RAS/AKT pathway mutations as predictive biomarkers in patients with colorectal cancer treated with the exportin 1 (XPO1) inhibitor selinexor (SEL) – inhibition of nuclear-cytoplasmic translocation of p27 as a mechanism of anti-tumour activity

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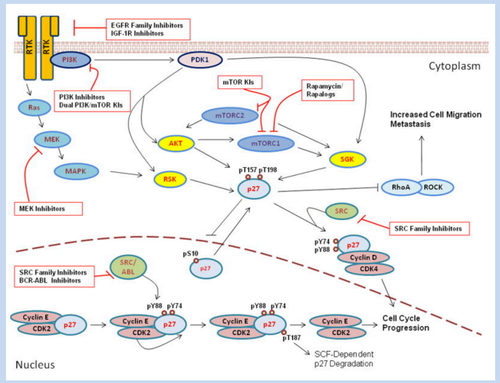
Background

Localization of p27 within a cell determines its function. Cytoplasmic sequestration of p27 promotes oncogenic activity while its nuclear retention inhibits tumorigenesis. RAS activation in tumours indirectly causes cytoplasmic sequestration of p27 via the activation of its effectors PI3K/AKT and Raf1/MEK/ERK pathway. Selinexor is a potent XPO1inhibitor that forces nuclear retention of multiple proteins including p27 resulting in tumour cell death.

Figure 1: Mechanism of action of selinexor



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Aims

To assess the predictive value of RAS and PIK3CA/AKT/mTOR pathway mutations in tumours following treatment with selinexor

Methods

Selinexor was administered orally to patients with advanced solid cancers. The phase 1 dose escalation study was initiated in a 3 + 3 design on:

Schedule 1
- Twice weekly continuous 28 day cycle at 40mg/m^2

Schedule 2
- Once weekly continuous every 28 days, starting at 50mg/m^2

Schedule 3
- Twice weekly for 2 weeks of a 21 day cycle, starting at 40mg/m^2

Schedule 4
- Three times a week continuous every 28 days, starting at 20mg/m^2

Patients were screened for ~2,800 COSMIC mutations in 50 cancer genes which included members of the RAS and PIK3CA/AKT/mTOR pathway using the Ion AmpliSeq^{TM} Cancer Hotspot Panel v2

Tumour PD:
Nuclear-cytoplasmic localisation of p27 in RAS and/ or AKT pathway activated tumours from tumour biopsies pre and post selinexor were determined together with other XPO1 cargo proteins including ki67, apoptag, cleaved caspase 3, and c-myc using immunohistochemistry.

Results

Table 1. Patient demographic

Characteristic	N = 22
Median age (range)	62.5 (56 – 79)
Male /Female	15 / 7
Median prior lines of treatment (range)	3.5 (2 – 9)
ECOG performance status, 0/1	11 / 11
Colon / rectal carcinoma	19 / 3
RAS mutation(KRAS/ NRAS/ BRAF)	11 /1 /1
RAS WT	9
PI3K/ AKT pathway (PIK3CA/ AKT/PTEN loss)	2 /1 /1

Figure 2: Mutation status of patient tumours

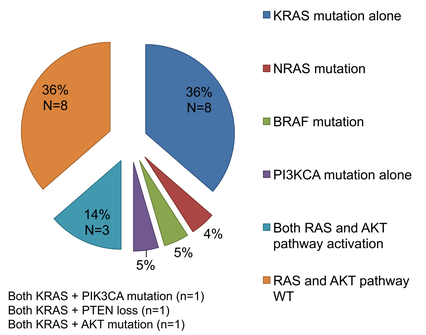


Table 2: Mutations detected in RAS and PIK3CA/AKT/mTOR pathway

Patient	Mutation identified	Patient	Mutation identified
KPT002	KRAS_G12V	KPT040	KRAS_G12D
KPT006	KRAS_G12D	KPT043	NRAS_G12V
KPT011	KRAS_G12V	KPT045	KRAS_G12V
KPT018	PIK3CA_C420R	KPT047	braf V600E
KPT022	KRAS_G13D PTEN_Y177D	KPT057	KRAS_G12D
KPT037	AKT1 G37D		

Clinical activity: best response and duration on study

Figure 3: Percentage change in size of target lesion from baseline at best response (n=19 evaluable patients)

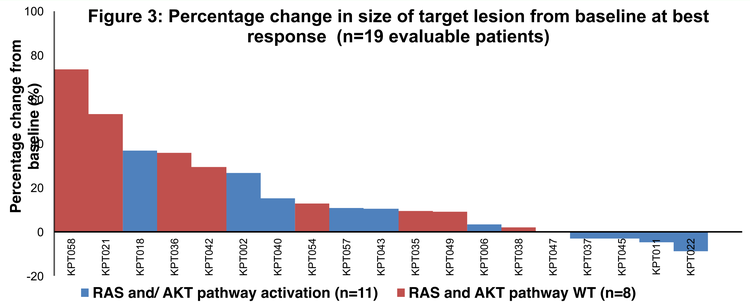


Figure 4: Tumor response for patients with colorectal cancer according to RAS and/ PI3K/ AKT pathway mutation (n=19)

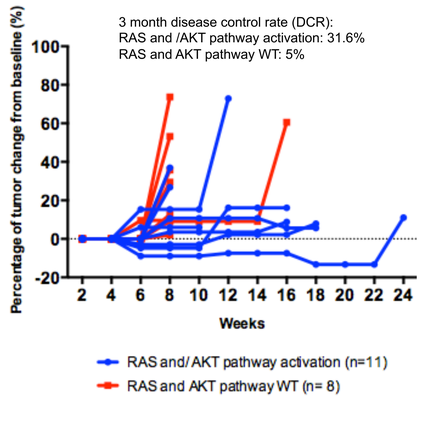


Figure 5: Duration on study according to RAS and/ PI3K/ AKT pathway mutation (n=19)

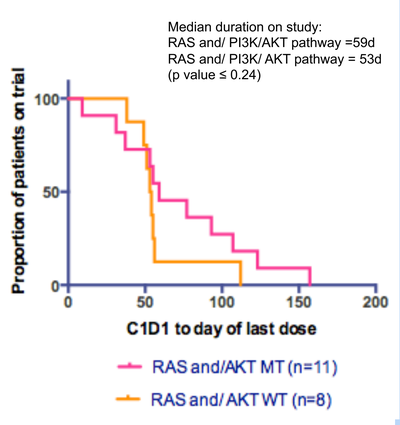
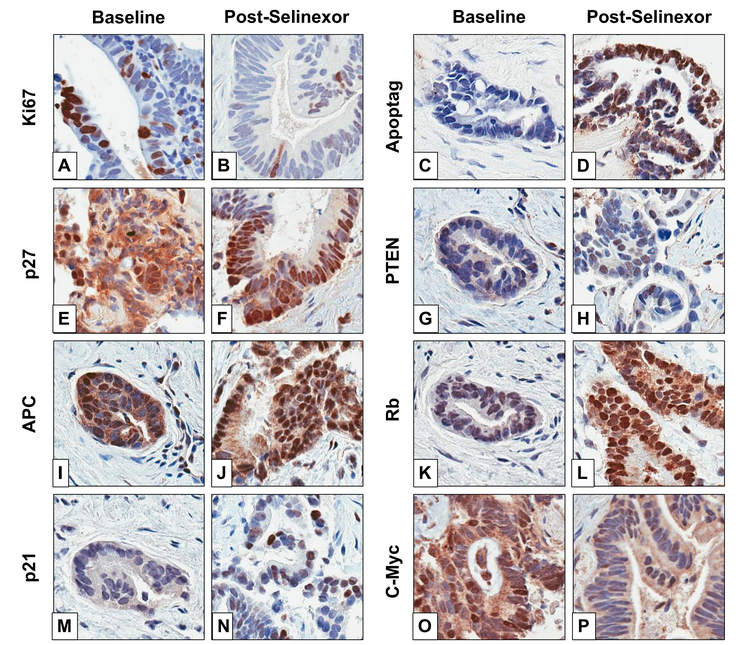


Figure 6: Increased nuclear retention of p27 and other XPO1 cargos, induction of apoptosis and reduction in proliferation in patients with KRAS mutant colorectal cancer pre and post selinexor treatment



Immunohistochemistry analysis of CRC patient biopsy samples collected at baseline and after treatment with selinexor. Note:
1. Decreased proliferation (Ki67, A and B), and increased apoptosis (Apoptag, C and D) after treatment
2. Decreased cytoplasmic and increased nuclear staining of p27 after treatment (E and F)
3. Increased nuclear staining of tumor suppressor proteins (PTEN, G and H; APC, I and J; Rb, K and L; and p21, M and N) after treatment
4. Decreased expression of the oncoprotein c-Myc after treatment (O and P).

(Panels A, B, E, F, O, and P from patient 1(KRAS mutant CRC), and panels C, D, G to N from patient 2 (AKT and KRAS mutant CRC).

Conclusion

- RAS and AKT pathway activated CRC appear to have a longer DCR with an increased number of patients achieving DCR of >3 months compared to WT tumours.
- Cytoplasmic translocation of p27 could be a key oncogenic mechanism in RAS and/or AKT pathway activated tumours and can be targeted by inhibition of XPO1
- Dose expansion cohort ongoing in patients with RAS and PIK3CA/AKT/mTOR pathway mutations in colorectal cancer as well as other solid malignancies (NCT02078349)

References

[1]Tan et al, Cancer Discov; 4(5); 527–37, 2014; [2] Serres MP et al, Oncogene; 30; 2846 – 2858, 2011 [3]Clin Cancer Res; 17(1); 12–8. ©2010 AACR

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