SELECTED OPPORTUNITIES IN ONCOLOGY

SLITRK6 as a target for cancers associated with activation of the MAPK pathway (e.g. Melanoma)(BIO17032)

Product factsheet

Preclinical

- **Target: SLITRK6**

- **Application:** inhibition of tumor cell resistance during MAPK pathway inhibitor treatment.

- **POC**:

- MAPK pathway inhibition activates a c-Jun/RhoB/AKT pathway that promotes tumor cell survival and further supports a role of this pathway in the resistance of melanoma to vemurafenib.

- Activation of c-Jun under MAPK pathway inhibition in BRAF-mutant melanoma cells induces the expression of SLITRK6 at the cell surface (SLITRK6 is poorly expressed by other tissues in normal conditions)

- The ASG-antibody against SLITRK6 binds its target specifically at the membrane only after MAPKi treatment

- The ASG -antibody against SLITRK6 internalizes its target specifically only after MAPKi treatment

- MMAE-ASG-conjugated antibody against SLITRK6 sensitizes cells to PLX4032

- ASG-15ME (an ADC antibody against SLITRK6) inhibits the growth of resistant melanoma in PDX models

- **Potential Product** : antibody drug conjugate (such as ASG-15ME) against SLItRK6

- ASG-15ME is currently in development by Astellas/Seattle Genetics NCT01963052:

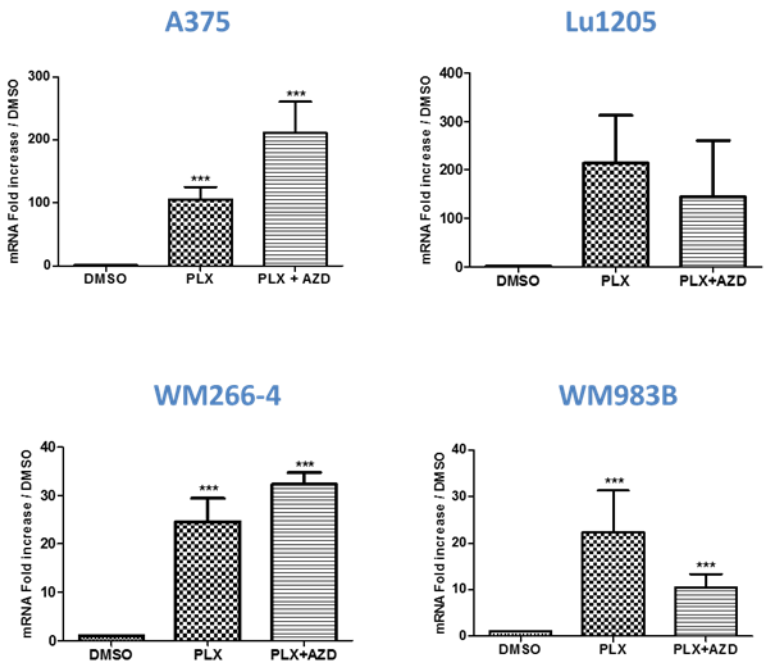
The clinical data from the phase I presented at ASCO in heavily pretreated metastatic bladder cancer patients show a manageable safety profile along with objective response rates that are higher than historical rates seen with taxanes," said Jonathan Drachman, M.D., chief medical officer and executive vice president, Research and Development at Seattle Genetics. "We will continue enrolling patients in the ongoing phase I clinical trials to determine the recommended dose for further development."

- **Patent Applications** : EP17305153.3 (10 February 2017)

Proof of concept

Preclinical

SLITRK6 mRNA expression is induced under MAPK inhibitor treatment in BRAF-mutant melanoma cells.

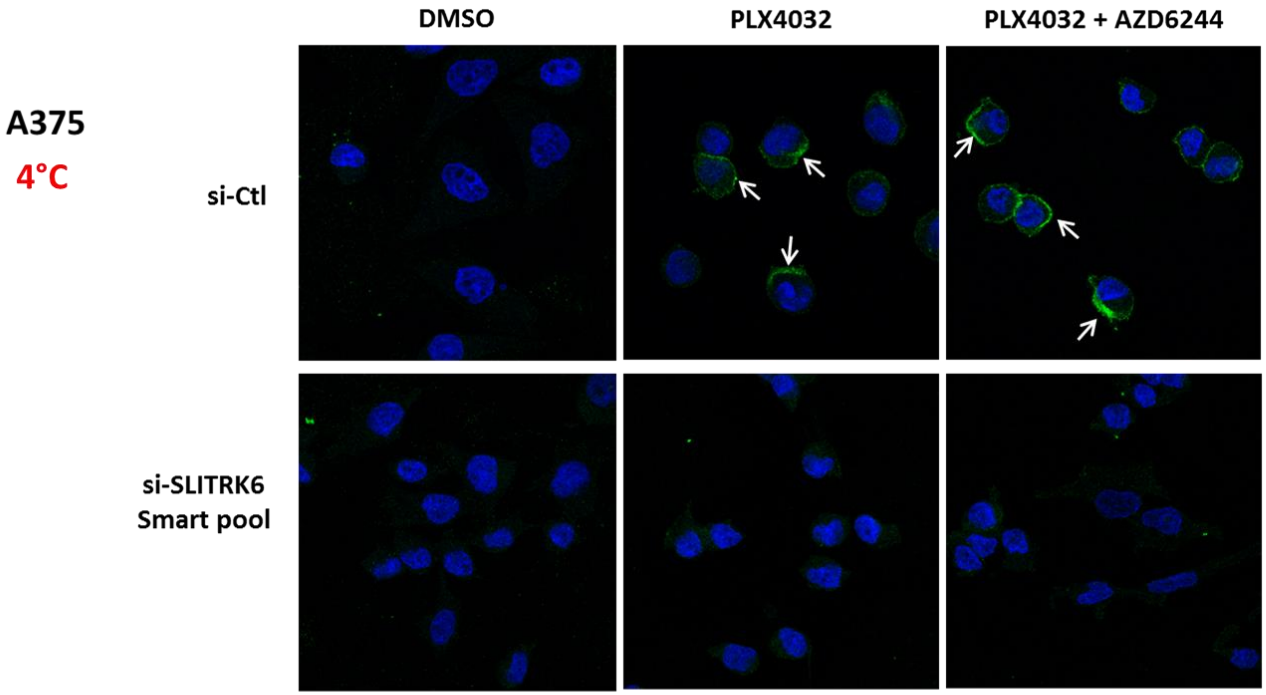


A375, Lu1205, WM266-4 and WM983B cell lines were treated with a BRAF inhibitor (PLX4032) at 1 µM alone or in combination with a 0.1 µM MEK inhibitor (AZD6244). mRNA fold increase relative to the DMSO control is determined by Q-PCR. The results are presented as the mean ± SD of the average of 3 independent experiments. *** p <0.001; T-test.

Proof of concept

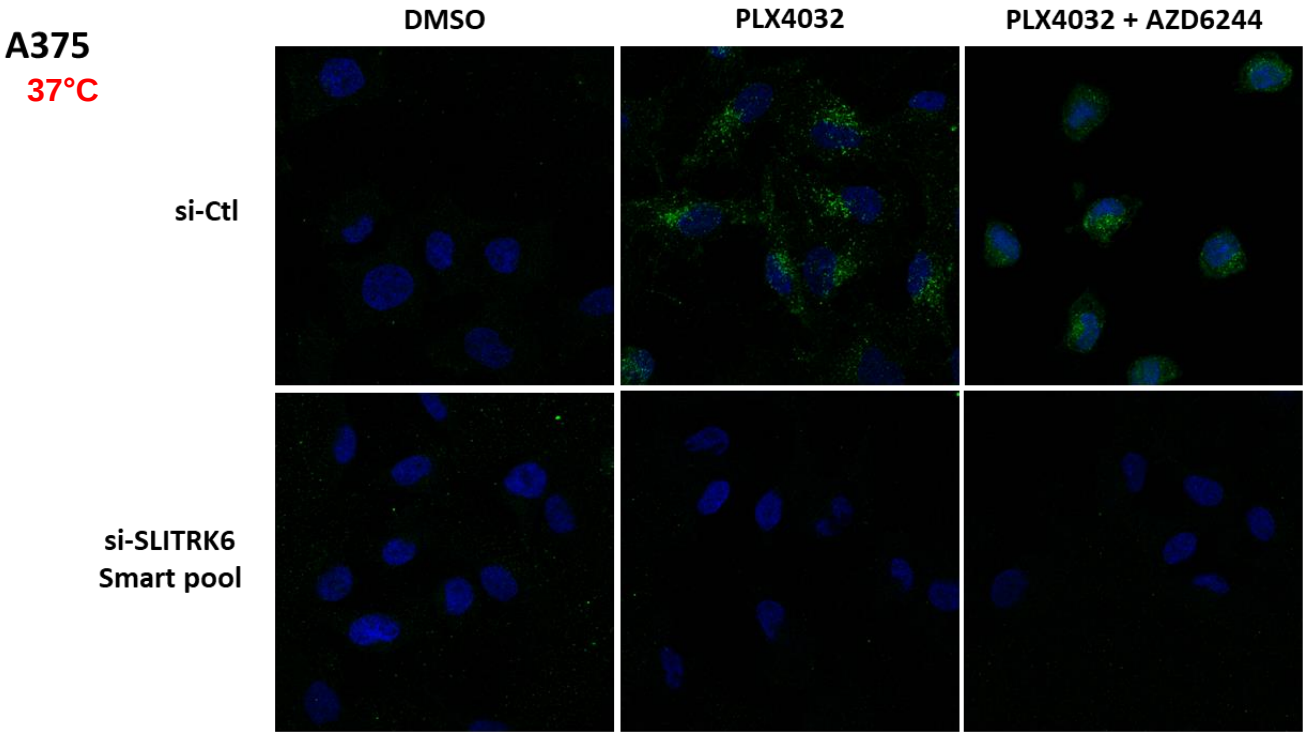
Preclinical

The ASG-antibody against SLITRK6 binds its target specifically at the membrane only after MAPKi treatment



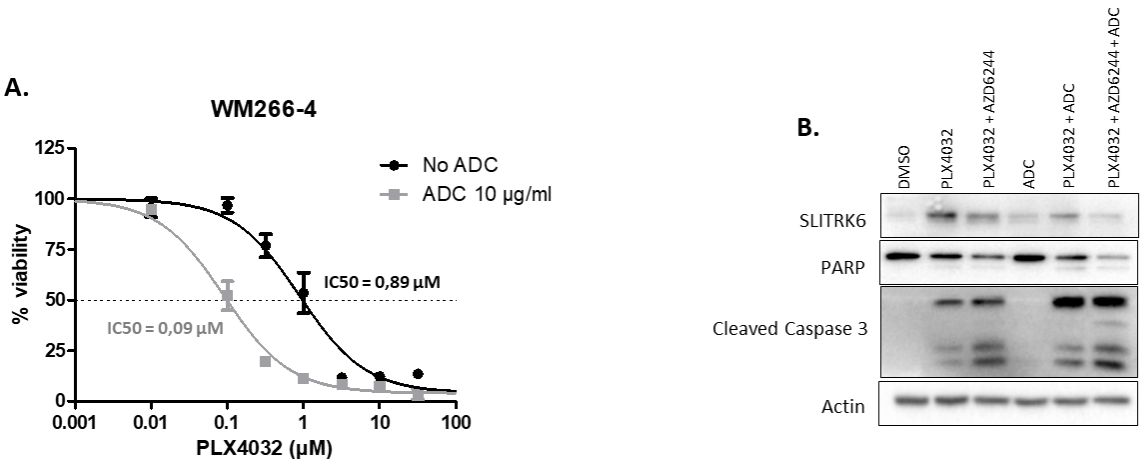
A375 cells were transfected with siRNA control (si-Ctl) or targeting SLITRK6 (si-SLITRK6) before treatment with PLX4032 (1 µM) alone or in combination with AZD6244 (0,1 µM) for 48h. Cells were then stained for SLITRK6 (green) and DNA was counterstained with DAPI (blue). These results are representative of 3 independent experiments.

The ASG -antibody against SLITRK6 internalizes its target specifically only after MAPKi treatment



A375 cells were transfected with siRNA control (si-Ctl) or targeting SLITRK6 (si-SLITRK6) before treatment with PLX4032 (1 µM) alone or in combination with AZD6244 (0,1 µM) for 48h. Cells were then stained for SLITRK6 (green) and DNA was counterstained with DAPI (blue). These results are representative of 3 independent experiments.

MMAE-ASG-conjugated antibody against SLITRK6 sensitizes cells to PLX4032



A. WM266-4 cells were treated for 72h with PLX4032 alone or in combination with antibody drug-conjugated against SLITRK6 (ADC) at 10 µg/mL. Cell viability was measured by MTS and the dose-response was analyzed. Data shown are the means ± standard deviation of triplicates of 1 experiment.

B. WM266-4 cells were treated for 48h with PLX4032 at 1µM alone or in combination with antibody drug-conjugated against SLITRK6 (ADC) at 10 µg/mL or in combination with AZD6244 at 0,1 µM. Cleaved caspase-3 and cleaved PARP were analyzed by Western blotting. Expression of SLITRK6 was analyzed in parallel. Actin was the loading control.

No effect of this antibody was observed on non-PLX4032 treated WM266-4 cells

ANNE.COCHI@INSERM-TRANSFERT.FR