Phase 1 Study of CB-839, a Small Molecule Inhibitor of Glutaminase, In Combination with Everolimus in Patients with Clear Cell and Papillary Renal Cell Carcinoma (RCC)

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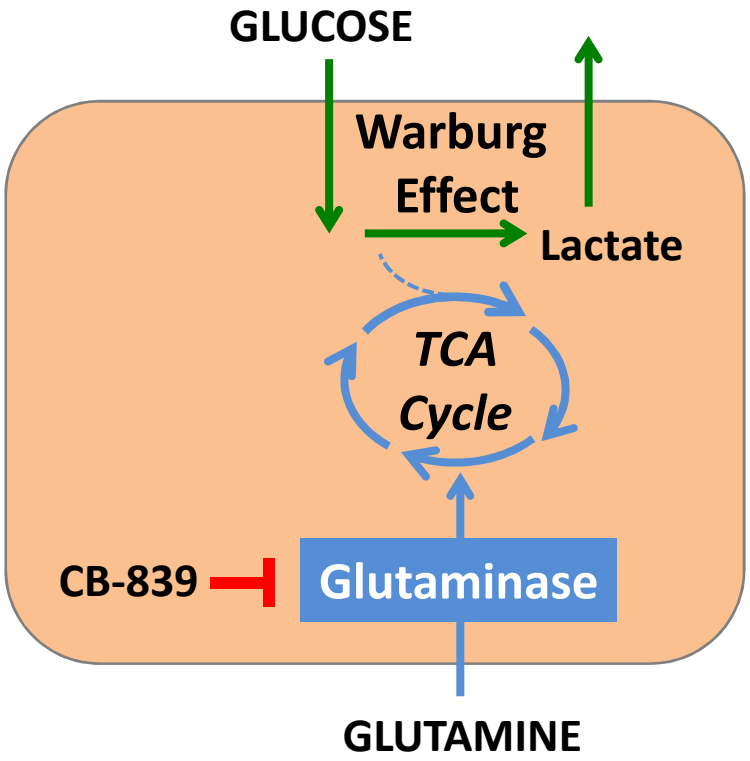
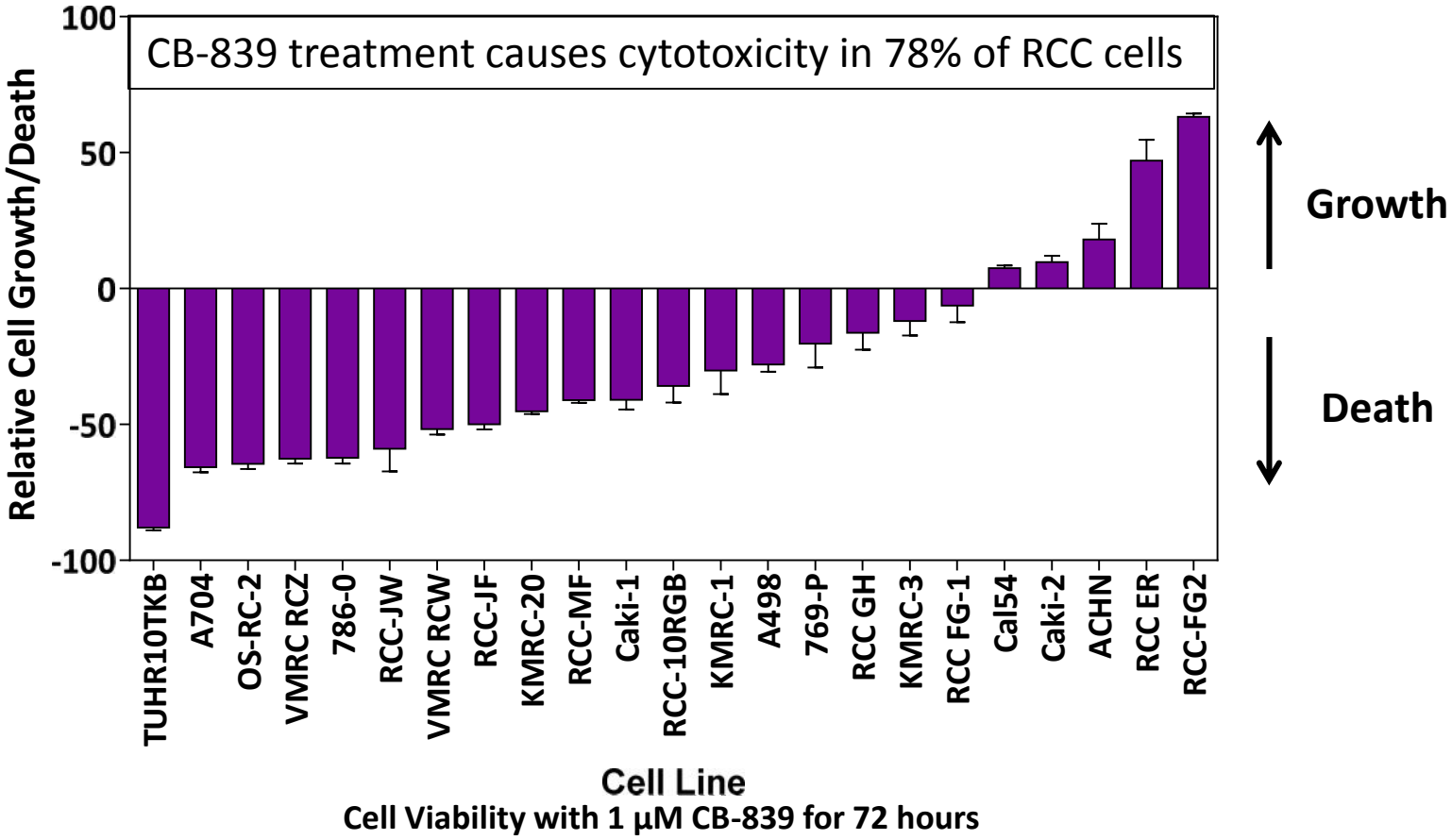
Targeting Tumor Metabolism

Blocking Glucose and Glutamine Metabolism in Tumors



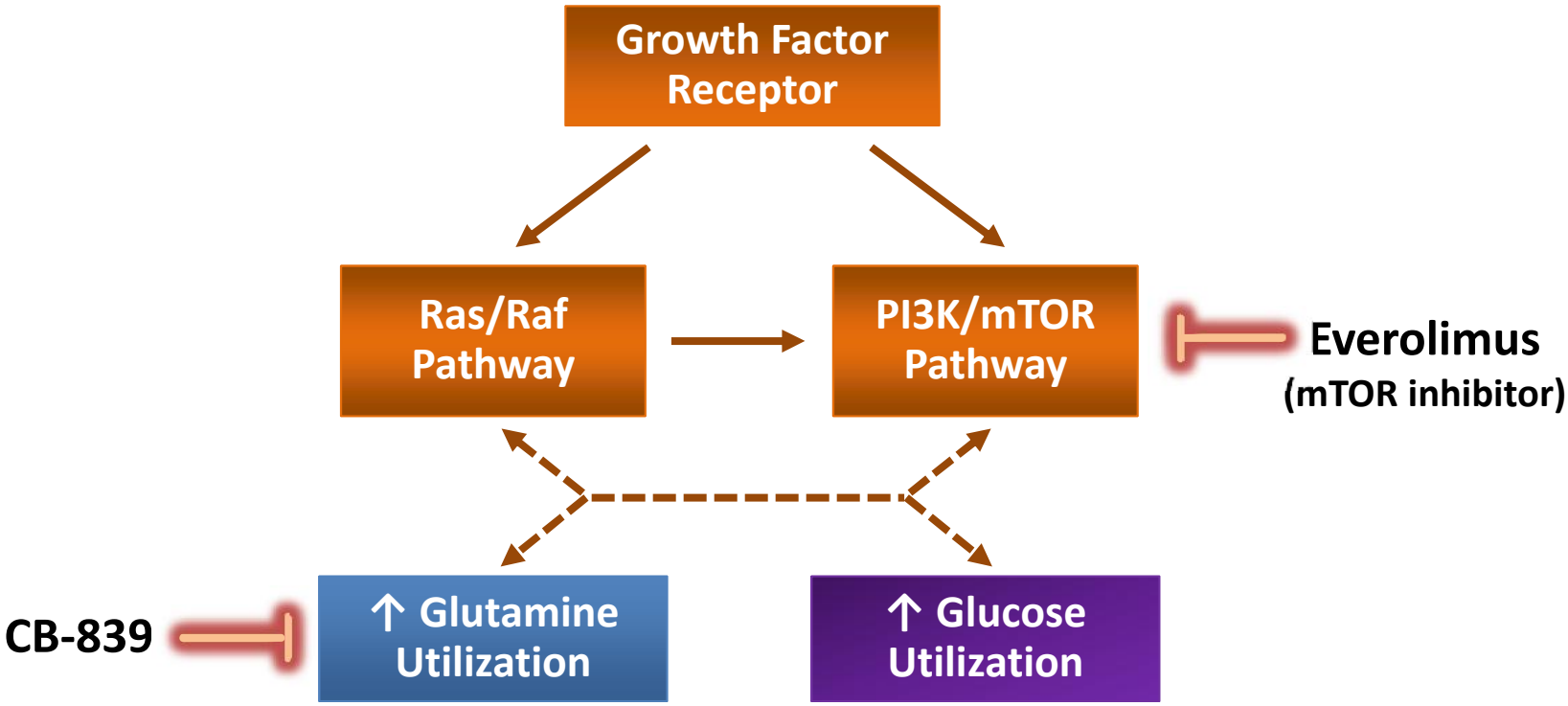
- Cancer cells require both glucose and glutamine for growth and survival
- The TCA cycle is a critical source of ATP for cellular energy, and key biosynthetic intermediates for production of amino acids, nucleotides and fatty acid
- Glutaminase is a mitochondrial enzyme that catalyzes the conversion of glutamine to glutamate. Glutamate subsequently is converted to alpha-ketoglutarate, entering TCA cycle.
- CB-839 is a first in class, small molecule, oral, highly specific, reversible, inhibitor of glutaminase.

CB-839 Has Anti-Tumor Activity in RCC Cells



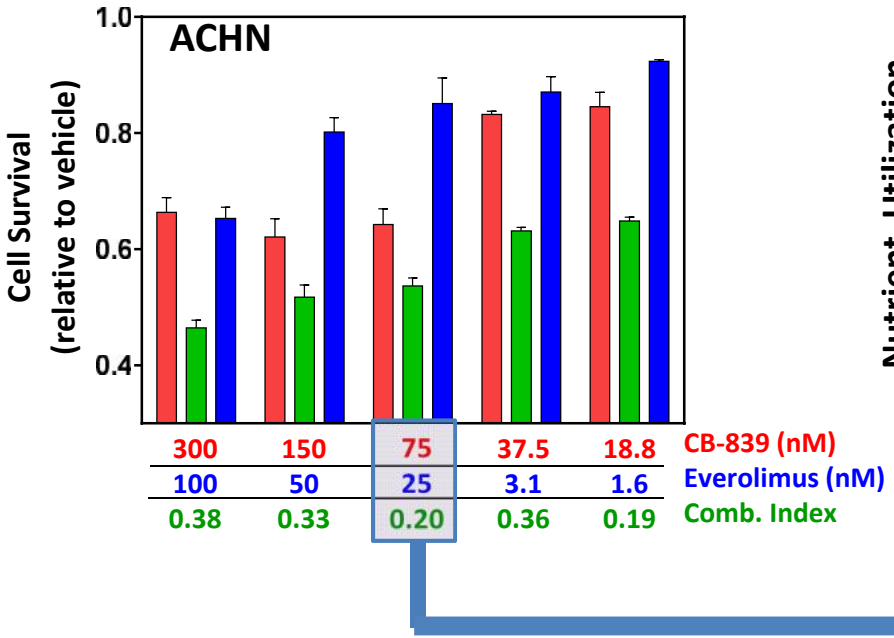
Cell Viability with 1 µM CB-839 for 72 hours

CB-839 and Everolimus Target Glucose and Glutamine Metabolism

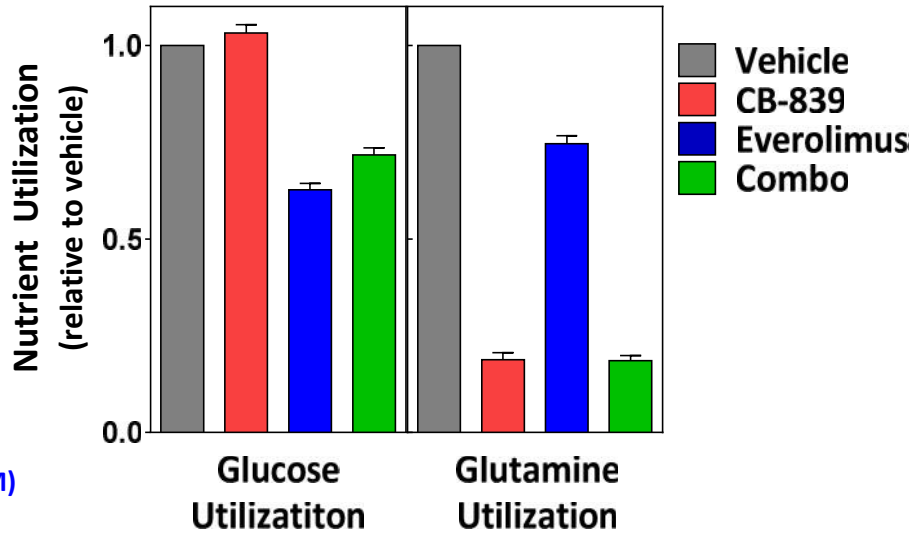


CB-839 and Everolimus are Synergistic in RCC

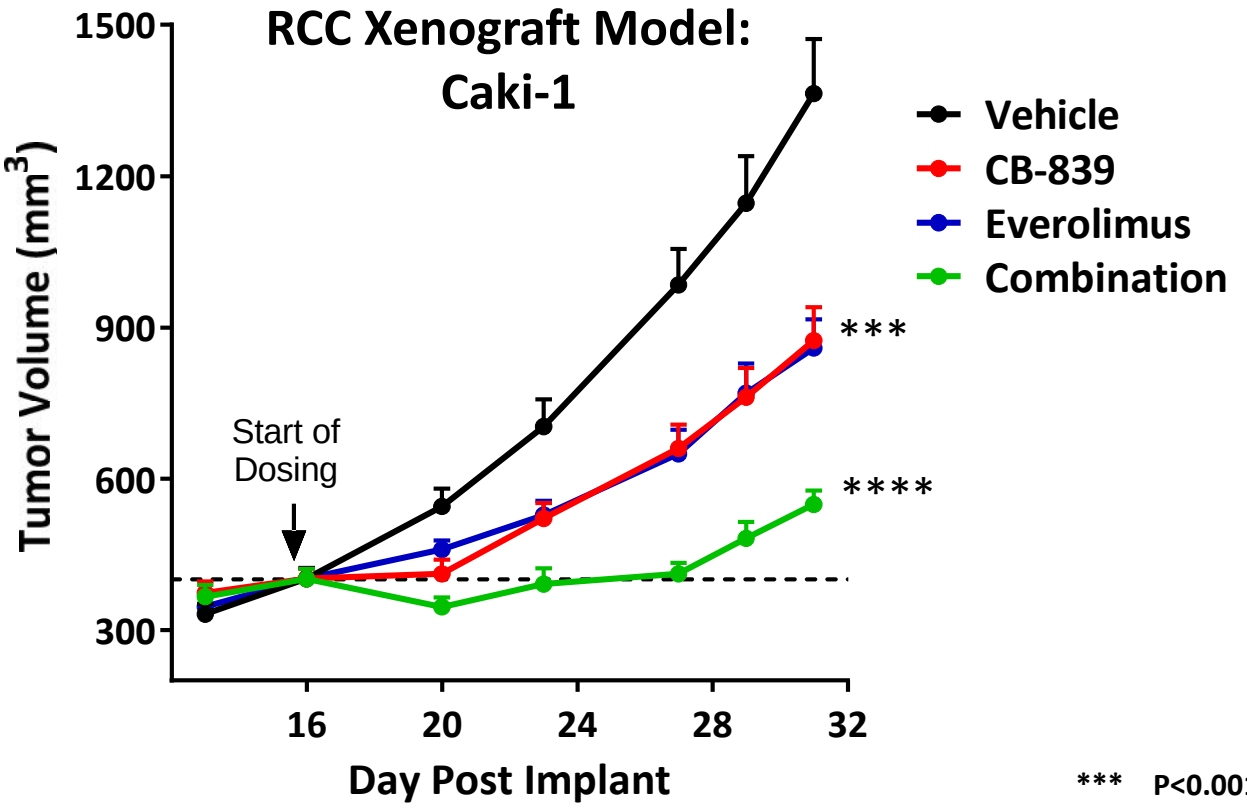
Synergistic antitumor activity



Inhibition of both glucose and glutamine utilization



CB-839 + Everolimus Combination Enhances *in vivo* Anti-tumor Activity



*** P<0.001; **** p<0.0001

Phase 1 CB-839 Clinical Study

CB-839 Monotherapy

Dose Escalation
- Adv/met solid tumors
- 100-800 mg TID/BID
- PK and PD

MTD/RP2D
Safety

Expansion cohorts
- Included RCC, TNBC, NSCLC

Combinations: CB-839 + Everolimus in RCC Patients

Dose Escalation
Advanced RCC

MTD/RP2D
Safety

Expansion Cohorts
1. Clear cell RCC
2. Papillary RCC

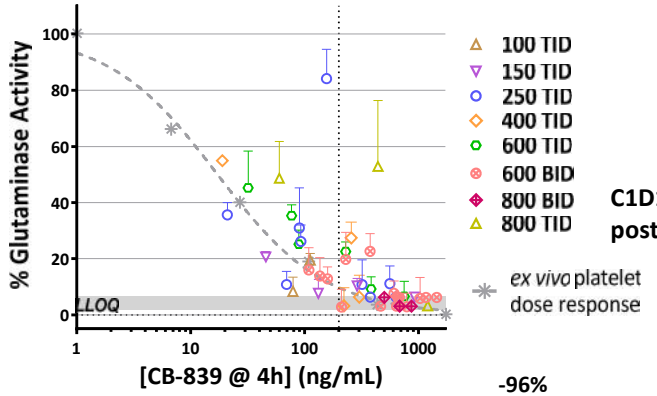
- Full dose everolimus 10 mg PO QD
- Metastatic /advanced RCC with clear cell or papillary histology
- Clear cell must have received at least 1 VEGF-targeting therapy
  - Up to four prior therapies allowed for expansion
- ECOG 0-1

CB-839 Monotherapy Conclusions

- Well tolerated at active doses
  - MTD not reached
  - 800 mg PO BID selected as RP2D
- Clear PK/PD relationship
  - Glutaminase inhibition tested in patients with solid tumors (n=88)
  - Sustained and near-complete inhibition of glutaminase in platelets and tumors
- CB-839 monotherapy was active in RCC pts (n=21)
  - 1 PR; on study 356 days
  - 52% SD, 2 longest ongoing at 25 mo and 15 mo

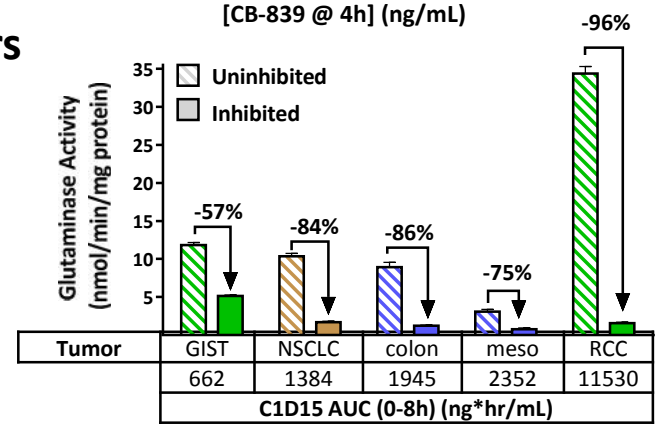
Pharmacodynamic Glutaminase Inhibition

Platelets



C1D1 4 hours post dose

Tumors



Approximately 3 weeks on study drug

CB-839 + Everolimus in RCC

Baseline Characteristics		N=17
	Age [median (range)]	62 (32-76)
	Female/Male [N (%)]	3 (18)/14 (82)
Histology [N (%)]	Clear Cell	14 (82)
	Papillary	3 (18)
CB-839 Dose [N (%)]	400 mg BID	5 (29)
	600 mg BID	9 (53)
	800 mg BID	3 (18)
Prior Therapies	Median (range)	2 (0-4)*
	mTOR inhibitor	2 (12)
	TKI	14 (82)**
	Checkpoint inhibitor	10 (59)
ECOG [N (%)]	0	6 (35)
	1	11 (65)
MSKCC Risk	Favorable/Intermediate/Poor	18% / 59% / 24%

*All ccRCC patients were 3rd line or later and 43% were ≥4th line

** All clear cell RCC patients received at least 1 prior TKI and 29% ≥ 2 prior TKIs

Safety: Drug-Related Adverse Events

CB-839 monotherapy

Drug-related AEs in ≥ 10% of subjects (N=88)

Adverse Event	Total N (%)	≥Grade 3 N (%)
Patients with Any AE	60 (68)	3 (3)
FATIGUE	21 (24)	0
NAUSEA	19 (22)	0
ALT INCREASED	13 (15)	2 (2)
PHOTOPHOBIA	12 (14)	0
AST INCREASED	10 (11)	1 (1)

CB-839 + Everolimus

Drug-related AEs in ≥ 15% of subjects (N=18) ^

Adverse Event	Total N (%)	≥Grade 3 N (%)
Patients with Any AE	17 (94)	10 (57)
DECREASED APPETITE	7 (39)	0
PROTEINURIA	5 (28)	0
AST INCREASED	4 (22)	0
CREATININE INCREASED	4 (22)	0
DIARRHOEA	4 (22)	1 (6)
HYPERGLYCAEMIA	4 (22)	2 (11)
ALT INCREASED	3 (17)	0
ANAEMIA	3 (17)	1 (6)
DYSGEUSIA	3 (17)	0
MUCOSAL INFLAMMATION	3 (17)	0
NAUSEA	3 (17)	0
STOMATITIS	3 (17)	0
VOMITING	3 (17)	0

^possibly related to either CB-839 or everolimus

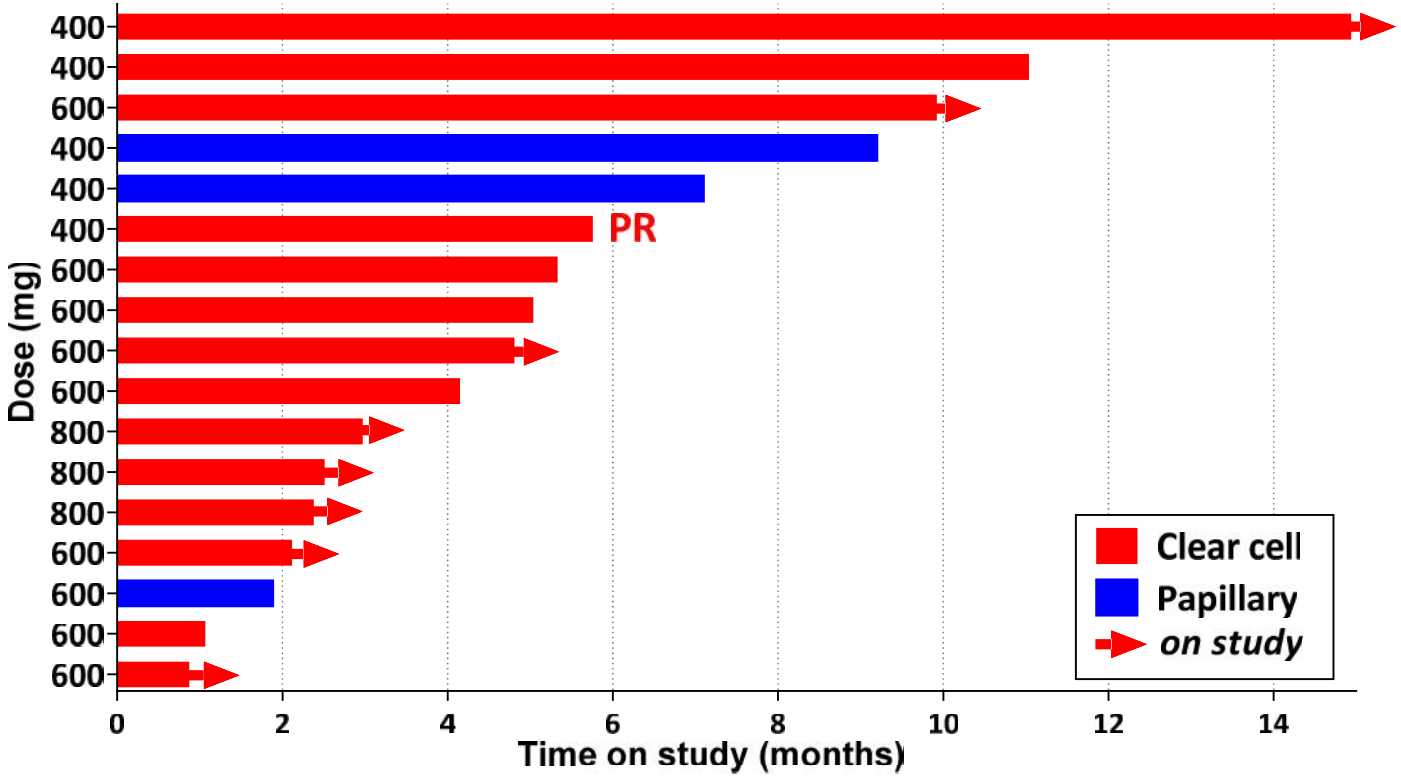
Safety Summary and Conclusions

- CB-839 is well tolerated as monotherapy
- CB-839 is well tolerated in combination with full dose everolimus
- CB-839 did not increase the severity or frequency of everolimus toxicities

Clinical Outcomes: Time on Study

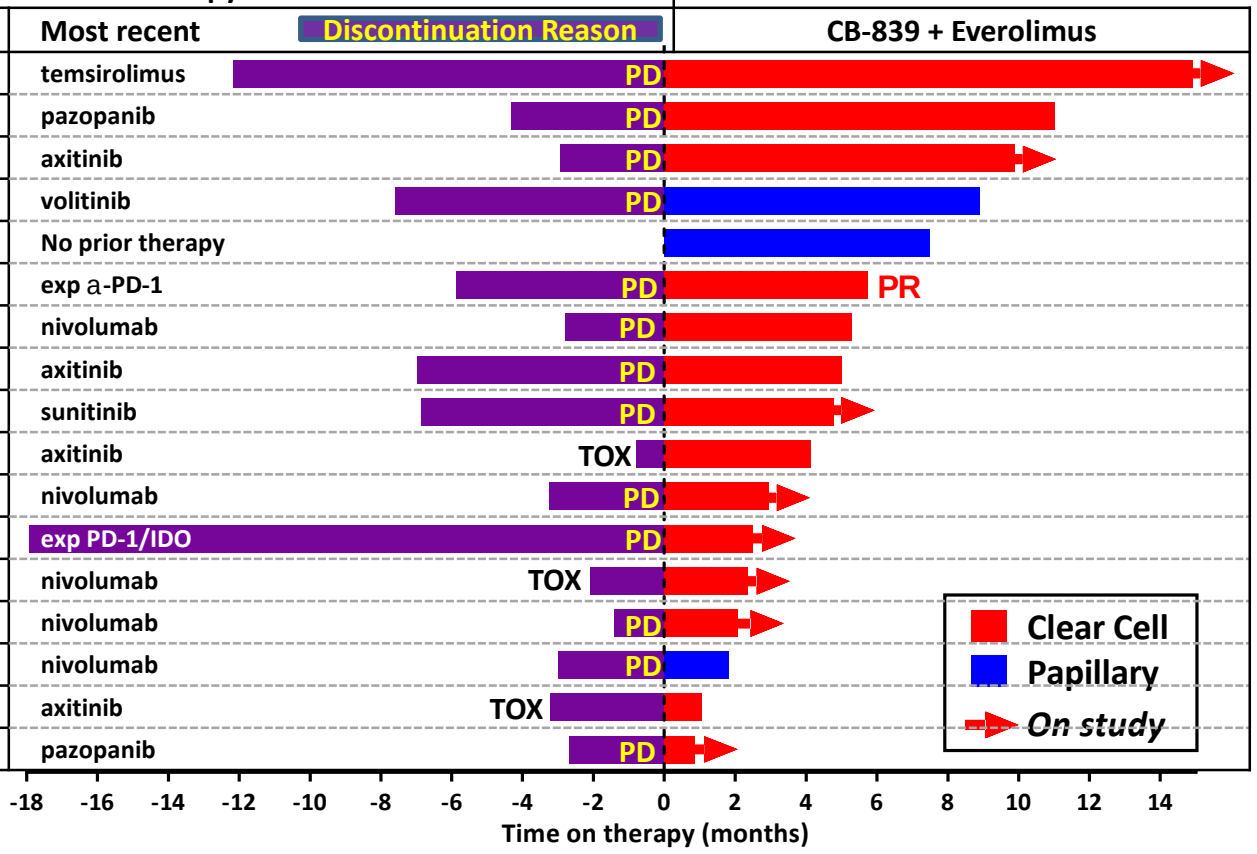
14 clear cell and 3 papillary RCC patients enrolled

8 clear cell RCC patients remain on study



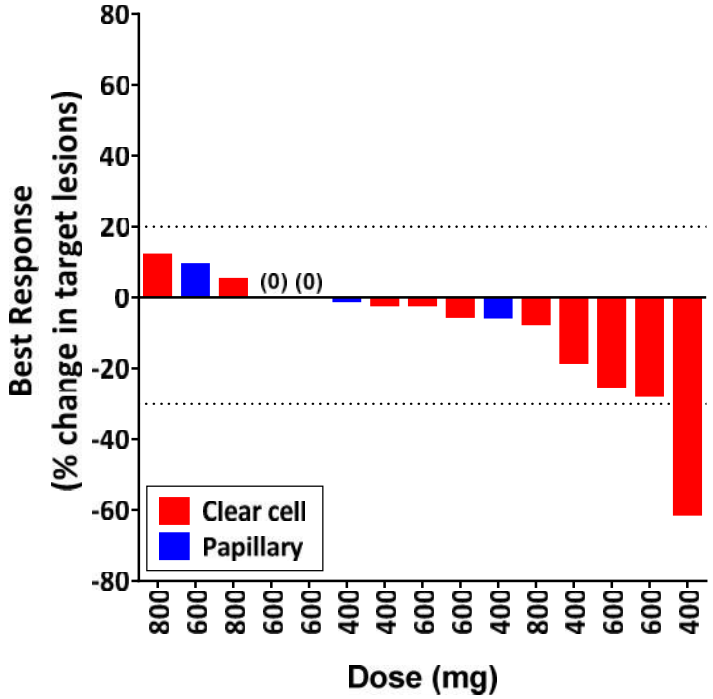
Clinical Outcomes: Prior Therapy

Prior lines of therapy	Prior Therapy				Most recent	Discontinuation Reason	CB-839 + Everolimus
	TKI	PD1	mTORi	Other			
2	✓		✓		temsirolimus	PD	
2	✓		✓		pazopanib	PD	
3	✓ ✓	✓			axitinib	PD	
1	✓				volitinib	PD	
0					No prior therapy		
2	✓	✓			exp a-PD-1	PD	PR
3	✓ ✓	✓			nivolumab	PD	
2	✓ ✓				axitinib	PD	
3	✓			✓ ✓	sunitinib	PD	
2	✓	✓			axitinib	TOX	
4	✓ ✓ ✓	✓			nivolumab	PD	
3	✓	✓		✓	exp PD-1/IDO	PD	
3	✓	✓		✓	nivolumab	TOX	
2	✓	✓ ✓			nivolumab	PD	
1		✓			nivolumab	PD	
2	✓			✓	axitinib	TOX	
2	✓	✓			pazopanib	PD	

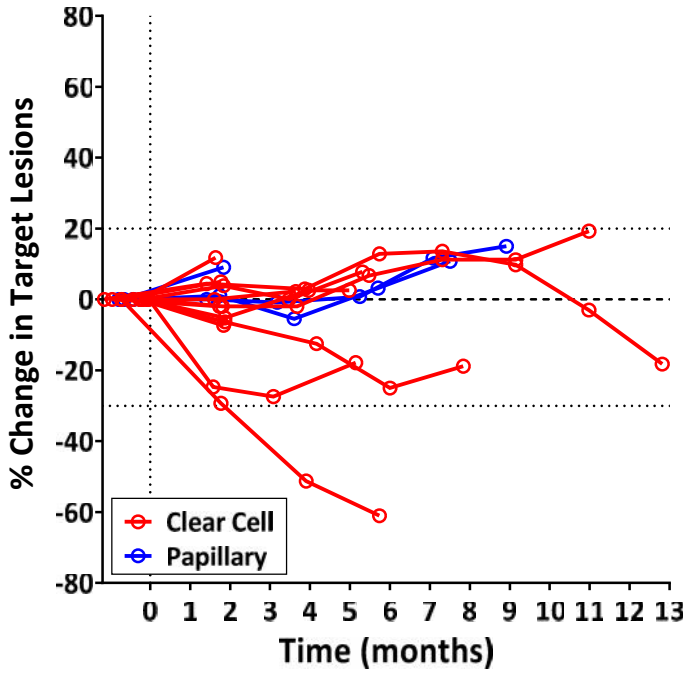


Clinical Outcomes: Tumor Burden

Best change in tumor burden



Tumor burden over time

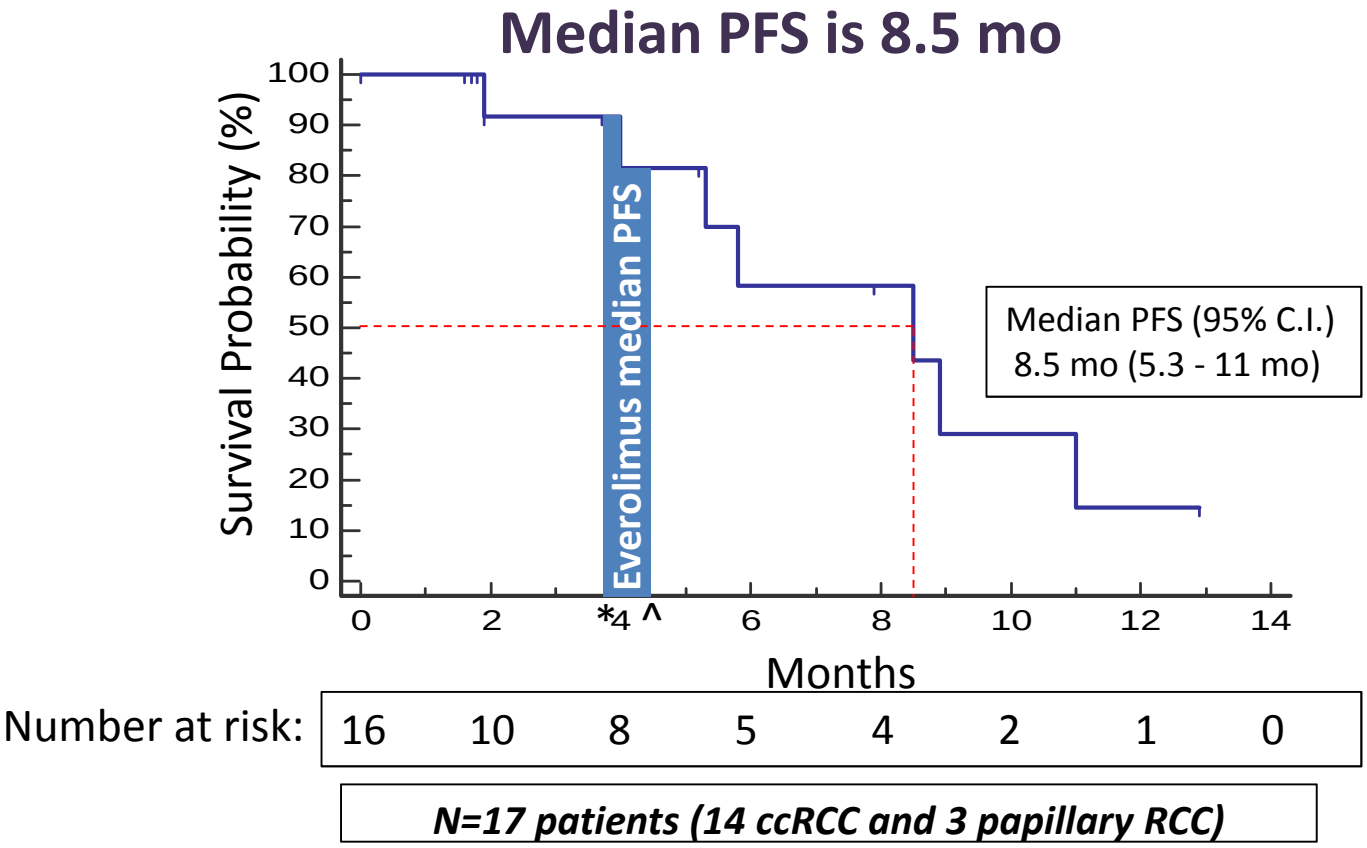


Clinical Outcomes: Response Summary

93% disease control rate (DCR); 100% in ccRCC and 67% in pRCC

	Total	Clear Cell	Papillary
Total Enrolled (N)	**17**	**14**	**3**
RECIST Response Evaluable (N)	**15**	**12**	**3**
PR	1 (7%)	1 (8%)	0
SD	13 (87%)	11 (92%)	2 (67%)
PD	1 (6.7%)	0	1 (33%)
DCR (CR + PR + SD)	14 (93%)	12 (100%)	2 (67%)
Not evaluable (N)	**2**	**2**	**0**
On study prior to first scan	1	1	0
Discontinued before tumor assessment	1	1	0

Clinical Outcomes: Progression Free Survival



^ Motzer et al, NEJM 2015

* Choueiri et al, NEJM 2015

Conclusion

- CB-839 + everolimus has encouraging safety and activity in late-line RCC patients
  - 93% DCR and preliminary PFS of 8.5 months in clear cell and papillary RCC
- There is a high unmet need for novel mechanisms and safe therapies in late line RCC
  - Recent approvals and Phase 3 investigational therapies are focused primarily on early lines of therapy for RCC
- These results support further development of CB-839 in late line RCC in combination with everolimus

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