BARCELONA 2024 ESMO congress

First-in-human results of STX-478, a mutant-selective PI3Kα inhibitor, in advanced solid tumor patients

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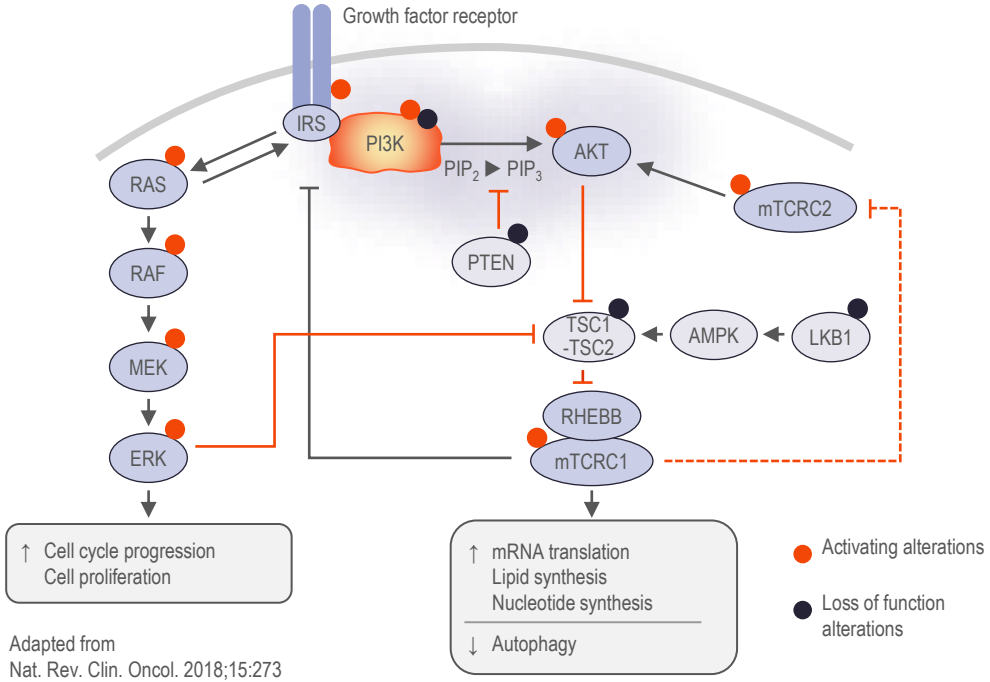
Declaration of Interests

Alberto J. Montero, M.D.

Honoraria: Gilead, AstraZeneca, OncoSec, Scorpion Therapeutics
Consulting or Advisory Role: Welwaze, Paragon Healthcare

The PI3K Pathway is Commonly Mutated in Cancer

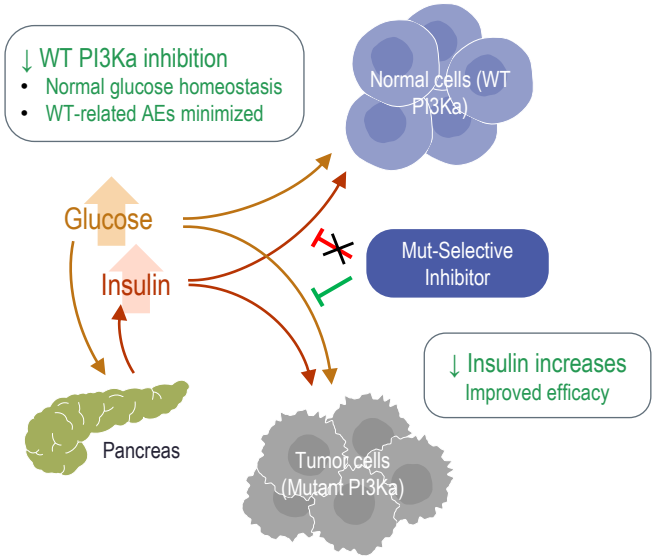


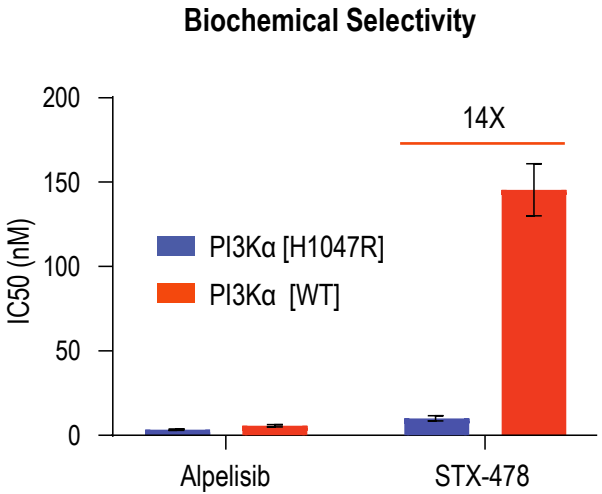
Adapted from
Nat. Rev. Clin. Oncol. 2018;15:273

- PI3K pathway alterations are a major driver in cancer
- PI3Kα is mutated in 36% of breast cancers and 12.7% of all cancers[1]

[1]MyCancerGenome.org 08/2024

STX-478 is an Oral, Allosteric, Mutant Selective PI3Kα Inhibitor



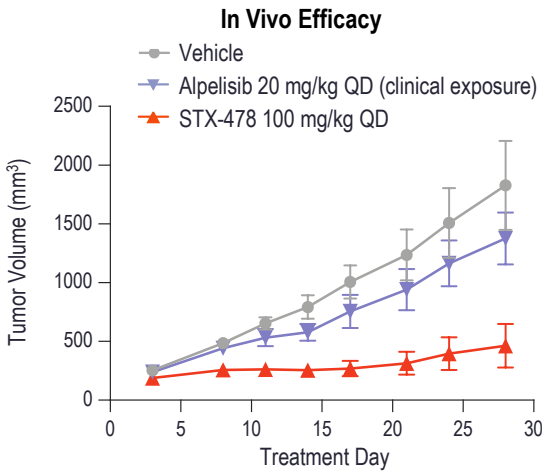


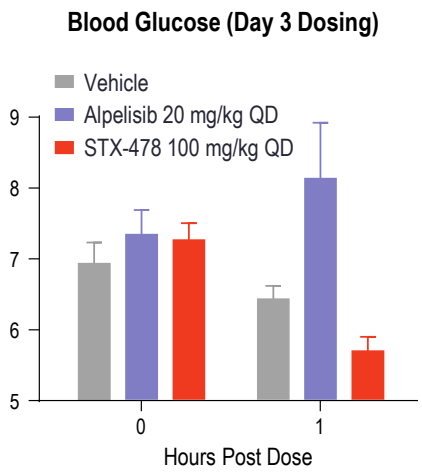
- STX-478 is an allosteric, mutant-selective inhibitor that selectively targets mutant PI3Kα and minimizes wildtype toxicities
- STX-478 is an oral, once-daily, low dose, CNS-penetrant molecule

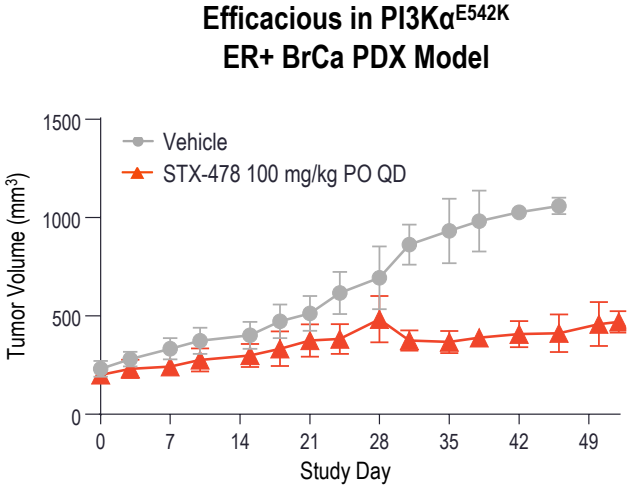
WT: wildtype

STX-478 is Metabolically Safe and Efficacious in PI3Kα Kinase and Helical Domain Mutant Tumors

Improved Efficacy & Selectivity vs Clinically-Relevant Dose Alpelisib in PI3Kα^{H1047R} Cal33 HNSCC CDX



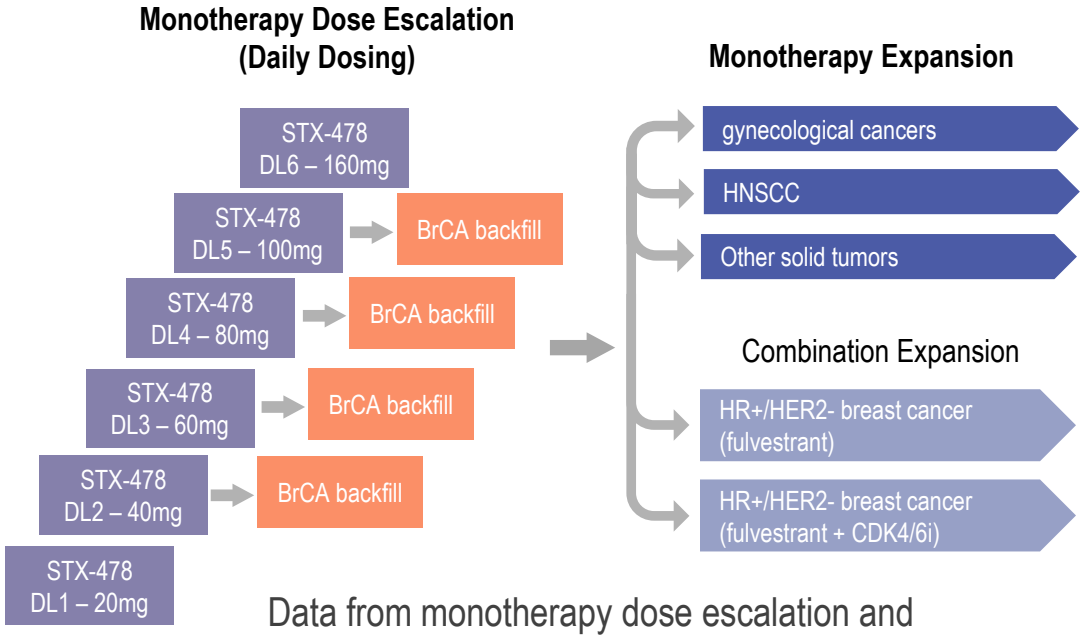




STX-478 demonstrated in vivo efficacy and safety in preclinical models superior to clinically-relevant doses of alpelisib, a non-mutant selective PI3Kα inhibitor

[1] Buckbinder, St. Jean, et al., 2023, BrCA: breast cancer, HNSCC: head and neck squamous cell carcinoma

First-in-Human Phase 1 Trial Design of STX-478 in Advanced Solid Tumors



Data from monotherapy dose escalation and initial monotherapy expansion are presented

Key Eligibility Criteria

- PIK3CA helical and kinase domain mutant advanced solid tumors who received prior SOC[1]
- ECOG 0-1
- Adequate organ function
- Fasting plasma glucose < 140 mg/dL and HbA1c < 7.0%
- Type 2 diabetics controlled on medications permitted
- Prior PI3K/AKT/mTOR inhibitor therapy permitted if stopped due to intolerance

Key Endpoints

- Safety and tolerability
- PK, PD, RP2D
- Anti-tumor activity assessed by ORR by RECIST v1.1, DOR, PFS, OS
- Patient reported outcomes via EORTC QLQ-C30 score

Data as of 21 June 2024

BrCA: breast cancer, DL: dose level, DOR: duration of response, HNSCC: head and neck squamous cell carcinoma, HR: hormone receptor, ORR: objective response rate, OS: overall survival, PD: pharmacodynamics, PFS: progression-free survival, PK: pharmacokinetics, RP2D: recommended Phase 2 dose, SOC: standard of care, [1]monotherapy cohorts

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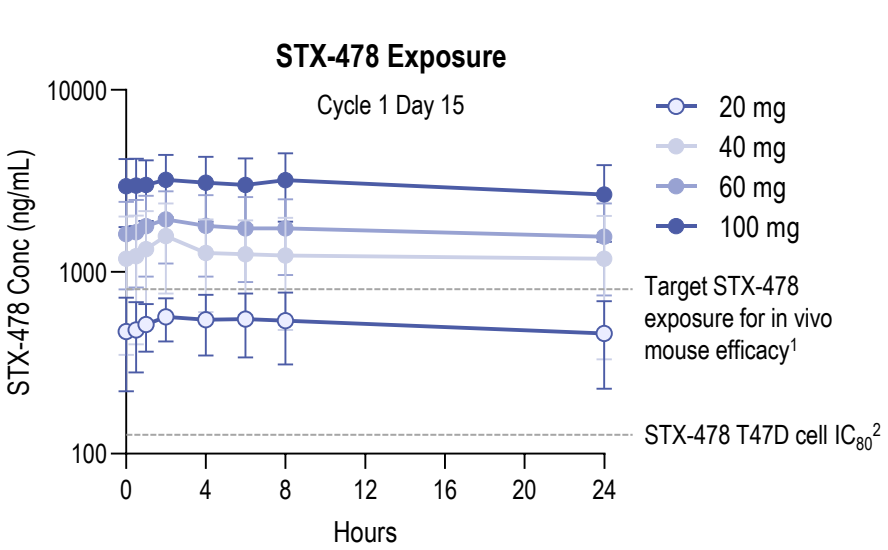
Patient Demographics and Baseline Characteristics

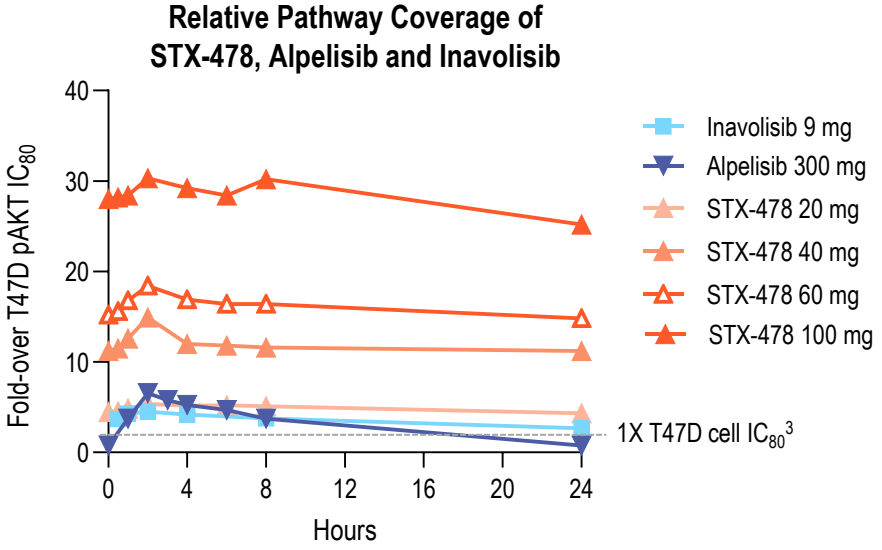
	All Tumors[1] (n=61)	HR+/HER2- Breast Cancer (n=29)	Other Solid Tumors (n=32)
Age, median (range), yr	64 (32–82)	64 (37 – 81)	65 (32 – 82)
Female, n (%)	50 (82)	29 (100)	21 (66)
Male, n (%)	11 (18)	0 (0)	11 (34)
ECOG, n (%)			
0	25 (41)	13 (45)	12 (38)
1	36 (59)	16 (55)	20 (63)
Glucose metabolism, n (%)			
Pre-diabetic	23 (38)	11 (38)	12 (38)
Type 2 Diabetic	10 (16)	4 (14)	6 (19)
PI3Kα-mutation, n (%)			
Kinase domain	33 (54)	17 (59)	16 (50)
Helical domain	22 (36)	8 (28)	14 (44)
Double mutant	5 (8)	3 (10)	2 (6)
Not available	1 (2)	1 (3)	0 (0)
Visceral disease (%)	46 (75)	25 (86)	21 (66)
Median prior metastatic therapies (range)	3 (1 – 7)	3 (1 – 7)	4 (1 – 7)
Prior CDK inhibitor, n (%)	28 (46)	28 (97)	0 (0)
Prior PI3Kα- or mTOR or AKT-inhibitor, n (%)	13 (21)	12 (41)	1 (3)

- Most common solid tumors enrolled include breast cancer (54%), endometrial cancer (11%), urothelial cancer (8%), HNSCC (5%), and CRC (5%)
- 54% of patients are prediabetic or have Type 2 diabetes, typically excluded from other PI3K inhibitor trials
- Patients are heavily pre-treated, including 41% of HR+/HER2- breast cancer patients receiving prior PI3K pathway inhibitors

[1] Data as of 21 June 2024, [2]definition based on HbA1c/fasting glucose levels, medical history and diabetic medication use
CRC: colorectal cancer, HR: hormone receptor, HNSCC: head and neck squamous cell

STX-478 Pharmacokinetic and Target Coverage Profile





- STX-478 exposure is dose proportional and linear, with an estimated half-life of around 60 hours
- At doses ≥ 40mg QD, STX-478 exceeded the average exposures needed for mouse in vivo efficacy
- STX-478 achieved target coverage significantly higher than other PI3K inhibitors at their RP2D

[1] Based on mouse efficacious exposure 100mg/kg in 3 CDX models
[2] Based on in vitro T47D (H1047R) pAkt assay
[3] Matched unbound pAkt suppression in head-to-head benchmarked in vitro assays

Summary of STX-478 Safety

Treatment-Related AEs (TRAEs), N=61 Patients

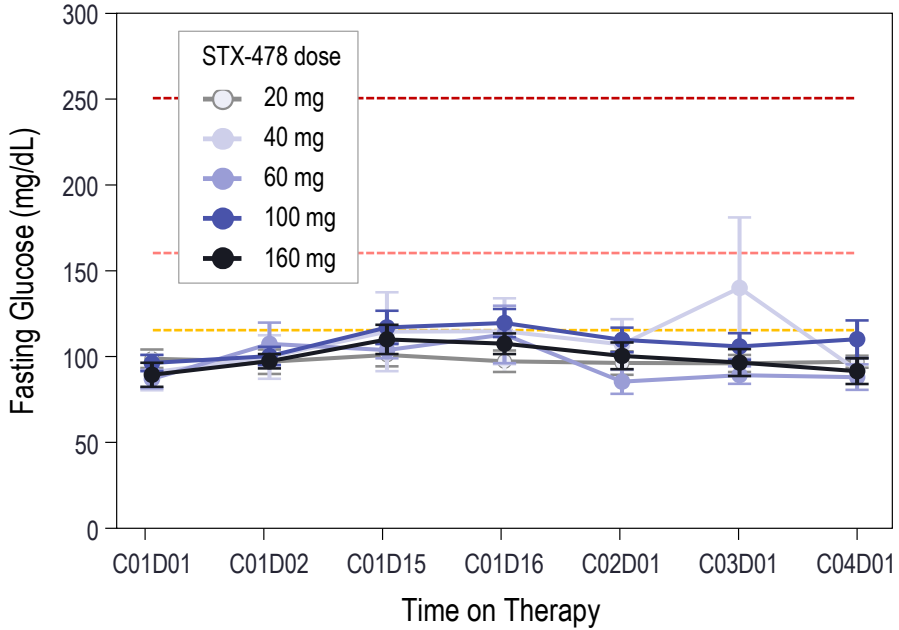
Adverse Event[1]	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
TRAEs occurring in ≥ 15%, n (%)					
Fatigue	5 (8)	8 (13)	5 (8)	0	18 (30)
Hyperglycemia	8 (13)	6 (10)	0	0	14 (23)
Nausea	11 (18)	1 (2)	0	0	12 (20)
Diarrhea	6 (10)	3 (5)	0	0	9 (15)
Other TRAEs of Interest, n (%)					
Rash[2]	5 (8)	1 (2)	0	0	6 (10)
AST/ALT increased[3]	2 (3)	0	5 (8)[4]	1 (2)[4]	8 (13)
Blood bilirubin increased	1 (2)	0	0	0	1 (2)
Neutropenia[5]	0	0	0	0	0
Anemia	1 (2)	0	0	0	1 (2)
Thrombocytopenia[6]	1 (2)	1 (2)	0	0	2 (3)
Creatinine increase	0	0	0	0	0
AEs leading to discontinuation	**0**	**0**	**0**	**0**	**0**

- STX-478 was well-tolerated with most toxicities mild/moderate and transient
- No Grade ≥ 3 PI3Kα wildtype toxicities (hyperglycemia, diarrhea and rash) seen
- MTD was reached at 100mg
  - 2 DLTs (Grade 3 myalgia and paresthesia) observed at 160mg and were transient, resolving rapidly after brief dose interruption
- AST/ALT elevations were asymptomatic, transient and reversible, with no Hy's Law criteria met
- No patient discontinued STX-478 due to an AE

No Grade 5 TRAEs were observed

[1]Per CTCAE v5.0, [2]includes all rash-related terms, [3]includes patients with either AST or ALT elevation, [4]one each occurred at 160mg dose, which exceeded the MTD of 100mg, [5]includes neutropenia and neutrophil count decreased, [6]includes thrombocytopenia and platelet count decreased

Impact of STX-478 on Fasting Glucose Levels



Alpelisib label management

Grade 3 (250-500 mg/dL)

Grade 2 (160-250 mg/dL)

Grade 1 (115-160 mg/dL)

Mean and standard error is shown

- Minimal changes in fasting glucose have been observed at all STX-478 dose levels
- No CTCAE v5.0 Grade 3 or higher hyperglycemia has been observed at any dose level

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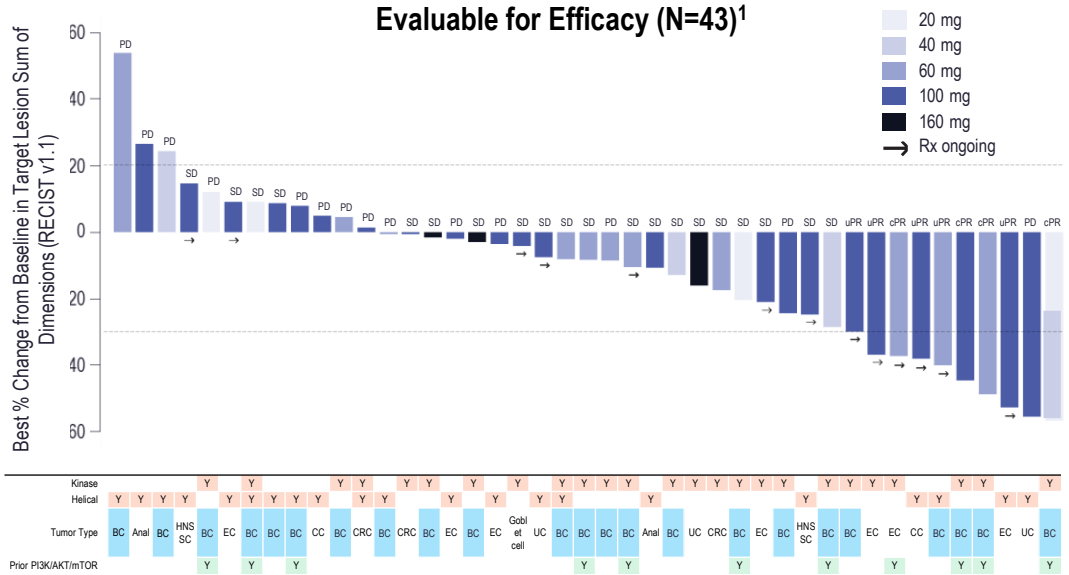
STX-478 Anti-Tumor Activity

Best overall response N (%)	All Tumors (n=43)	HR+/HER2- breast (n=22)	Gynecologic tumors (n=9)
ORR[2] (cPR + uPR)	**9 (21)**	**5 (23)**	**4 (44)**
DCR (CR+PR+SD)	29 (67)	15 (68)	6 (67)
cPR	4 (9)	3 (14)	1 (11)
uPR*	5 (12)	2 (9)	3 (33)
SD	20 (47)	10 (46)	2 (22)
PD	14 (33)	7 (32)	3 (33)

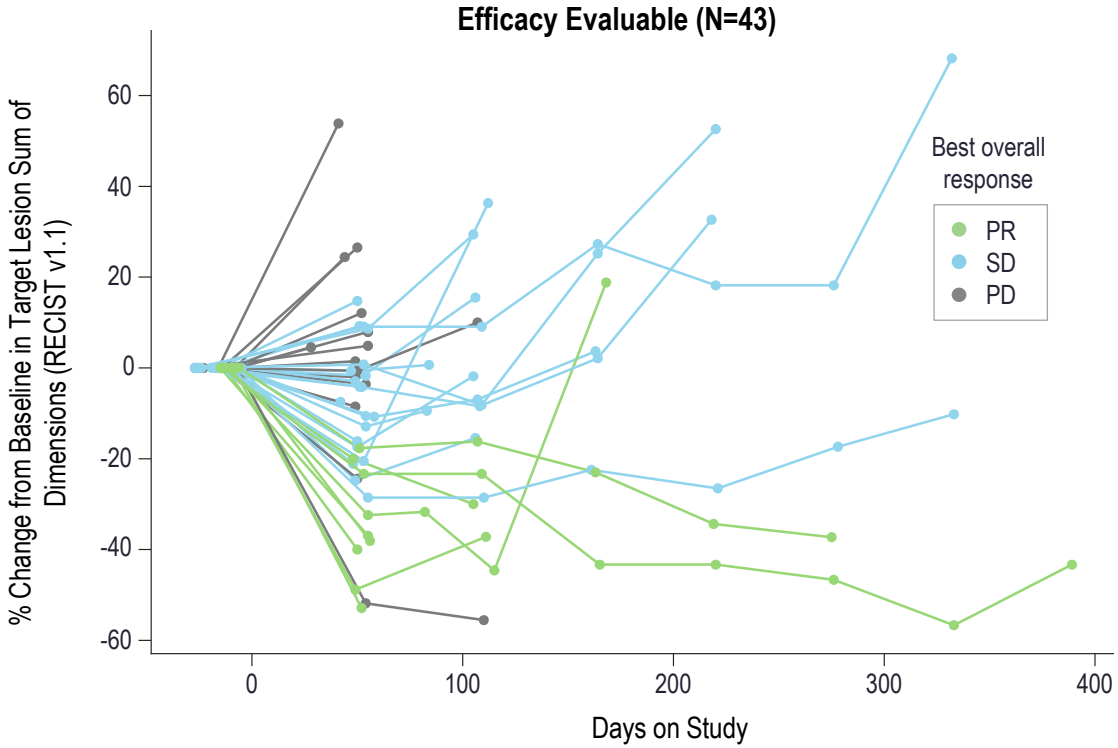
*All 5 patients with uPRs have converted to cPRs after the data cut



- STX-478 monotherapy ORR of 21 – 23% in all-comers and breast cancer, respectively, compares favorably to approved PI3K pathway inhibitors (monotherapy ORR 4 – 6%)[3,4]
- Multiple responses are seen in both PIK3CA kinase and helical domain mutations, in multiple solid tumors, at multiple STX-478 dose levels, and in patients receiving prior PI3K/AKT/mTOR inhibitors

[1] Efficacy evaluable and measurable disease patients shown, [2]includes unconfirmed and confirmed PRs, [3]Banerji et al., 2018, [4]Juric et al., 2018. BC: breast cancer, CC: cervical cancer, cPR: confirmed partial response, CRC: colorectal cancer, DCR: disease control rate, EC: endometrial cancer, HNSCC: head and neck cancer, UC: urothelial cancer, uPR: unconfirmed partial response

STX-478 Duration of Treatment and Response

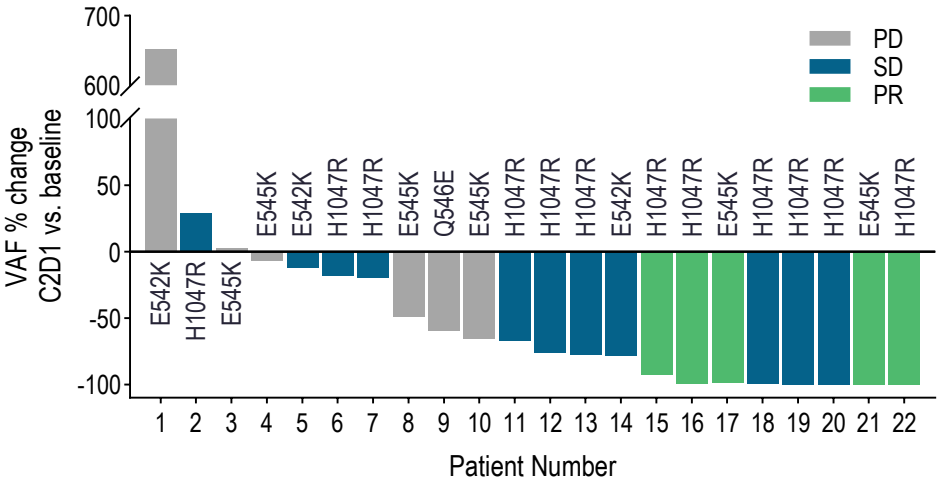


- Median duration of treatment for all enrolled patients is 1.9 months (range 0.03 – 13 months)
- Median time to response is 1.8 months (range 1.6 – 7.2)
- Multiple responding patients have deepened their responses over time on therapy
- Patient longest in PR has been on treatment >12 months

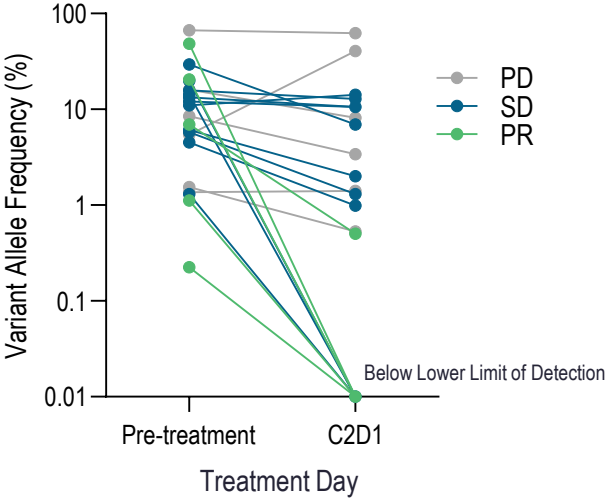
Median follow-up is 1.8 months (range 0.1 – 12.8 months)

PIK3CA Mutant Variant Allele Frequency and Correlation with Response

The Majority of Patients Assessed Have Decreases in PIK3CA ctDNA



Depth of ctDNA Decrease Correlates with Clinical Response[1]



Patients with available longitudinal ctDNA are included. Left: patients 13 and 15 have two PIK3CA mutations, only one represented

[1] Neogenomics Invision 37 gene liquid biopsy test (including PIK3CA) utilized

VAF: variant allele frequency

Case Report 1: Patient with PIK3CA Mutant Endometrial Cancer (Partial Response)

Patient History

- 71 year-old woman
- Metastatic endometrial cancer (uterine papillary serous carcinoma) with PI3Kα^{H1047R} kinase domain mutation

Prior Metastatic Treatment

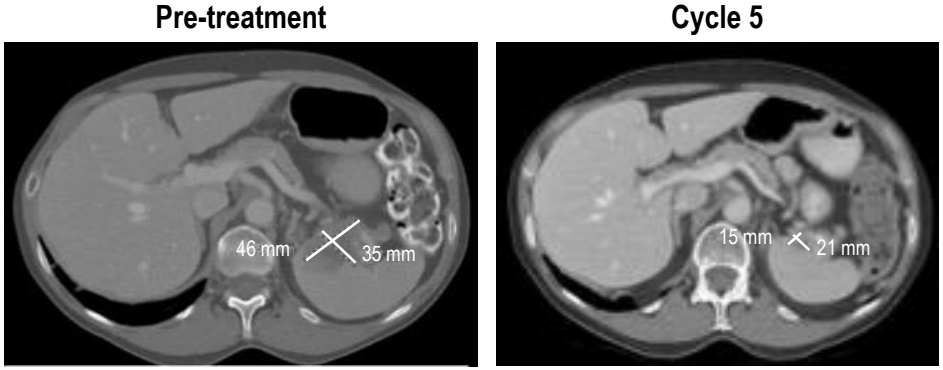
6 prior lines of therapy, refractory to last 3 prior lines

1. Carboplatin + paclitaxel
2. Liposomal doxorubicin
3. Gemcitabine + cisplatin
4. Docetaxel
5. Gemcitabine + cisplatin
6. CLN-418 (B7H4 x 4-1BB bi-specific)

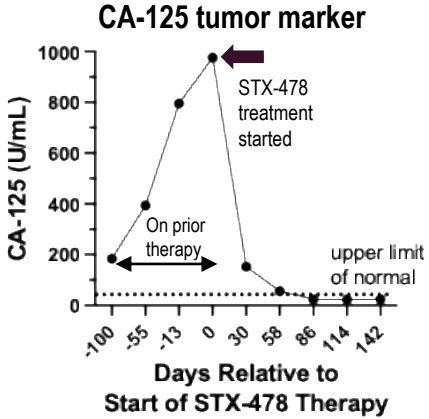
Best response: PD

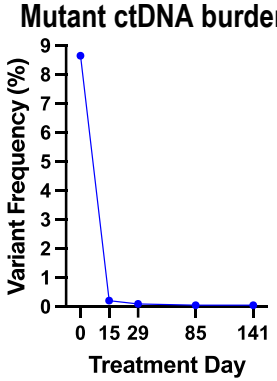
STX-478 Treatment and Response

- Treated with STX-478 at 100mg PO QD
- 97% decline in CA-125 tumor marker
- 99.4% decline in mutant allele burden
- uPR (37% reduction) at Cycle 3
- cPR (54% reduction) at Cycle 5, occurring after the data-cut



Target lesion





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Case Report 2: Significant Reduction in Tumor Lesions in a Patient with Head and Neck Squamous Cell Cancer

Patient History

- 76 year-old male
- HPV+ metastatic HNSCC with PI3Kα^{E545K} helical domain mutation
- Type 2 diabetes mellitus on metformin

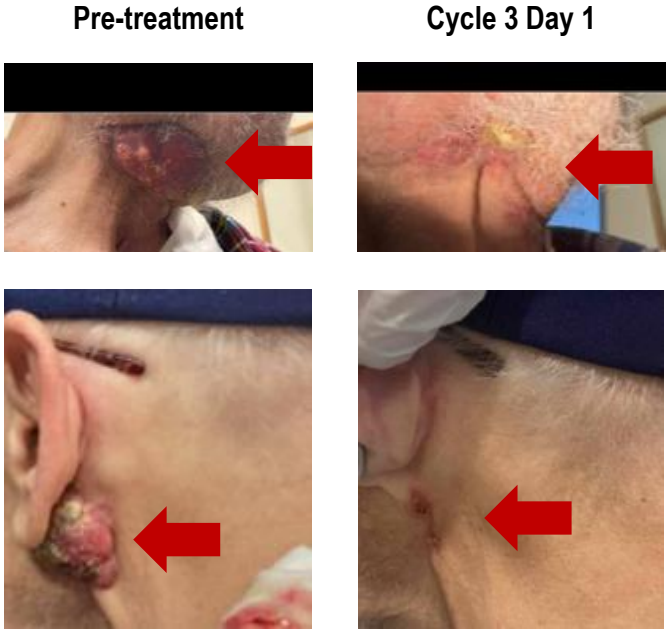
Prior Treatment

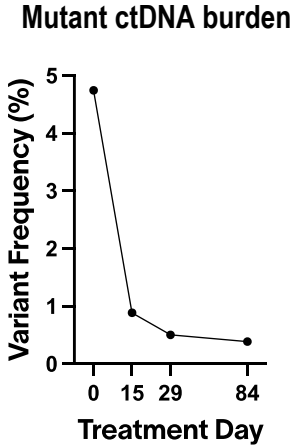
5 prior lines of therapy

1. Pembrolizumab (adjuvant)
2. Cetuximab (adjuvant)
3. Carboplatin + paclitaxel
4. SGN-B6A (integrin beta-6 ADC)
5. Carboplatin + gemcitabine

STX-478 Treatment and Response

- Treated with STX-478 at 100mg PO QD
- Significant/rapid reduction of external lesions
- 92% decline in mutant allele burden
- 25% reduction (SD) in target lesions on Cycle 3 Day 1





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Conclusions

- STX-478 is a potential best-in-class oral, allosteric mutant-selective PI3Kα inhibitor
- STX-478 is well-tolerated with limited PI3K wildtype toxicities in a high-risk patient population, including those with diabetes and/or intolerant to other PI3K inhibitors
- STX-478 dosing achieves target coverage several fold higher than other PI3Kα inhibitors
- STX-478 is active in breast cancer and other solid tumors, with a monotherapy ORR exceeding that of approved PI3K pathway inhibitors
- Efficacy is observed in patients with both PIK3CA kinase and helical domain mutations, with multiple responses deepening over time
- Enrollment is ongoing, including STX-478 combinations with fulvestrant +/- CDK4/6 inhibitors in patients with HR+/HER2- breast cancer

Acknowledgements

- We thank all the participants who participated on this trial, their families and loved ones who supported them, and the clinical investigators and medical staff who cared for them
- This study is sponsored by Scorpion Therapeutics (Clinicaltrials.gov identifier NCT05768139)