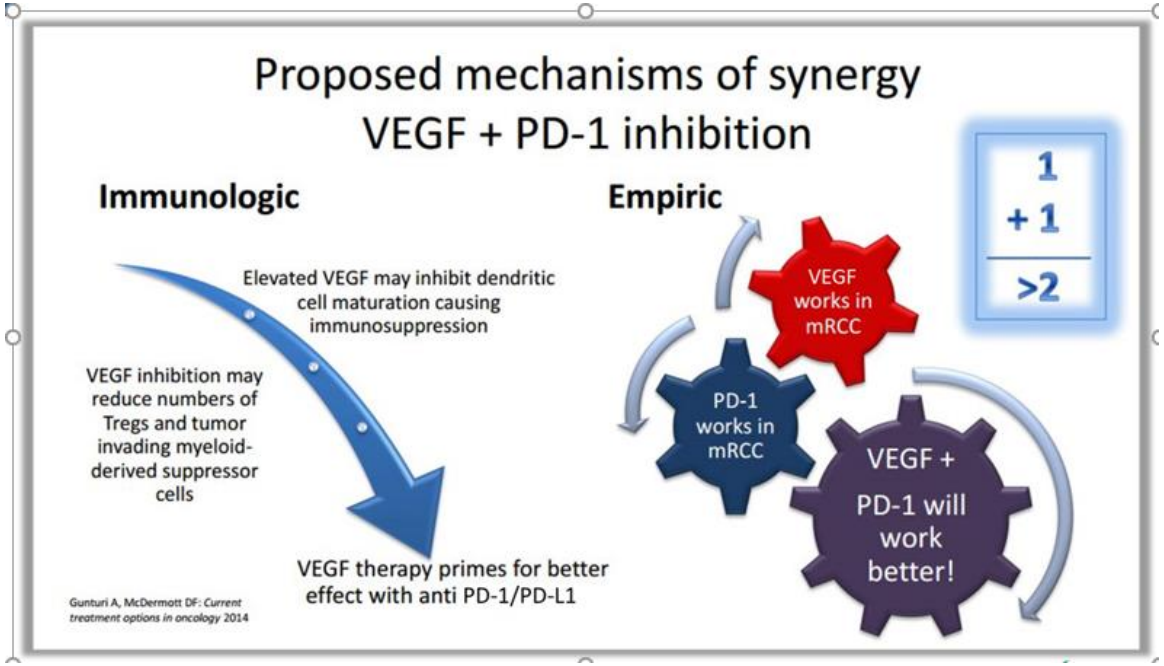


Pawlowski N et al. AACR 2013. Poster 3971.

Study Rationale (III)

- Combinations of checkpoint inhibitors and VEGFR-TKIs demonstrated high rates of Grade 3-4 adverse events

- We hypothesize that the combination of Tivozanib and Nivolumab will have a favorable adverse event profile



TiNivo Ph I Study Schema:

- Metastatic renal cell carcinoma (all histology)
- Mesurable disease
- No prior use of nivolumab or tivozanib
- ECOG PS ≤ 1
- Life expectancy ≥ 3 months

Dose Level 1

Tivozanib 1.0 mg QD/21 days
+ Nivolumab 240 mg Q2 weeks

Dose Level 2

Tivozanib 1.5 mg QD/21 days
+ Nivolumab 240 mg Q2 weeks

1º safety, tolerability, and maximum tolerated dose

2º antitumor activity

3+3 dose escalation design - DLT Period: 28 days (cycle1)

DLTs definition:

- Grade 3 nonhematologic toxicity lasting > 3 days despite optimal supportive care.
- Grade 4 nonhematologic toxicity
- Hematologic toxicities (Neutropenia that is: Grade 3 or 4 (ie, ANC < 1000 per mm3) and associated with fever (oral temperature ≥ 38.5ºC) or sepsis ; Grade 4 (ie, ANC < 500 per mm3) and sustained (duration ≥ 5 days) and Grade 4 thrombocytopenia (ie, platelets < 25,000 per mm3) or bleeding requiring a platelet transfusion.)
- Toxicity of any grade that results in inability to complete Cycle 1 of dosing.

Patient Population

Number of patient		6
Median age (year)		59 (37-67)
Gender	male	4
	female	2
Nephrectomy	yes	5
	no	1
Prior therapy	0	3
	≥1	3
Pathology	clear cell	5 (including 1 with sarcomatoid features)
	papillary	1
ECOG	0	4
	1	2

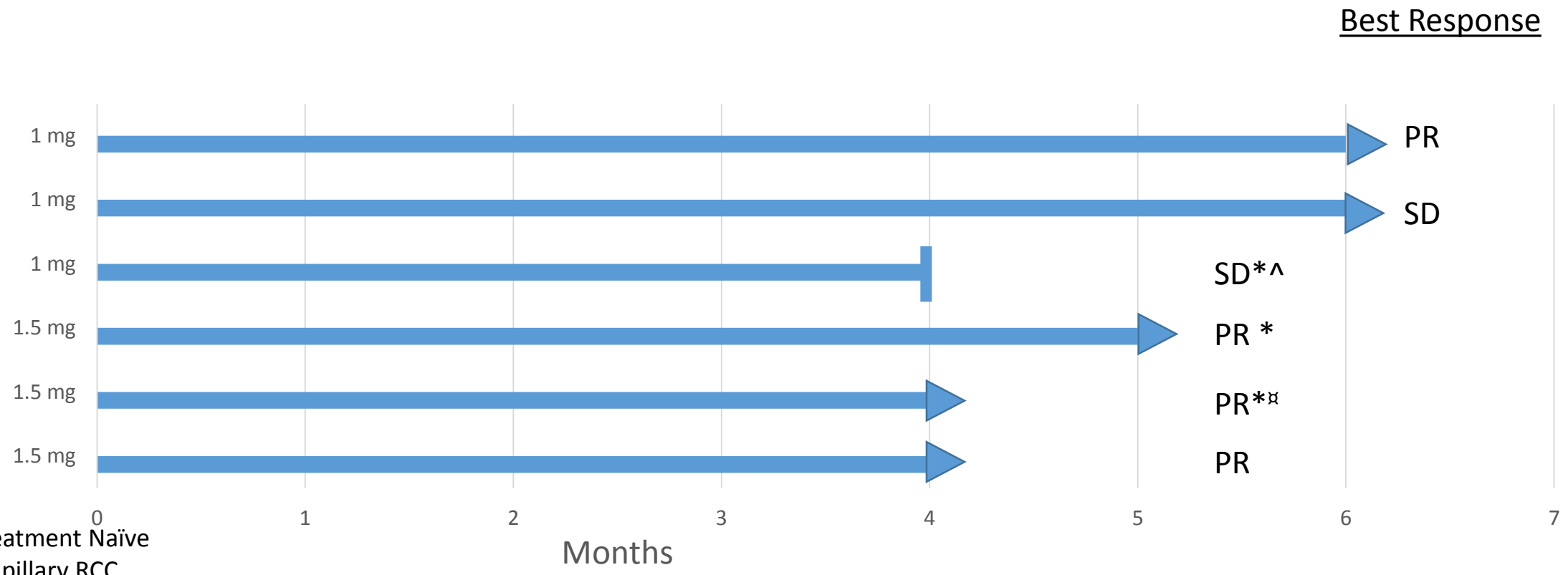
Results: Safety

- No DLTs observed in Cycle 1 in any patient (n=6)

	Any Grade	Grade 3	Grade 4
Adverse events	6 (100%)	2*	0
Hypertension	3		
Asthenia	3		
Decreased Appetite	3		
Diarrhea	2		
Nausea	2		
Stomatitis	2	1	
Hand-Foot Syndrome	2		
Pruritis	2		
Arthralgia	2		
Dysphonia	2		
Increased creatinine	2		
Increased ALT	1	1	

*occurred beyond cycle 1

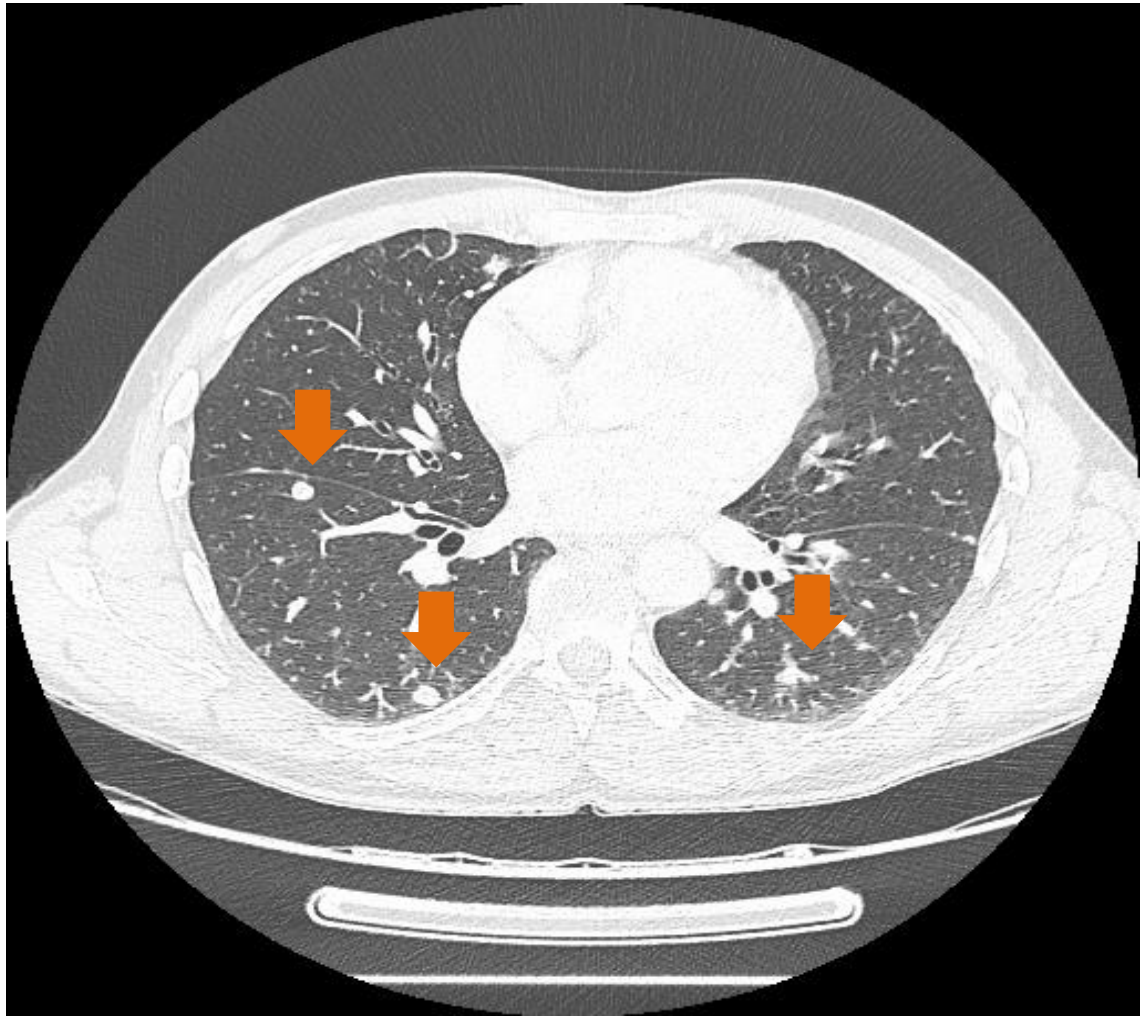
Results: Duration of Treatment



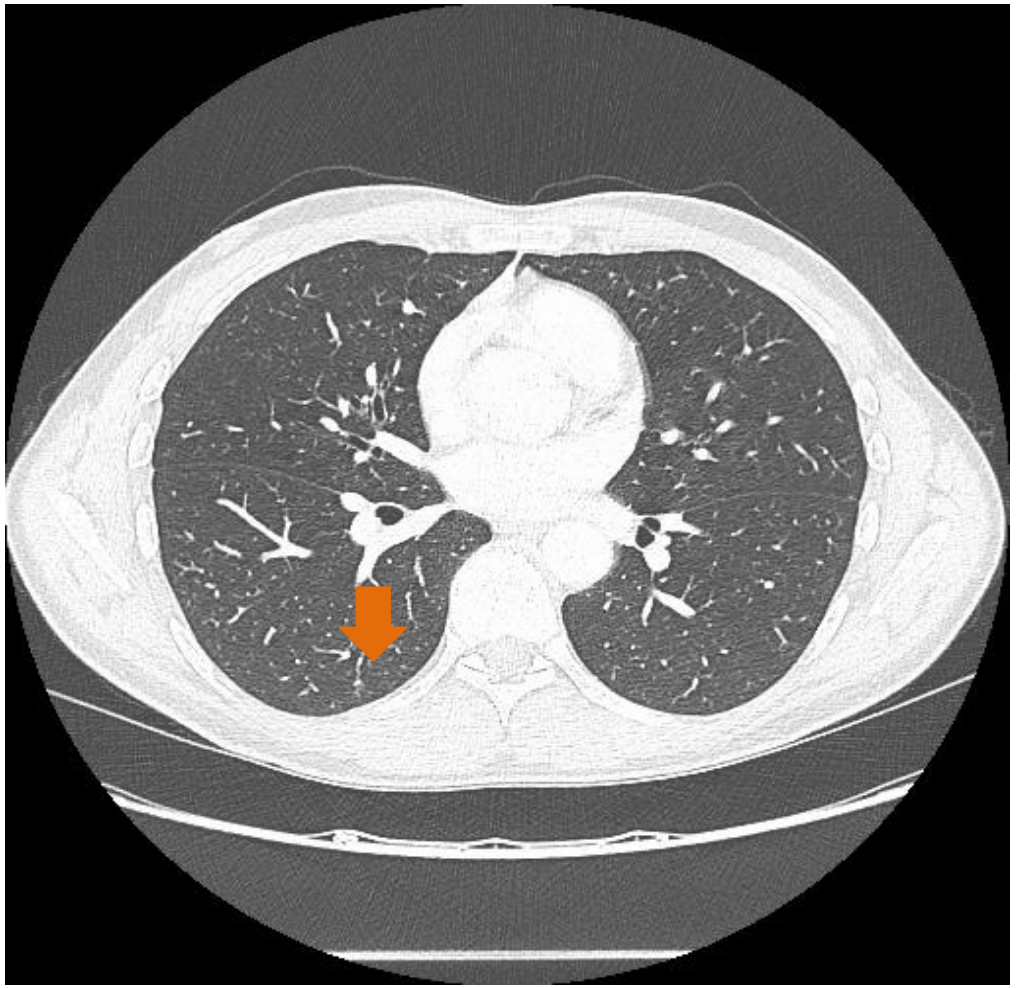
*Treatment Naïve
¤ papillary RCC
^unconfirmed best response

Clear cell with sarc features

Baseline



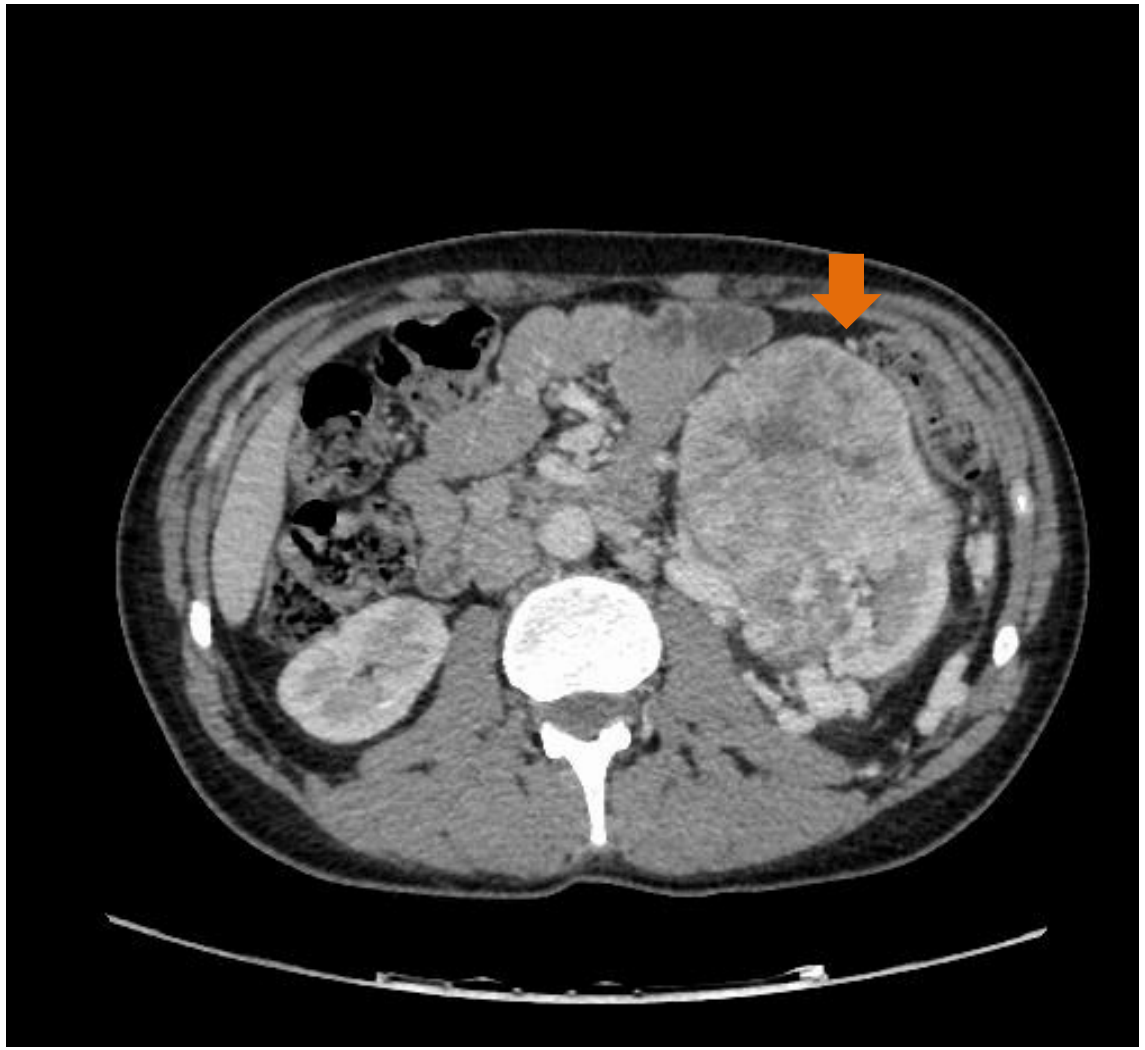
Confirmed CT assesment



courtesy P Barthelemy, Strasbourg

Clear cell with sarc features

Baseline



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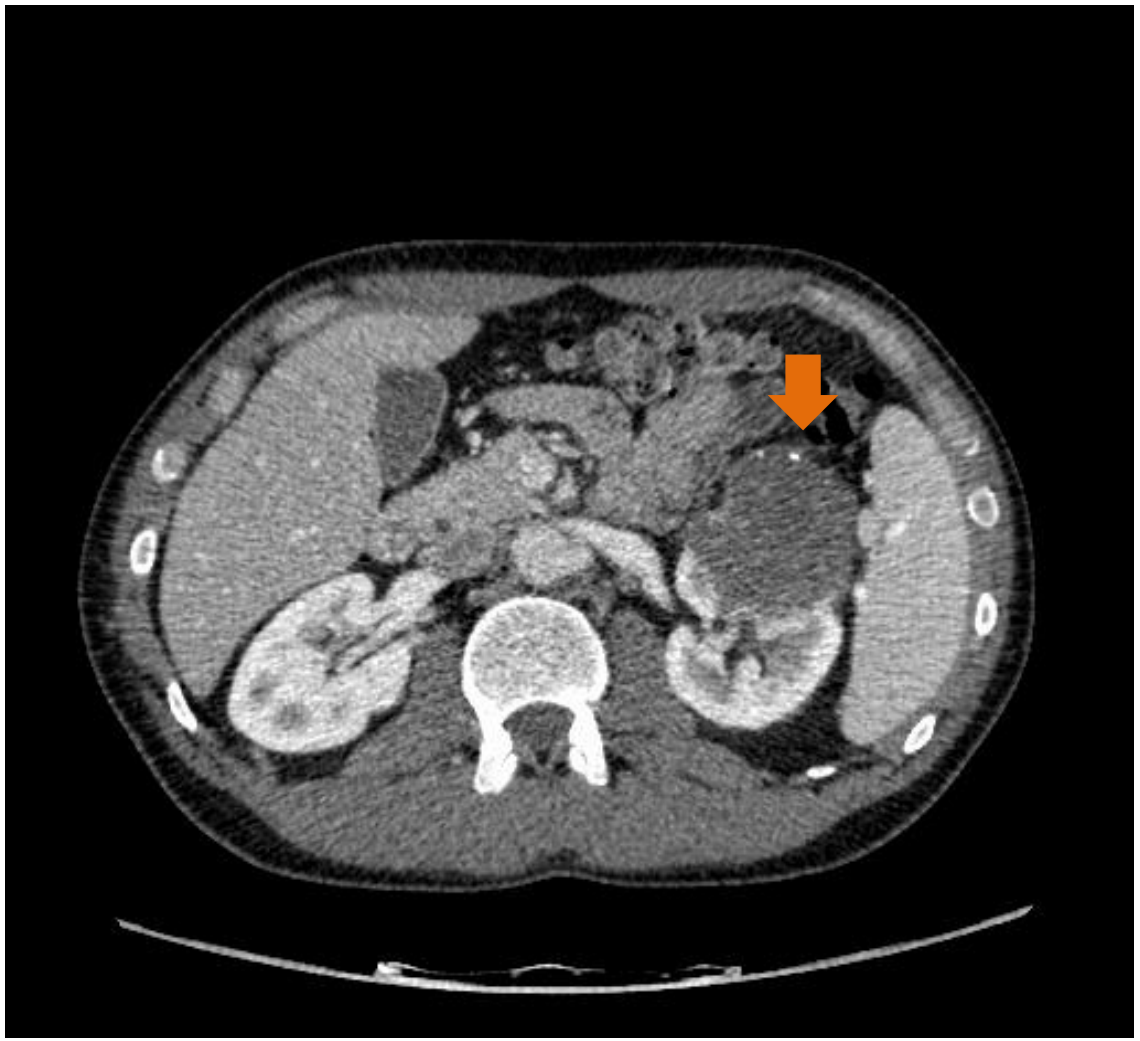
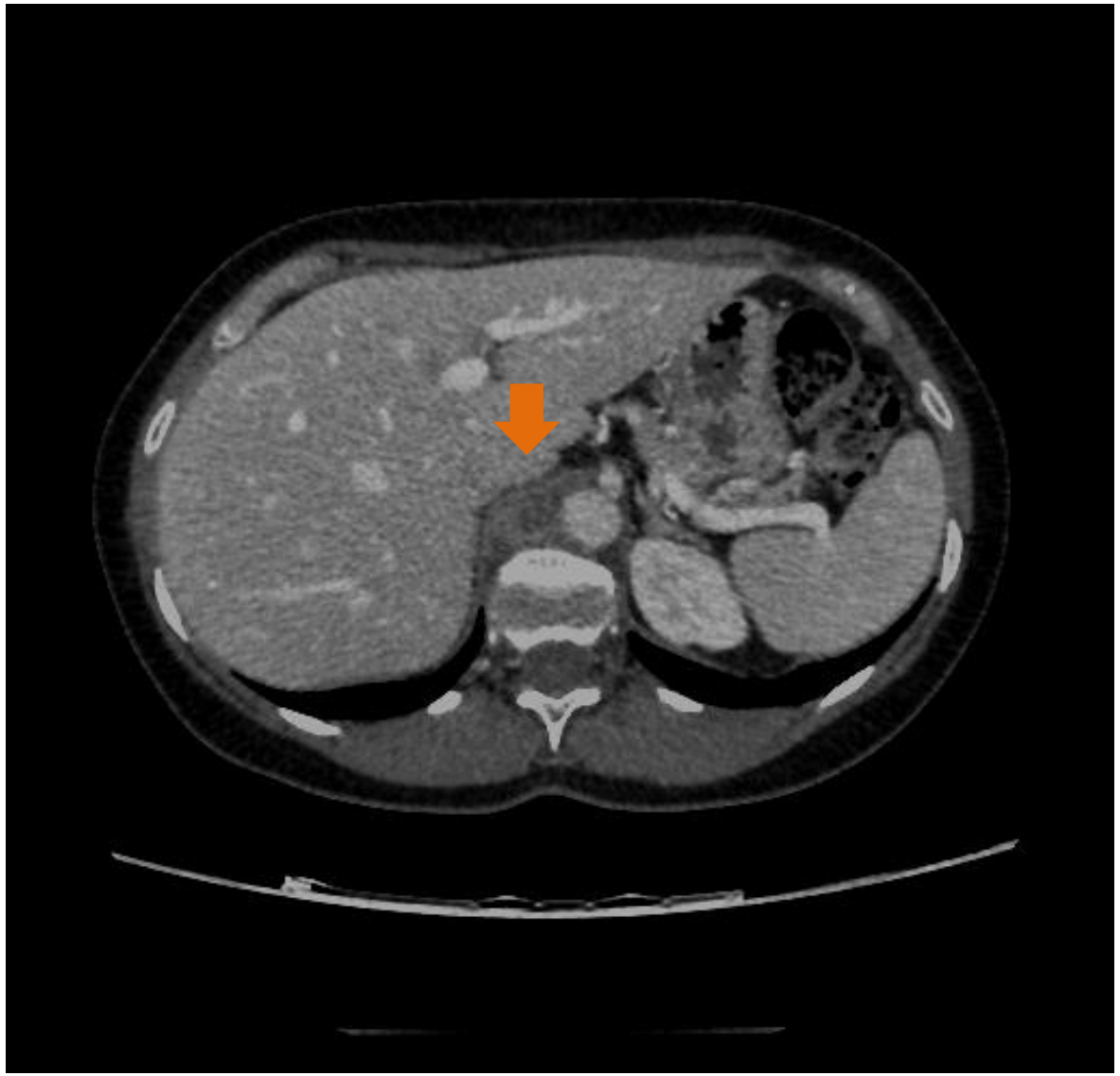


courtesy P Barthelemy, Strasbourg

Papillary RCC pt

Baseline



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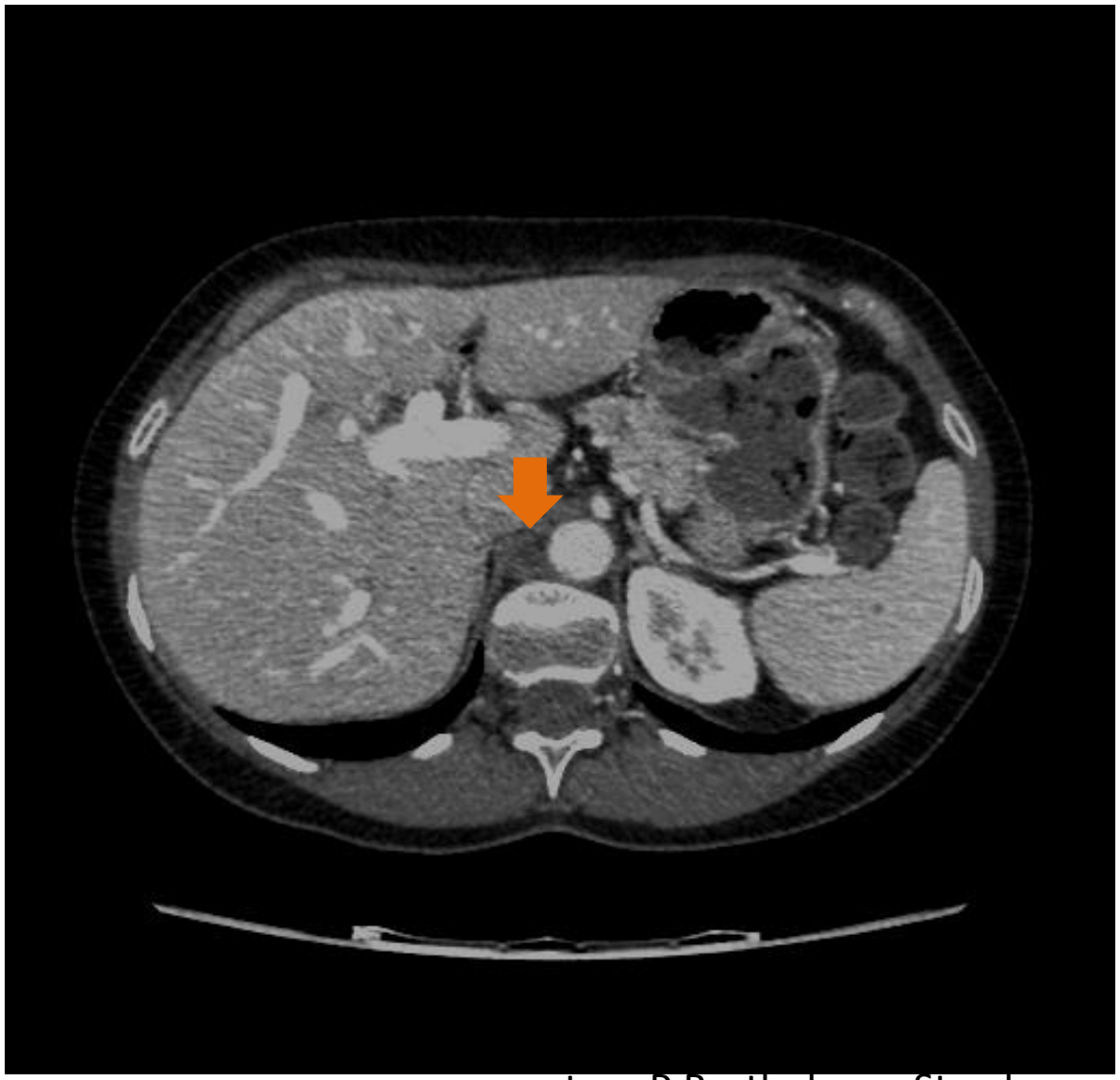
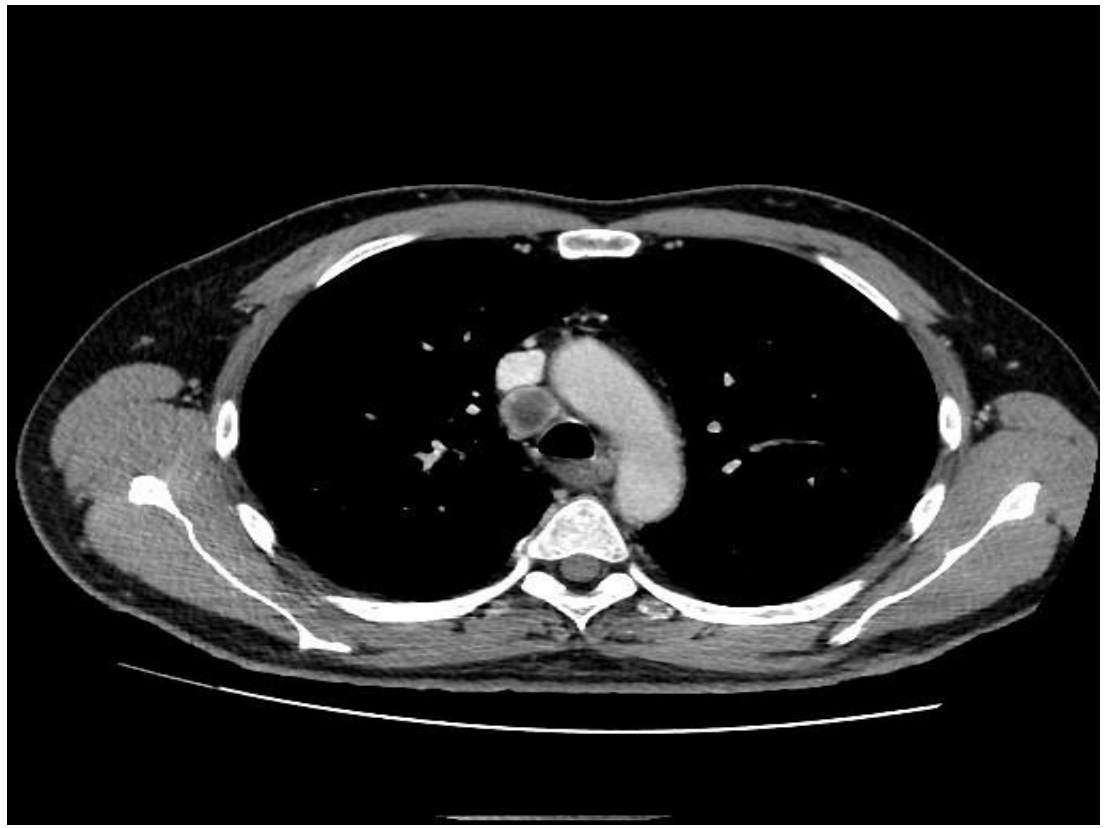


courtesy P Barthelemy, Strasbourg

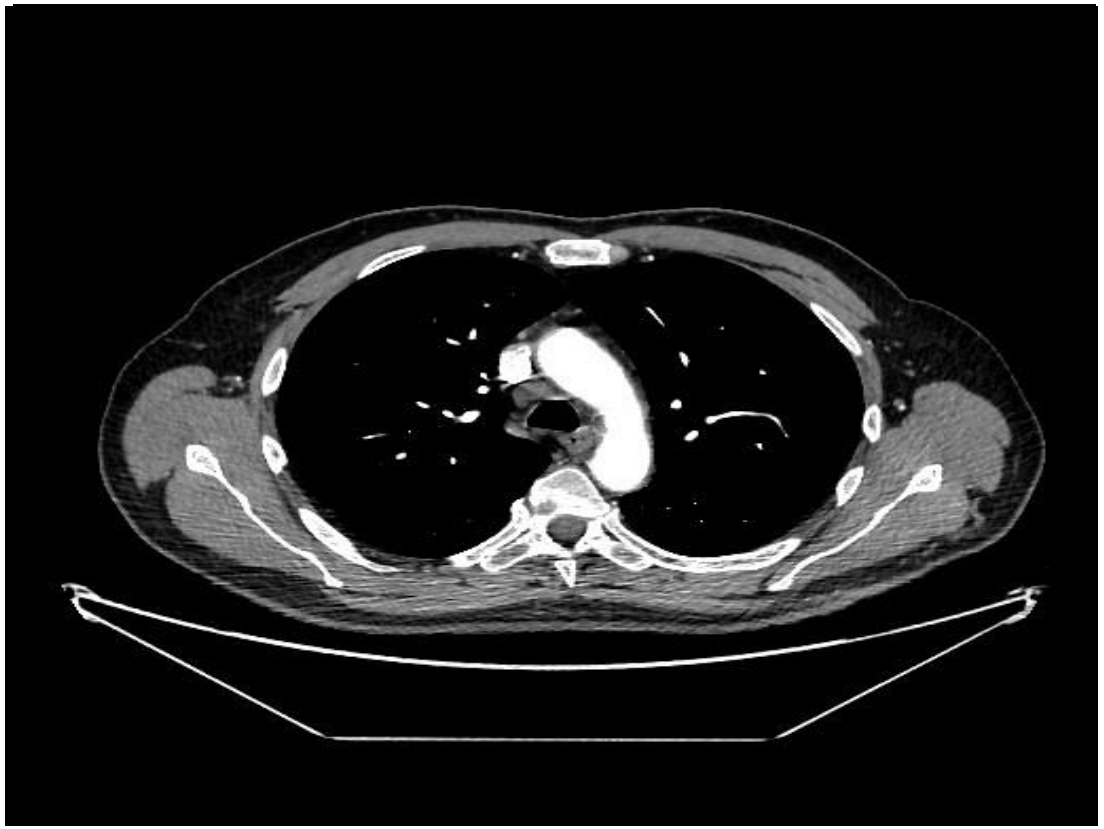
ccRCC

prior treatments with sunitinib, sorafenib, everolimus

Baseline 26/04/2017



27/06/2017



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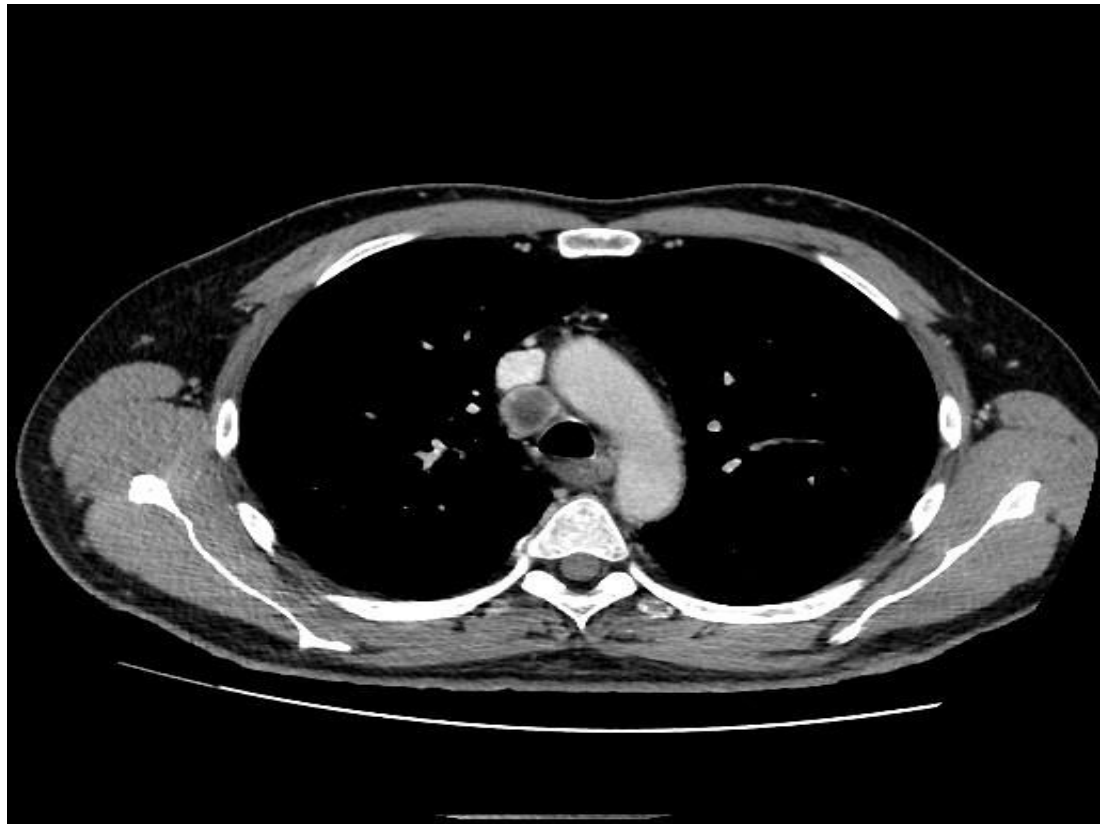
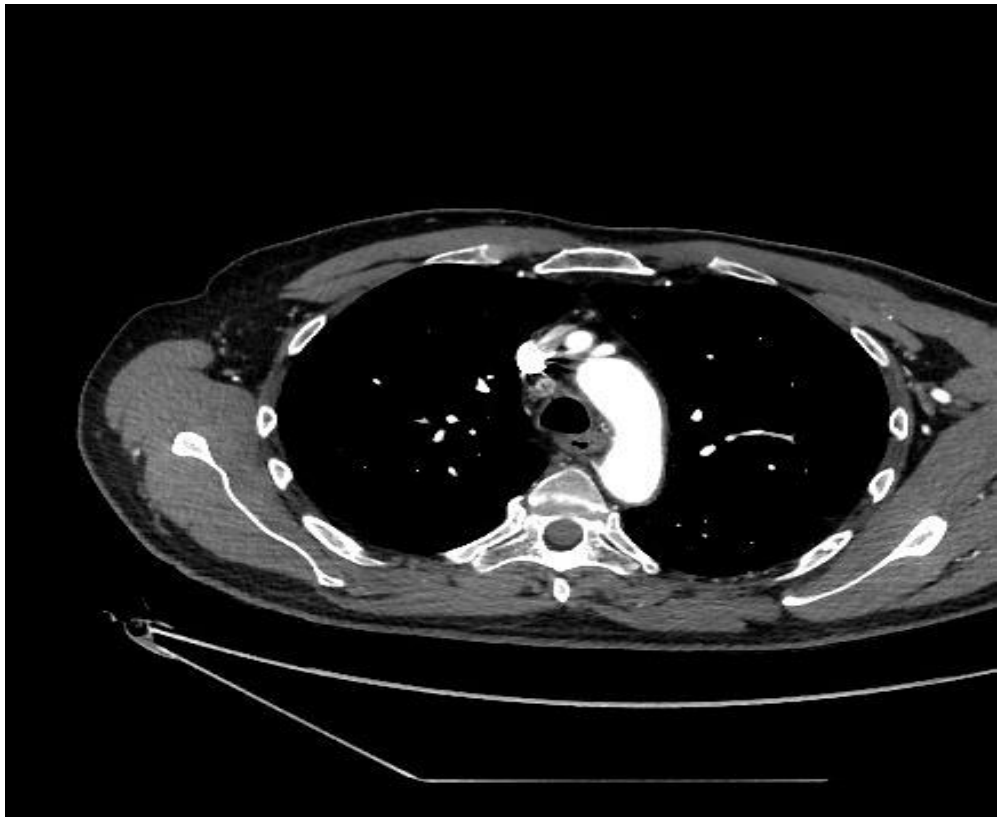


13/10/2017



Conclusions

- Tivozanib at full dose can be combined with nivolumab at full dose.
  - Tivo 1.5 mg p.o. daily x 21 days followed by a 7 day rest
  - Nivolumab 240 mg i.v every 14 days
- Preliminary safety data is promising and appears to support the importance of TKI specificity.
- Promising early signs of efficacy (67% PR; 100% Disease Control Rate).
- Currently enrolling approximately 20 patients in the phase II expansion.

Acknowledgements

Patients and family

Co investigators – Bernard Escudier, Philippe Barthelemy

AVEO – Michael Needle

Bristol Myer Squibb – Sushant Hardikar