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STX-478, a mutant-selective PI3Kα inhibitor clinical candidate with a best-in-class profile: Pharmacology and therapeutic activity as monotherapy and in combination in breast cancer xenograft models

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Introduction

Selective targeting of mutant PI3Kα is expected to improve anti-tumor activity and reduce toxicities associated with inhibiting the wild-type enzyme in normal tissues, which are frequently observed with alpelisib[1], the only approved drug for this target.

STX-478 is a CNS-penetrant, mutant-selective, allosteric PI3Kα inhibitor with excellent drug-like properties and exceptional kinome selectivity.[2] STX-478 demonstrated minimal risk of drug-drug interactions in vitro, supporting the potential for combinations with a wide range of therapeutics and explored here in cellular assays and xenograft studies.

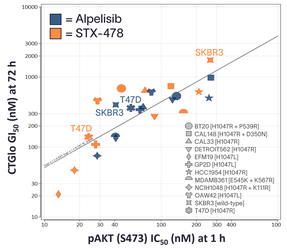
PIK3CA kinase domain mutations were the strongest predictor of STX-478 sensitivity in a high throughput cell viability screen. In this study, STX-478 also selectively inhibited the proliferation of cell lines containing PI3Kα helical domain mutations. In xenograft models STX-478 treatment yielded tumor growth inhibition of both kinase and helical domain mutant tumors at doses that did not cause metabolic dysfunction.

STX-478 has the potential to provide a best-in-class treatment to improve outcomes in patients harboring prevalent PI3Kα kinase domain mutant cancers as well as for the treatment of helical domain mutant tumors. STX-478 is expected to enter human clinical trials in 2023.

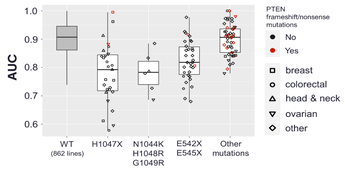
Results

STX-478 is a potent, highly-selective mutant PI3kα inhibitor in cellular assays

Correlation between target engagement and cell viability

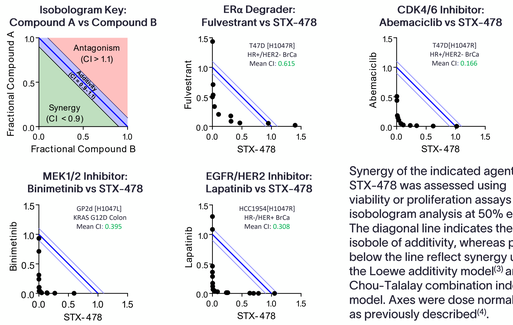


STX-478 demonstrated selective growth inhibition of kinase and helical domain mutant cell lines in vitro



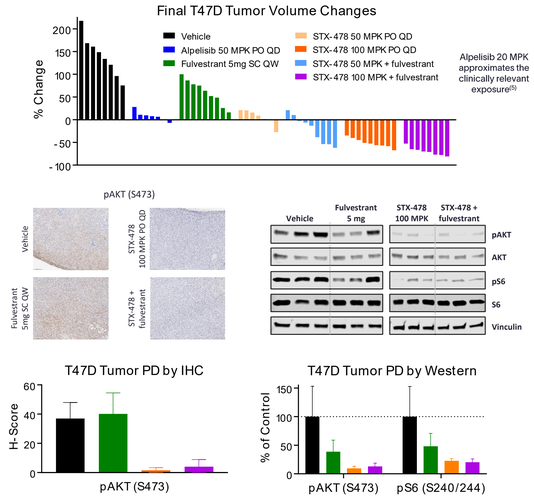
Mutant selectivity is observed when comparing STX-478 in mutant vs wild type cells. The graph correlates cellular target engagement and viability (left). STX-478 was profiled in the PRISM screen (https://theprismlab.org) with ~900 cell lines from multiple lineages as indicated in the legend (right). Cell line sensitivities were separated by PIK3CA mutations and colored by PTEN status as indicated. The results indicate STX-478 selectively inhibited viability in cell lines with mutations in the PIK3CA kinase domain and helical domain.

Combinatorial synergy between STX-478 and relevant co-treatments in vitro



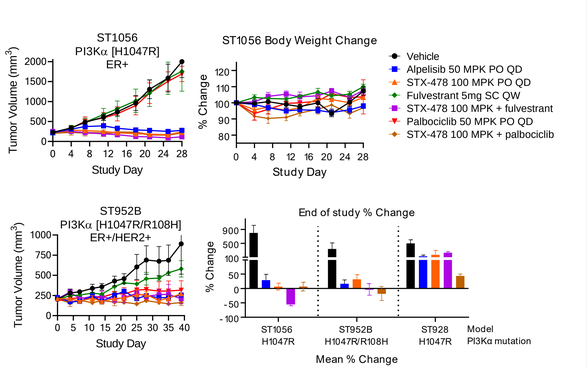
Synergy of the indicated agents with STX-478 was assessed using viability or proliferation assays and isobologram analysis at 50% effect. The diagonal line indicates the isobole of additivity, whereas points below the line reflect synergy using the Loewe additivity model[3] and the Chou-Talalay combination index (CI) model. Axes were dose normalized as previously described[4].

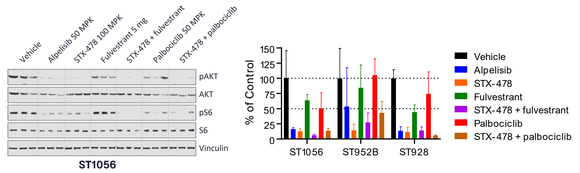
Efficacy of STX-478 in combination with fulvestrant in T47D xenograft tumors



T47D human tumor cells and 17-β-estradiol tablets were implanted SC in NSG mice. Treatment was initiated when tumors were ~180mm³ for 21 days (Top). Single-dose PK/PD were performed in tumors collected 4 hrs post 100mg/kg STX-478 and 24 hrs after 5mg fulvestrant. pAKT was measured by IHC (left) and pAKT and pS6 were measured by quantitative western blot (right).

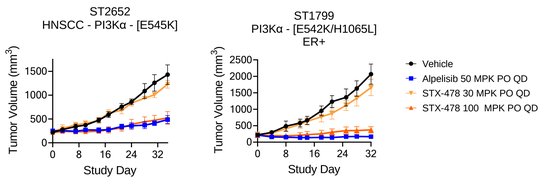
STX-478 was efficacious and well tolerated in combination with fulvestrant or palbociclib in PI3Kα mutant ER+ breast cancer PDX models





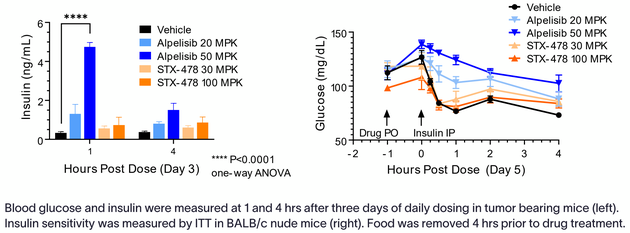
The indicated ER+ breast cancer models were implanted as tumor fragments SC in BALB/c nude mice given 17-β-estradiol in water (n=3/group). Treatment was initiated when tumors reached ~200-250mm³. At the end of the study, tumors were collected 4 hrs post STX-478/palbociclib and 24 hrs after fulvestrant. Tumor lysate proteins were analyzed by western blot for pAKT (S473), pS6 (S235/236), total S6, and total AKT (bottom left); and pAKT levels quantified (bottom right).

Growth inhibition of helical domain mutant PDX tumors by STX-478



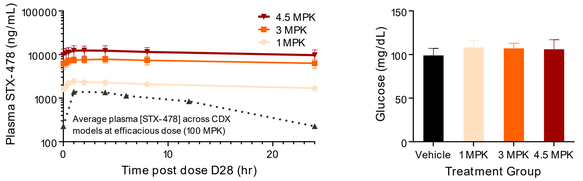
The indicated PDX models were implanted as fragments subcutaneously in BALB/c nude mice. Mice implanted with the ST1799 model were supplemented with 17-β-estradiol in water. Treatment was initiated when tumors reached ~200-250mm³.

STX-478 did not cause metabolic dysfunction in rodents at efficacious doses



Blood glucose and insulin were measured at 1 and 4 hrs after three days of daily dosing in tumor bearing mice (left). Insulin sensitivity was measured by ITT in BALB/c nude mice (right). Food was removed 4 hrs prior to drug treatment.

Chronic dosing of STX-478 (QD*28 d) did not cause hyperglycemia in dogs



4.5 MPK represents approximately 30-fold coverage over the mouse efficacious exposure (24 hr AUC), derived from CDX models (left). Blood glucose was measured on day 29 following once-daily dosing of STX-478 for 28 days; no statistically significant change observed at any dose (n=10) (right). STX-478 was well tolerated at all doses.

Conclusions

- **STX-478 showed robust synergy with current standard-of-care agents**
  - Deep tumor regression as monotherapy and with fulvestrant in the T47D CDX model
  - In ER+ BrCa PDX models, STX-478 was well tolerated and highly efficacious alone and in combination with fulvestrant or palbociclib
- **STX-478 exhibited significant activity against helical domain mutations**
  - STX-478 selectively inhibits cell viability of both kinase and helical domain mutant cell lines
  - In PDX models with helical domain mutations, STX-478 inhibited tumor cell growth and was efficacious at doses that did not cause metabolic dysfunction
- **STX-478 displayed strong efficacy without metabolic dysfunction**
  - STX-478 did not alter insulin or glucose levels in mice at efficacious doses
  - No hyperglycemia observed in dog at 30x margin over efficacious mouse exposure
- **STX-478 is a potential best-in-class, CNS-penetrant, mutant-selective allosteric inhibitor of PI3Kα expected to enter Ph1 clinical studies in 2023**
  - Long half-life, minimal peak-to-trough plasma concentrations, and low efficacious dose predicted in humans
  - STX-478 has the potential to improve outcomes in patients harboring both kinase and helical domain mutations

References

1) Andre 2019, NEJM , 380, 1929-40
2) Buckbinder 2022, Cancer Research, 82 (12_Supplement): LB194
3) Loewe and Muischnek 1926, Arch. Exp. Pathol. Pharmakol. 114: 313-326
4) Chou 1991, Pharmacological Reviews 58, 621-681
5) NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212526} Document {Piqray, Alpelisib}