FDG PET status in the era of targeted therapy in lymphoma

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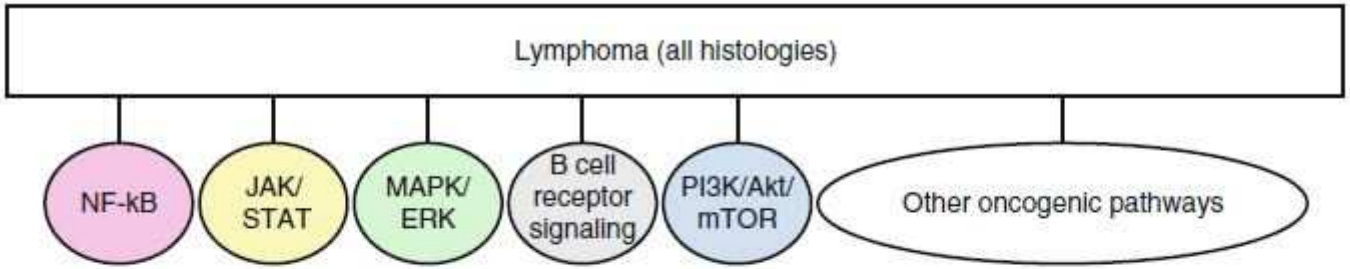
Increased number of drugs targeting activated oncogenic pathways proposed in relapsed/refractory Lymphoma



Pathway	Drug	Target	% response rate in different histologies					
			DLBCL %	FL %	MCL %	SLL/CLL %	T-Cell %	HL %
PI3K/AKT/ mTOR	Everolimus	mTOR	30	50	32	18	63	53
	Temsirolimus	mTOR	36	56	38	10	–	–
	CALI-101/ GS-1101	PI3K	0	55	67	30	–	–
B cell receptor (BCR)	Fostamatinib	Syk	22	10	11	55	0	–
	Ibrutinib	Btk	17	23	69	67	–	–

Younes, Lymphoma (Younes,Coiffier eds) 2013

Evaluation of targeted therapy 1

- Predictive biomarkers are critical
- Regression of lymphoma during therapy is an important end-point
  - Evaluation of response early in the course therapy with a biomarkers could
    - Optimize treatment modalities (combined targeting)
    - Avoid ineffective treatment
    - Reduce cost

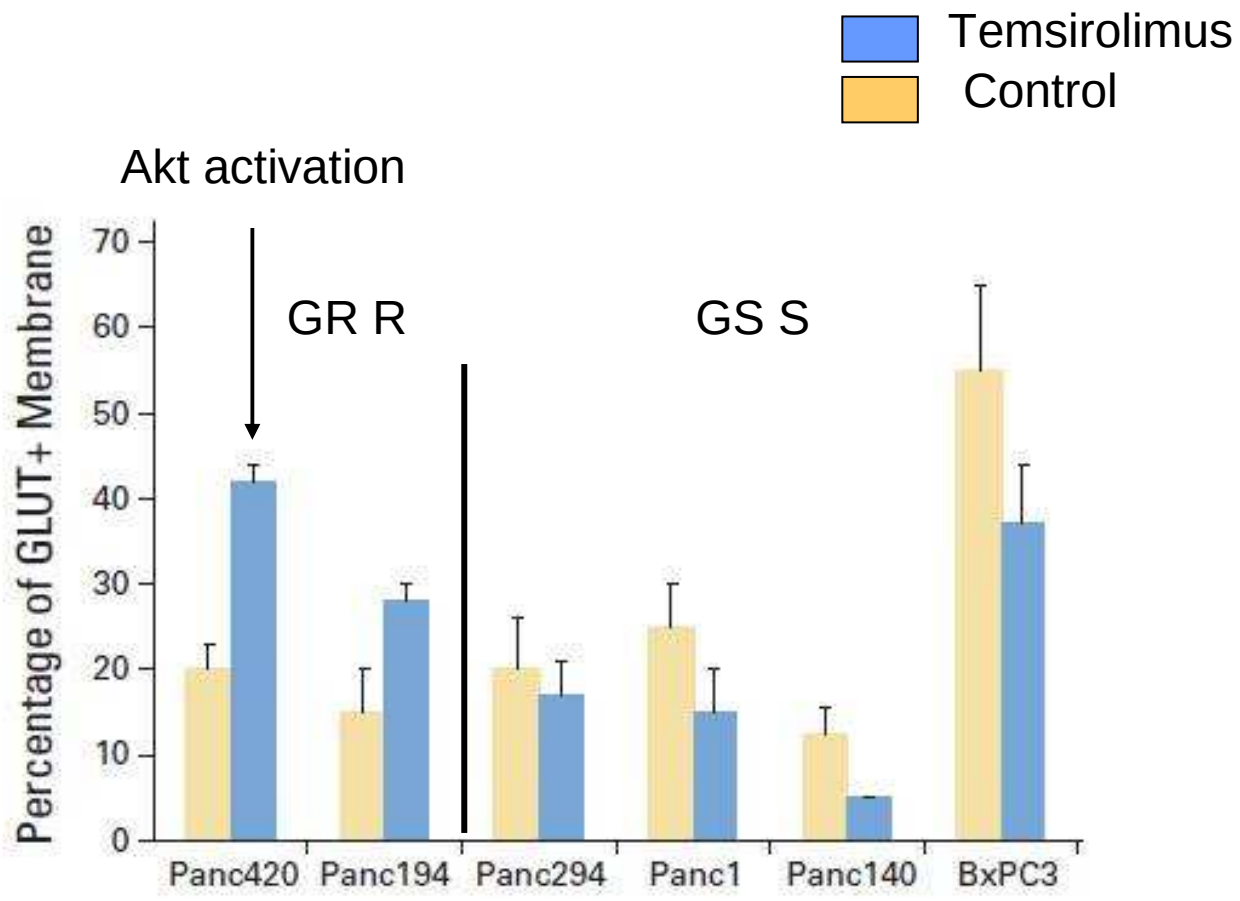
Evaluation of targeted therapy 2 which biomarkers?

- Pharmacodynamic biomarkers
  - assess target inhibition
  - assess pathway downregulation
  - ➢ This does not necessarily equate clinical benefit
- Many biomarkers assays not standardized
- Is there a place for metabolic imaging?
  - detect response and resistance before conventional Imaging

Use of Glucose analog FDG as a biomarker

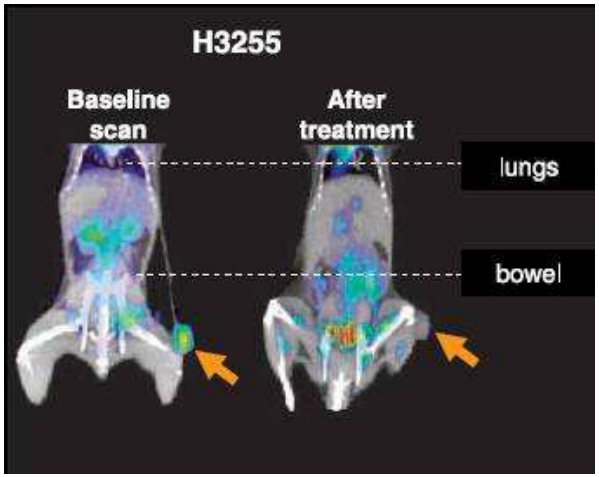
- Intensity of FDG uptake
  - Membrane glucose transporters (GLTU1,GLUT3)
  - Hexokinase activity
- Activation oncogenic pathways in tumour cells
  - Increased glycolysis
  - Up-regulation and overexpresion of GLTU1, GLUT3
- Drug inhibition of these pathways alters the tumour cell glycolysis

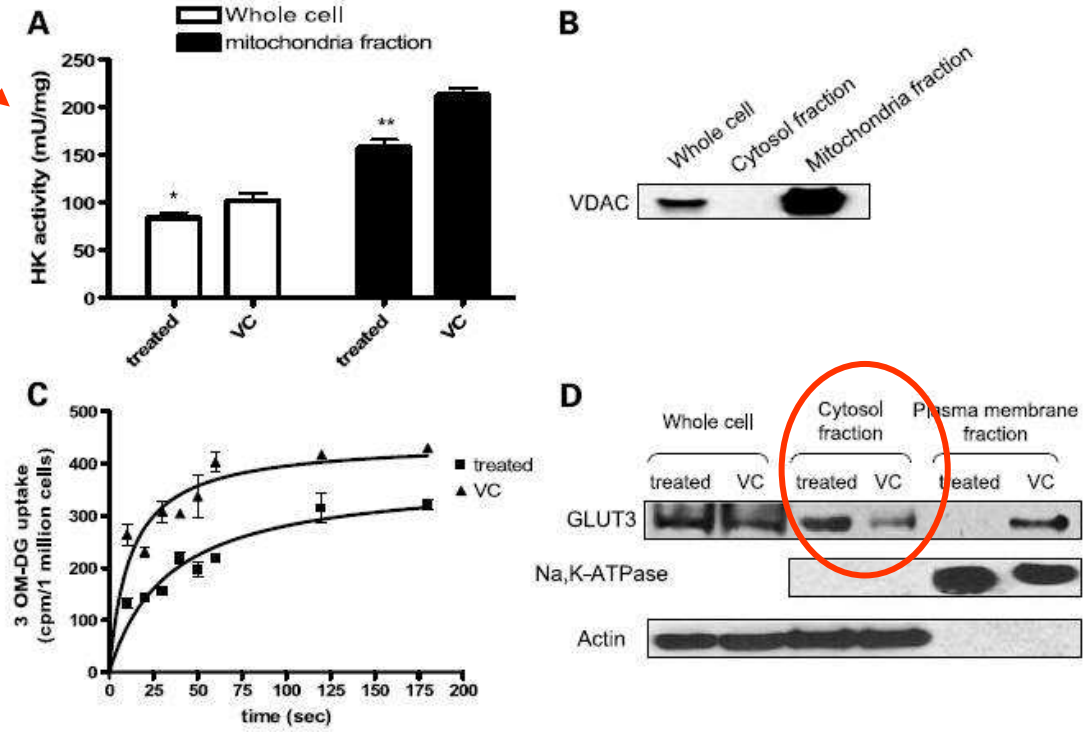
Akt activation increases GLUT1 membrane localization in pancreatic adenocarcinoma cells resistant to Temsirolimus (AkT/mTOR pathway)



Ma et al. J Clin Oncol, 2009

AktT inhibition by gefitinib (EGRF inhibition) induces a GLUT3 translocation from membrane to cytosol





NSCLC cell lines

Su et al , Clin Cancer Res 2006

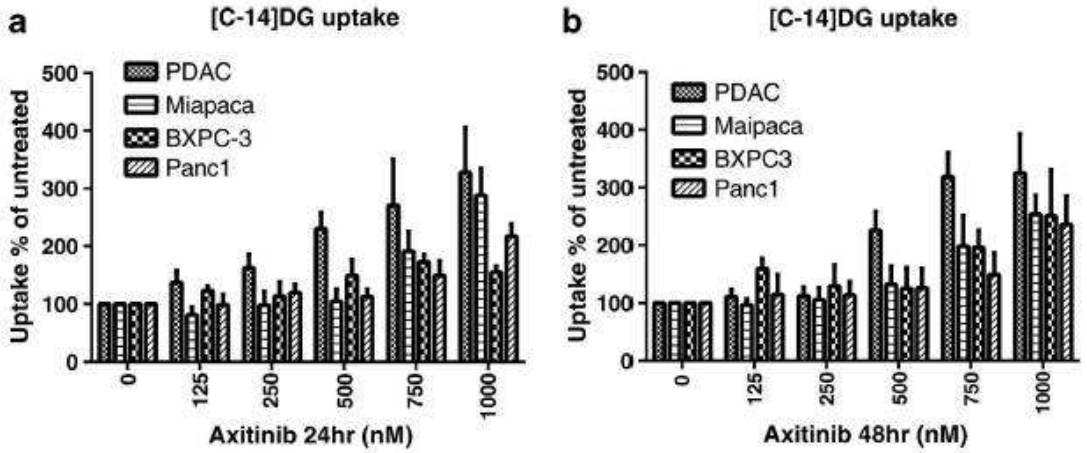
Many sources of complexity

To interpret imaging results with FDG after targeted therapy:

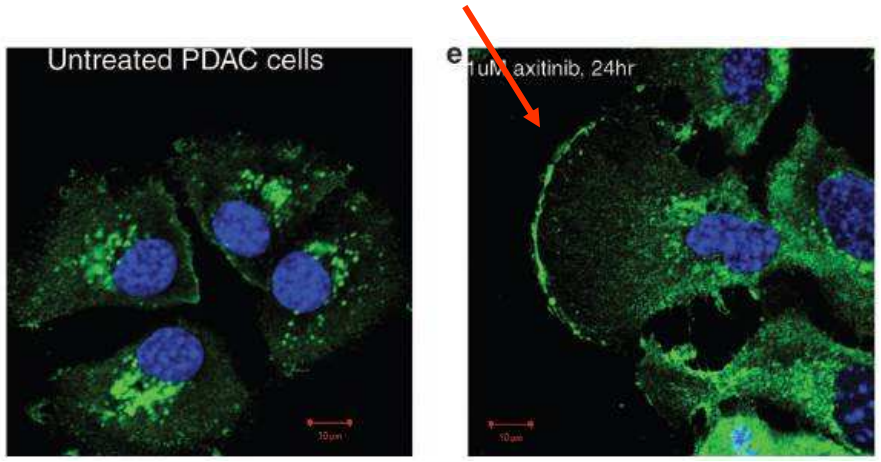
1. Interrelationship between oncogenic pathways and existence of resistance feed back loops
2. Time lag between effects on glucose transporter, effects on cell cycle, apoptosis and the effectiveness of receptor blockage
3. Differences between tumor types

Negative feed back loop:

Treatment of pancreatic adenocarcinoma cells by a TKI inhibitor Axitinib induced activation of Akt pathways and a GLUT1 translocation to the membrane



PDAC cell lines

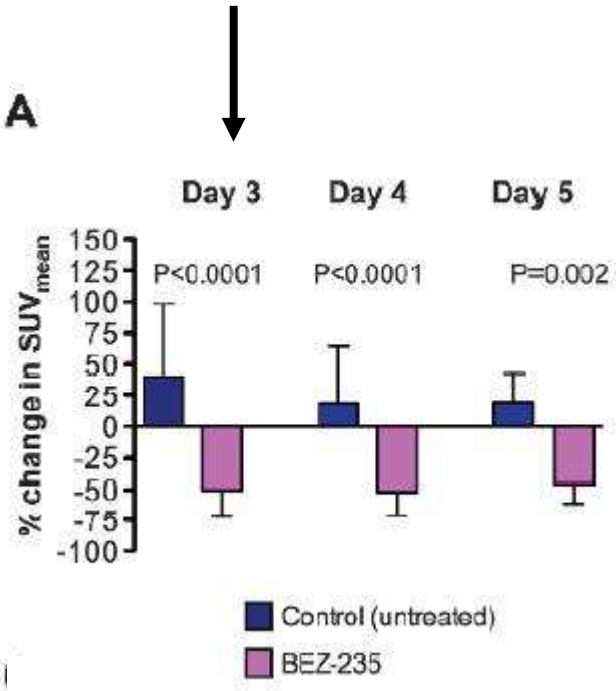


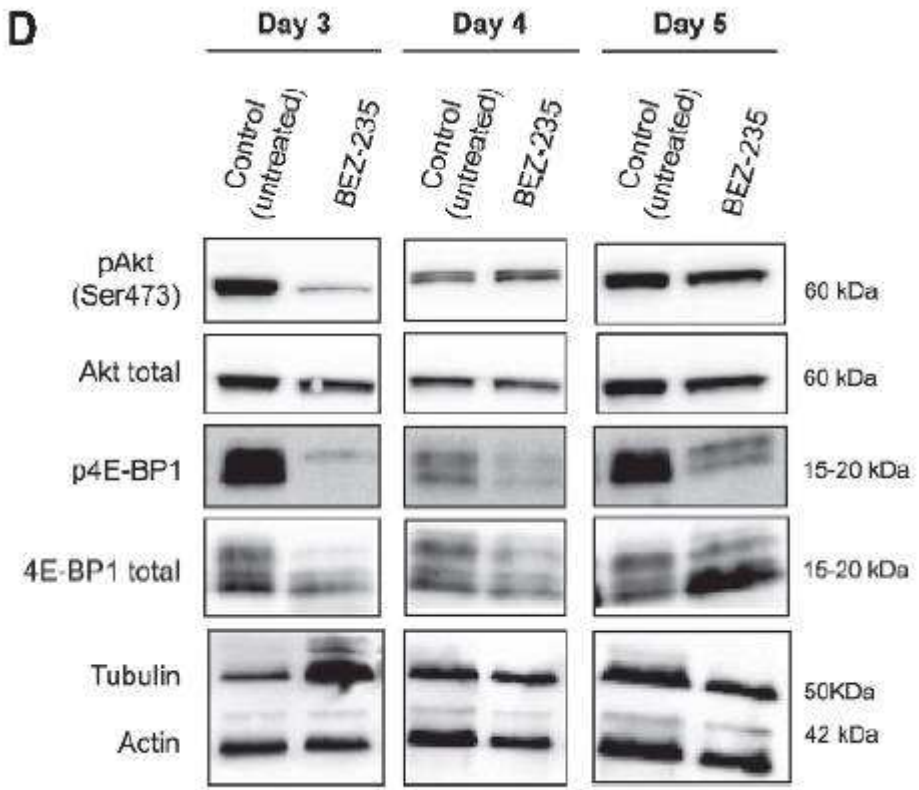
Warrants combined therapy

Hudson et al, Cell Death and Disease, 2014

Lag between withdrawal of the drug, target recovery (PI3K/mTOR) and metabolic recovery in an animal model of ovarian tumour

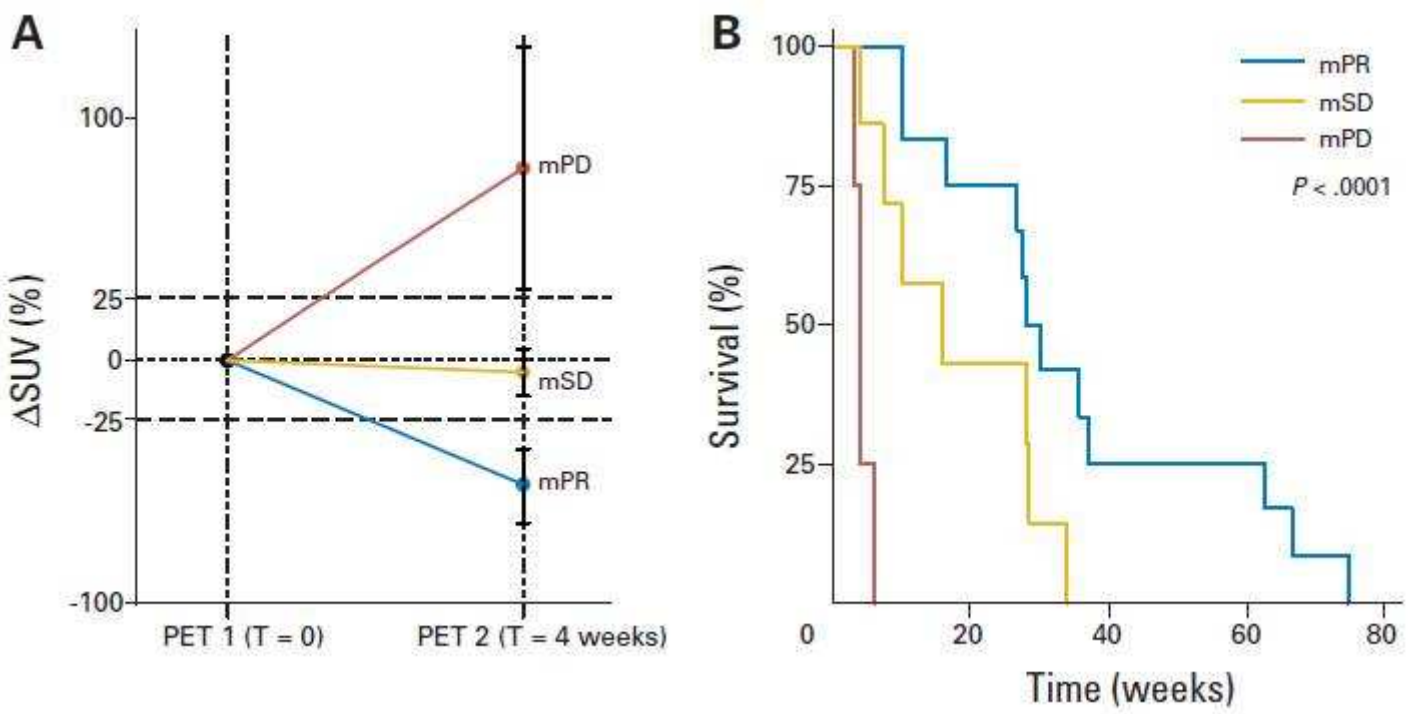
BEZ-235 withdrawal





Lheureux Translational Oncology, 2013

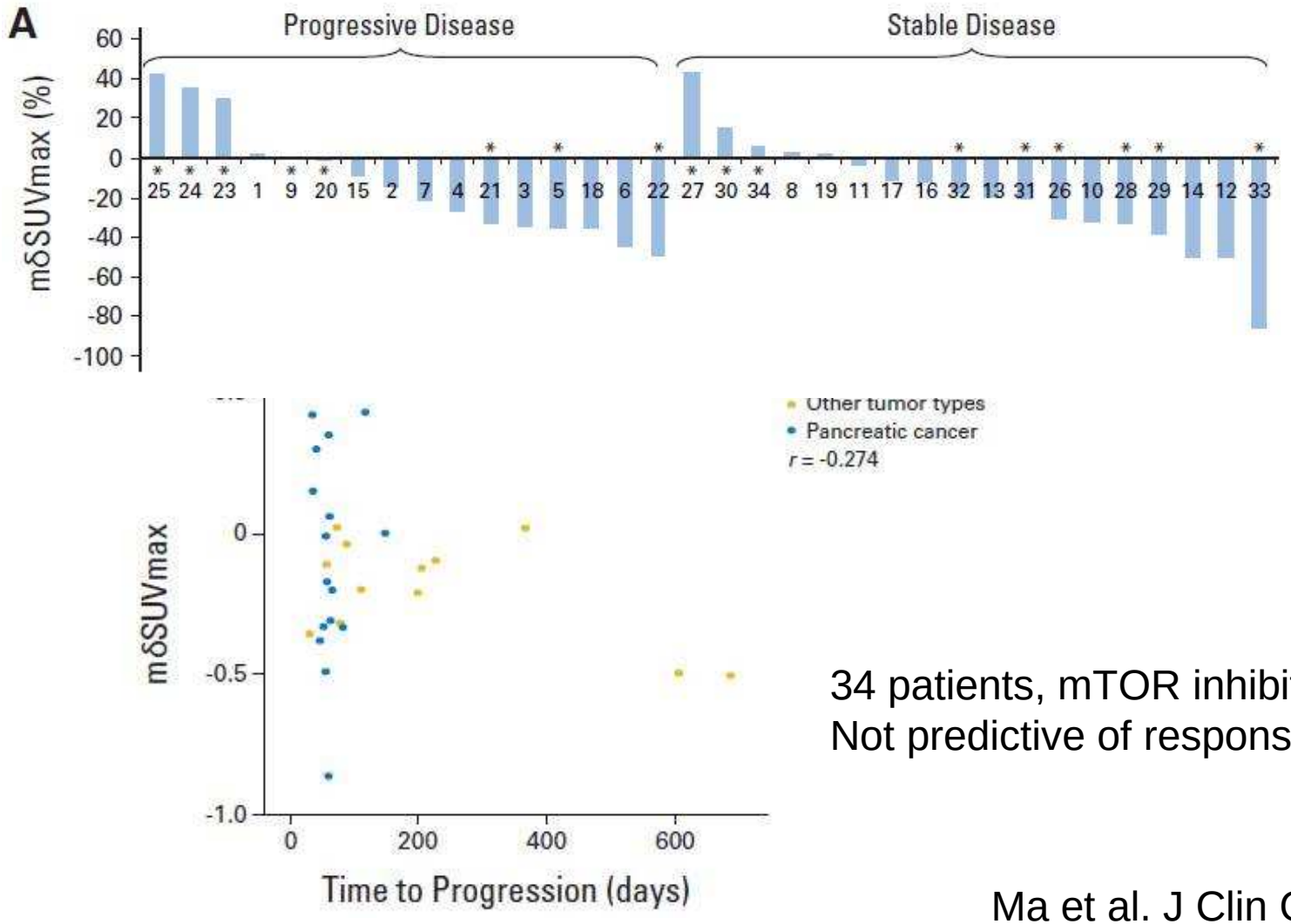
FDG as a prognostic biomarker: variable clinical results 1



Early prediction of response to Sunitinib
23 GIST patients after Imatinib failure

Prior J Clin Oncol 2009

FDG as a prognostic biomarker: variable clinical results 2



34 patients, mTOR inhibition
Not predictive of response and TTP

Ma et al. J Clin Oncol, 2009

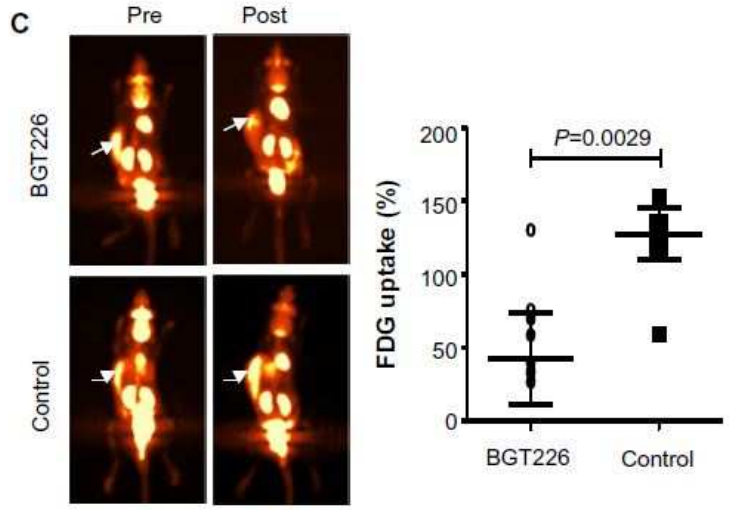
FDG PET in lymphoma patients treated with targeted therapy

- Data are scarce*
  - Complexity and diversity of the mechanims involved in oncogenic pathways in lymphoma
  - Trend to treat with combined agents to avoid negative feedback
  - Optimal timing for response assessment undefined in the setting of a continuous daily long term treatment

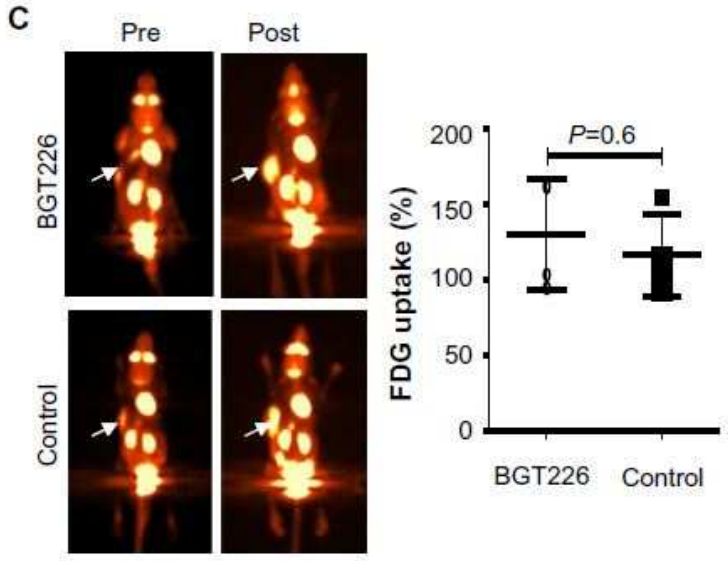
  Evaluation of a targeted therapy is more focussed on appropriate definition of its CT variations

*Case report and one study including 11 patients (ALK+ NHL)

ALK+ ALCL animal model :7 day treatment with a dual PI3K/mTOR inhibitor



Sensitive SU-DHL-1 xenograft



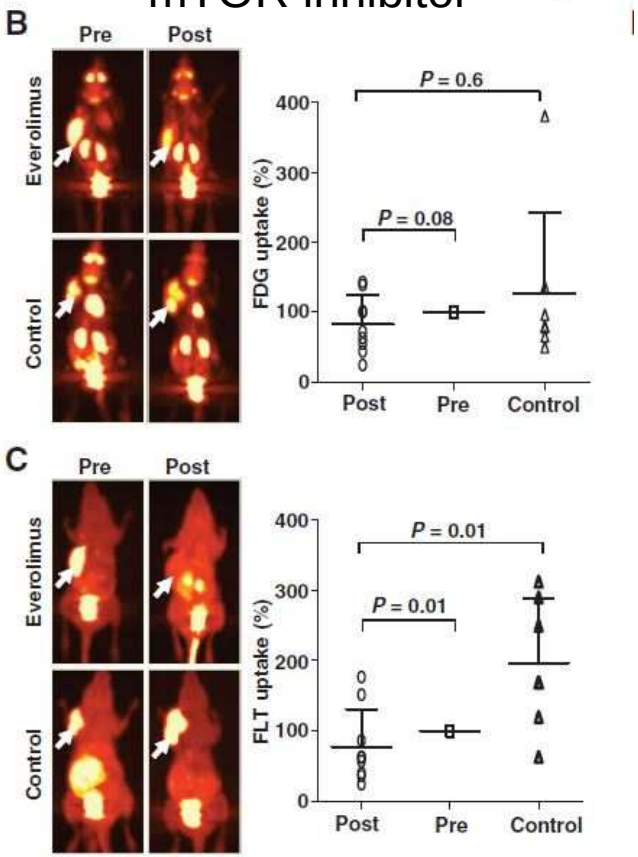
Resistant Karpas 299 xenograft

- FDG PET
  - Discriminates very early sensitive from resistant lymphoma
  - reduced metabolic activity correlates with
    - decrease of proliferation marker Ki67
    - increase of apoptotic marker (cleaved caspase-3)

Graf et al. OncoTargets and Therapy 2014

Is FLT thymidine analog as a biomarker > FDG?

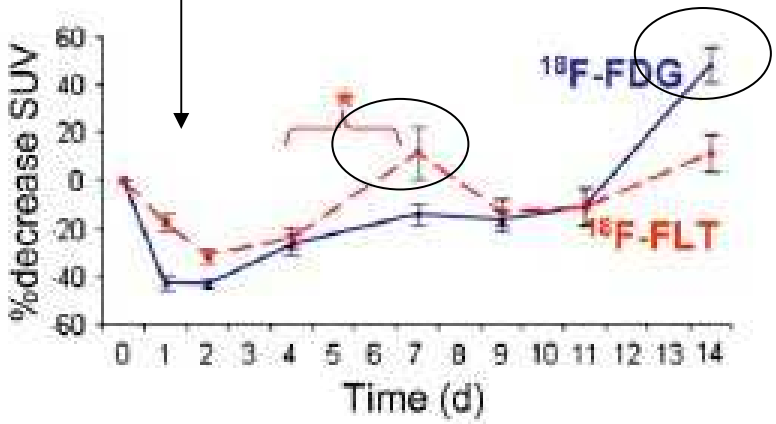
ALK+ ALCL cell lines
mTOR inhibitor



SU-DHL-1 xenograft

Granta 519 cells from human MCL

Temsirolimus withdrawal



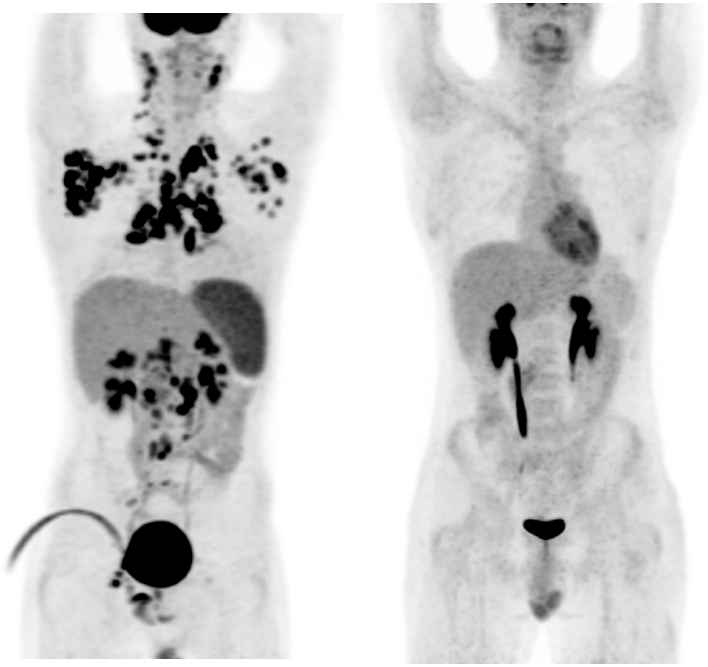
FLT>FDG in some experimental models.
Different kinetics reported after drug withdrawal attributed to inflammatory reaction.

Li et al Cancer Res 2012

Brepoel et al J Nucl Med 2009

Advanced chemoresistant ALK+ Lymphoma patients treated by Crizotinib

Courtesy of Pr Ch Messa, Pr L Guerra



July 27th 2010 August 12th 2010

- 11 refractory and relapsed patients
- 73% 2y OS and 64% 2y PFS
- FDG-PET performed before during and after therapy
- FDG-PET demonstrates sensitivity to inhibition within a few days of continuous administration
- FDG-PET predictive value in this short series cannot be assessed

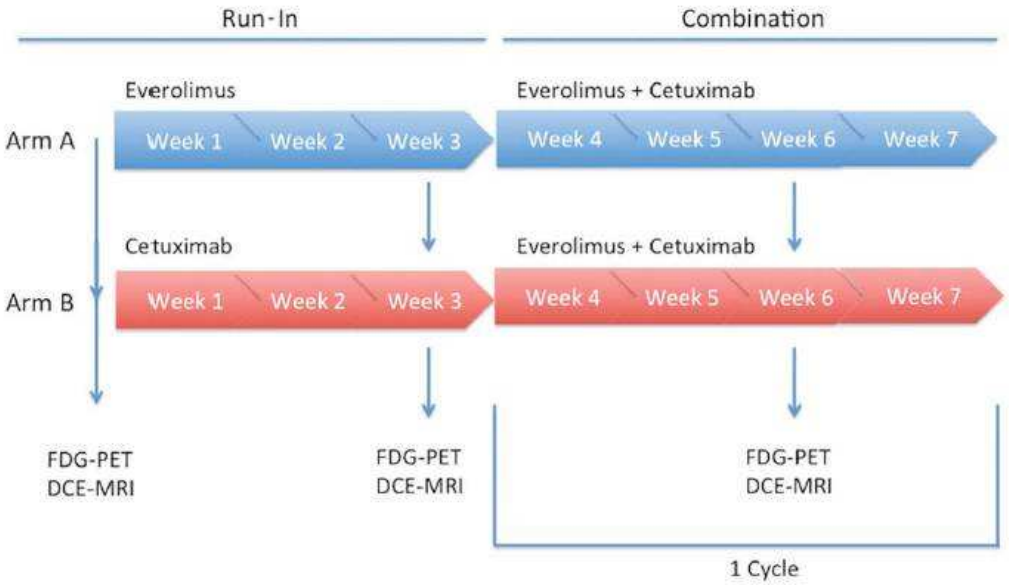
Gambacorti Passerini et al, N Engl J Med 2011, J Natl Cancer Inst 2014

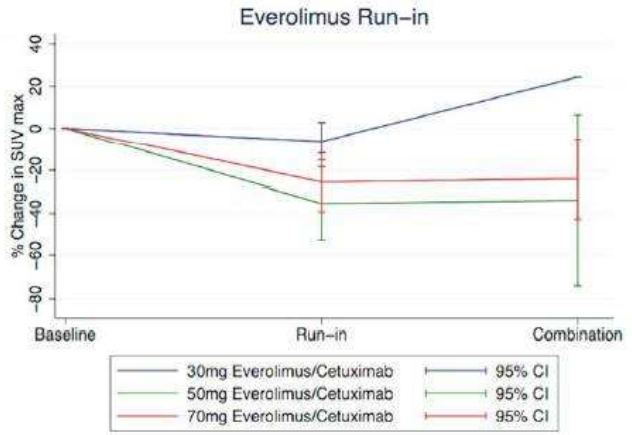
Conclusions

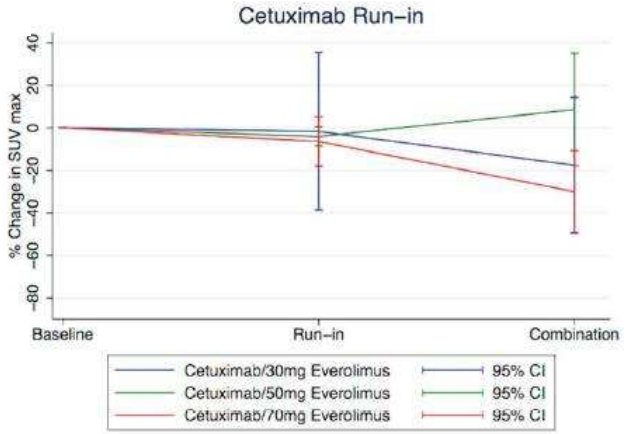
- In theory FDG as a biomarker of targeted therapy
  - Gives high possibilities to investigate glycolysis linked to oncogenic pathways.
  - Detects sensitivity to the drug (is it target effect of real sensitivity to the inhibitor?)
  - Quantifies the metabolism via ΔSUVmax
- Optimal timing of imaging unkown
- Prediction value for tumor regression and outcome is unknown
  - is FDG reduced uptake a false negative results relative to tumor regression and outcome?
- Well-organized ancillary trials based on preclinical results are warranted to define a possible role of FDG in response assessment to targeted therapy in lymphoma.

Back up slides

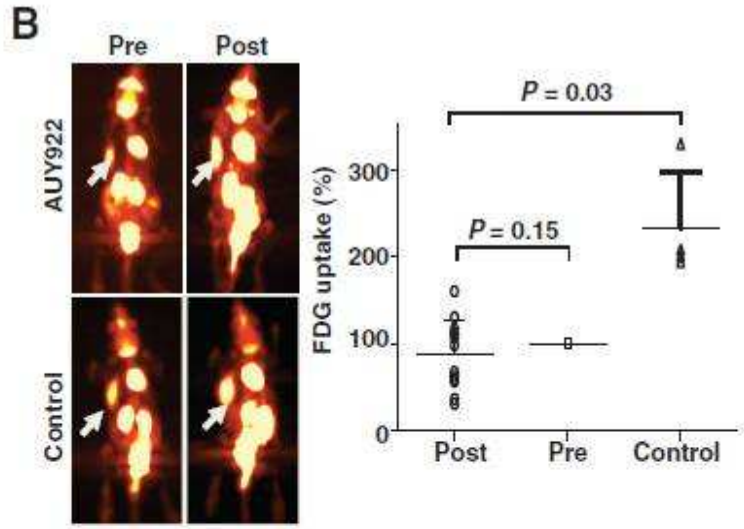
Dose related SUV_{max} reduction

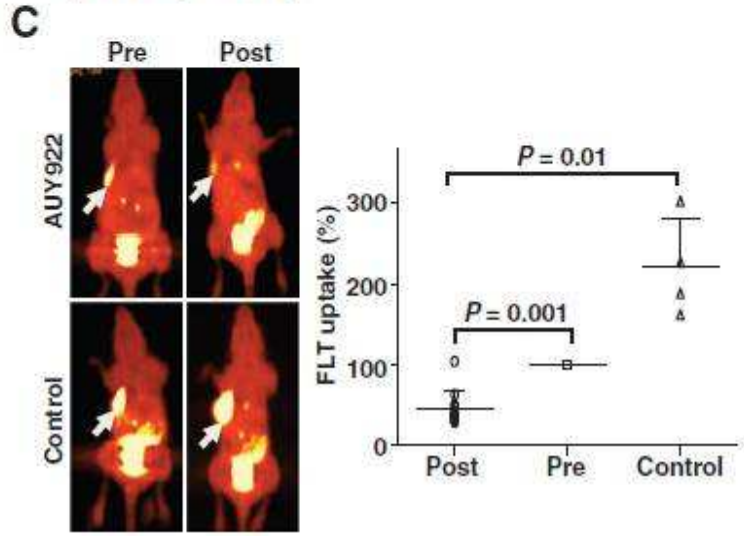


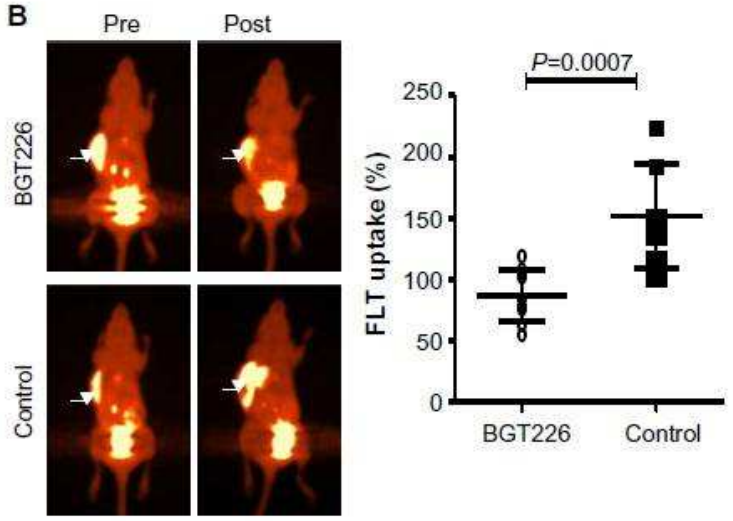


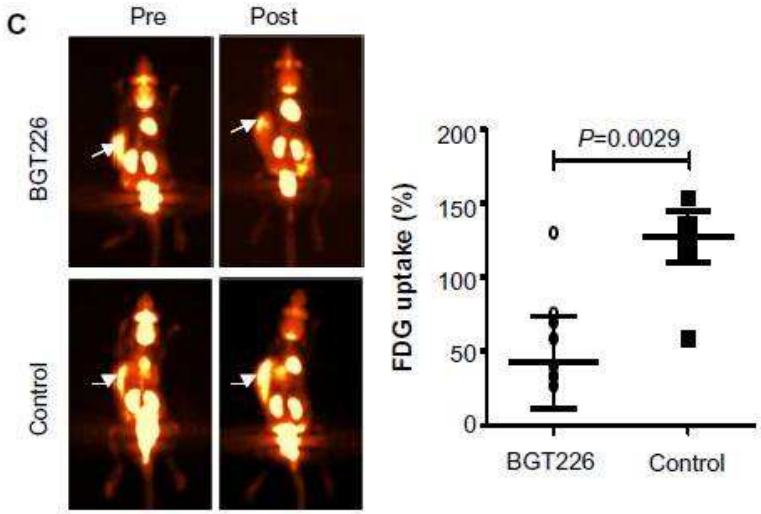


Ciunci et al. Cancer 2014


B
Pre
Post
AUY922
Control
P = 0.03
P = 0.15
FDG uptake (%)
300
200
100
0
Post
Pre
Control


C
Pre
Post
AUY922
Control
P = 0.01
P = 0.001
FLT uptake (%)
300
200
100
0
Post
Pre
Control


B
Pre
Post
BGT226
Control
P=0.0007
FLT uptake (%)
250
200
150
100
50
0
BGT226
Control


C
Pre
Post
BGT226
Control
P=0.0029
FDG uptake (%)
200
150
100
50
0
BGT226
Control