Patient CH

-32 F, fit with no co-morbidities
-No family Hx malignancy
-Presented with LUQ mass between stomach and spleen and moderate ascites
-Laparoscopy, ascites drained: atypical cells only
15/1/2018: laparotomy and excision of mass

Histology: 'malignant epithelioid tumour' can't be classified
Positive for: MNF116; AE1/3; CD99; CK 8/18; INI-1
Negative for: S100; CD117; DOG-1, desmin, LCA; TTF-1; WT1; calretinin
Mitotic rate: 32/50 hpf
Sent to Chris Fletcher in Boston: undifferentiated malignant neoplasm with rhabdoid features ? Immunophenotypically aberrant carcinoma, melanoma or undifferentiated sarcoma

Patient CH

Relapsed Sept 2018:
-Extensive peritoneal recurrence confirmed radiologically and laparoscopically
-Given extent of disease and biology not considered appropriate for peritonectomy
Consensus: check BRAF/ PD-L1 status and arrange WGS
- offer empiric systemic "sarcoma style" therapy

- BRAFm not detected and PD-L1 negative.

Commenced Doxo/Ifosfamide Nov 2018
- 2 cycles, tolerated poorly
Repeat PET staging: progressive disease including new sites (pre-sacral and rectus abdominus muscle deposit)

Patient CH

Offered second line therapy:
- Gemcitabine + Taxotere
- Pazopanib

Patient not keen for further chemotherapy and has recently started Pazopanib

WGS results now available

Somatic Findings Patient CH:
Clinical Report: No findings
Pan Cancer Report: Returns the following

Tumour Burden:	5.6 Mutations/Mbp
Tumour Purity Estimate:	61-100%

Somatic Mutations Summary

There were 3 reportable variants found in this sample.

Gene	Mutation	Consequence	Variant Allele Frequency
TSC1	NP_000359.1:p.Ser1043del	inframe_deletion	3.6%
KMT2D	NP_003473.3:p.Gln3919del	inframe_deletion	4.6%
ASXL1	NP_056153.2:p.Gly645ValfsTer58	frameshift_variant	4.4%

- No clinically Relevant CNV

ASXL1 and KMT2D are tumour suppressors with no prognostic information

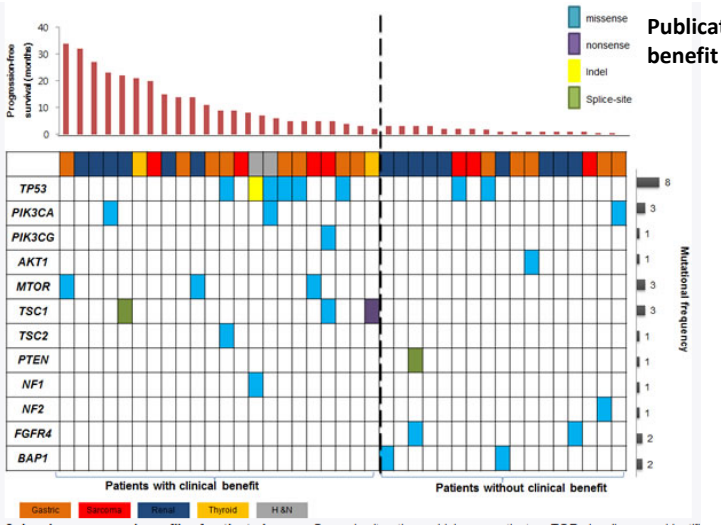
TSC1/TSC2 for a heterodimer and is part of mTOR pathway important to cell growth and proliferation, metabolism, and angiogenesis

A quick summary form Cancer Genome Interpreter:

Observed alteration	Biomarker	Drugs	Effect	Resi	Tumor type	Evidence level	Reference
TSC1 (S1043*)	TSC1 oncogenic mutation	Everolimus (MTOR inhibitor)	Responsive		GCA	FDA guidelines	FDA
TSC1 (S1043*)	TSC1 oncogenic mutation	Everolimus (MTOR inhibitor)	Responsive		RA	FDA guidelines	FDA
TSC1 (S1043*)	TSC1 oncogenic mutation	Everolimus (MTOR inhibitor)	Responsive		BLCA	Early trials	PMID:22923433
TSC1 (S1043*)	TSC1 oncogenic mutation	Everolimus (MTOR inhibitor)	Responsive		R	Case report	PMID:24622468 PM...
TSC1 (S1043*)	TSC1 oncogenic mutation	Everolimus (MTOR inhibitor)	Responsive		S, ST	Case report	PMID:26859683
TSC1 (S1043*)	TSC1 oncogenic mutation	MTOR inhibitors	Responsive		RA	Early trials	PMID:23312829 PM...

- GCA: Giant Cell Astrocytoma
- RA: Renal Angiomyolipoma
- R: Renal
- BLCA : Bladder Cancer
- S: Sarcoma
- ST:Stomach

Is mutation likely to be relevant in this rare cancer?



Lin et. al. **Next-generation sequencing reveals somatic mutations that confer exceptional response to everolimus** Oncotarget. 2016 Mar 1;7(9):10547-56.

Publication hypothesis that other cancer types may benefit from mTOR screening based on Renal Cancers

Figure 2:
39 patients with 5 different tumour types sequenced

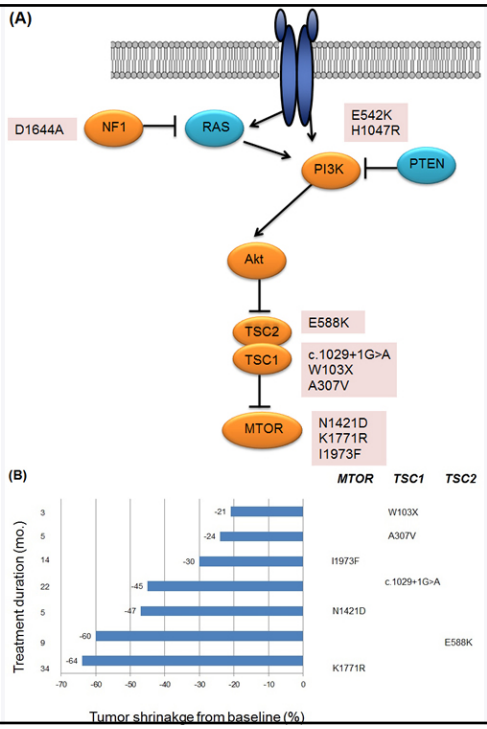
TSC1/2 mutations in

Renal (Dark Blue x1)
Sarcoma (Red) x1
Gastric (Brown) x1
Thyroid (Yellow) x1

Figure 3 right

Overall, genomic alterations which may activate mTOR signaling were identified in 10 of 22 (45%) patients with clinical benefit (Figure 3A**). In particular, TSC1/TSC2/MTOR mutations were key components in determining everolimus sensitivity (Figure 3B). The incidence of these mutations were 31.8% (7/22) in patients with clinical benefit as compared with 0% in those with non-clinical benefit (P=0.012).** The prevalence of these recurrently mutated genes and their correlation with clinical benefit strongly suggest that they confer sensitivity to everolimus.

While **TSC1/TSC2/MTOR alterations were exclusively found in patients with clinical benefit**, we also searched for recurrently mutated genes that were exclusively identified in patients with non-clinical benefit….



Other Publications of note TSC1 is a particularly relevant biomarker for mTOR inhibition response:

Wagner et al. *Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors*. J Clin Oncol. 2010 Feb 10;28(5):835-40. doi: 10.1200/JCO.2009.25.2981. Epub 2010 Jan 4.

"Moreover, 2 out of 3 patients with malignant perivascular epithelioid cell tumors who had clinical response to sirolimus showed TSC1/2 loss"

Voss MH etal. *Tumor genetic analyses of patients with metastatic renal cell carcinoma and extended benefit from mTOR inhibitor therapy*. Clinical cancer research. 2014; 20:1955-1964.

TSC1 and TSC2 may be screened as predictive biomarkers of everolimus in renal cell carcinoma patients who progressed on VEGF-targeted therapy. This report on metastatic renal cell carcinoma patients with extended benefit from mTOR inhibitor showed that TSC1 and TSC2 offer explanation for treatment response

Recommendations?

1) ATGC should reissue clinical report to PQ of Pan-Cancer Type?
2) Drug access

TSC1 with specific mention of TSC1 S1043N