Novel ROS1 mutations reveal a predictive mutational model for TKI sensitivity

In tumors with tumor-specific genetic alterations (i.e. 20-40% lung cancers), cancer cells are highly dependent on the function of a single oncogene, defined as ‘driver oncogene’ for their proliferation and survival. Many oncogene alterations have been identified in cancer – including ALK (Anaplastic Lymphoma Kinase), FGFR1-4 (Fibroblast Growth Factor Receptor), EGFR (Epidermal Growth Factor), BRAF, ROS1 and HER2 (Erb-B2 Receptor Tyrosine Kinase 2).

Cancer treatment options have therefore been enriched by a ‘targeted therapy’ based on individual tumor biology. This novel therapeutic approach often increases the median survival in metastatic cancers. Unfortunately, most tumors are capable of adapting to the treatment thereby limiting the clinical benefit of these new targeted therapies.

	Sensitivity in a ROS1 positive patient			
Theoretical ROS1 mutations	crizotinib	ceritinib	lorlatinib	ALK mutations
1981Tins				1151Tins
L1982F/R				L1152R
S1986Y/F				C1156Y
M2001T				I1171N/S/T
F2004C/V				F1174C/V
L2026M				L1196M
G2032R				G1202R
D2033N				D1203N
G2101A				G1269A

detected in patients	sensitive	resistant
	validated	predicted

Fig. 1. Predictive model for drug sensitivity of ROS1 mutations.

Here we studied the case of a 63 year-old male never-smoker diagnosed with stage IV NSCLC

(non small cell lung cancer) adenocarcinoma with diffuse lymph node and pleural involvement. This patient harbored an *ezrin* (*EZR*)-*ROS1* fusion gene. The first generation ALK/ROS1 kinase inhibitor, crizotinib, allowed disease control and excellent clinical tolerability over 22 months of treatment. At relapse, a biopsy was performed in order to elucidate the mechanism of acquired resistance to crizotinib. Sequencing of the tumor revealed the presence of novel S1986Y and S1986F mutations.

In vitro functional studies were undertaken to investigate the potency of next generation ALK/ROS1 TKIs on those mutations and held a decisive influence on therapeutic strategies. Using Ba/F3 cells expressing native or mutated *EZR-ROS1*, we functionally demonstrated that S1986F/Y substitutions confer crizotinib and ceritinib resistance. However, the third generation ALK/ROS1 inhibitor lorlatinib, more potent against WT ROS1 maintained strong growth inhibition of $ROS1^{S1986F/Y}$ mutated cells. The patient's clinical response confirmed the potency of lorlatinib against S1986Y/F mutations and the disease remains controlled without any signs of progression after 13 months of therapy.

Modeling theoretical sensitivity of ROS1 patients according to their mutational status can provide therapeutic guidance and generate significant clinical benefits by avoiding worthless treatments in the presence of novel resistance mutations. Therefore, we took advantage of the structural homology of ROS1 and ALK to build a predictive model for drug sensitivity to most relevant ALK/ROS1 inhibitors regarding ROS1 mutations expected to emerge in the clinic (Fig. 1).

This work supports three main concepts:

1) It emphasizes the invaluable contribution of molecular analyses on tumor specimens at different moments of disease evolution.

2) It illustrates how preclinical studies can provide therapeutic decisions guidance.

3) It provides a mutational model which would generate significant clinical benefits and avoid worthless treatments when novel ROS1 resistance mutations appear.

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Publication

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